ISSN 0362-1197, Human Physiology, 2017, Vol. 43, No. 2, pp. 222–228. © Pleiades Publishing, Inc., 2017.
Original Russian Text © E.V. Potapova, V.V. Dremin, E.A. Zherebtsov, I.N. Makovik, A.I. Zherebtsova, A.V. Dunaev, K.V. Podmasteryev, V.V. Sidorov, A.I. Krupatkin, L.S. Khakhicheva, V.F. Muradyan, 2017, published in Fiziologiya Cheloveka, 2017, Vol. 43, No. 2, pp. 116–124.

Evaluation of Microcirculatory Disturbances in Patients with Rheumatic Diseases by the Method of Diffuse Reflectance Spectroscopy

E. V. Potapova[a, *], V. V. Dremin[a], E. A. Zherebtsov[a, b], I. N. Makovik[a], A. I. Zherebtsova[a], A. V. Dunaev[a], K. V. Podmasteryev[a], V. V. Sidorov[c], A. I. Krupatkin[d], L. S. Khakhicheva[e], and V. F. Muradyan[e]

[a] *Orel State University named after I.S. Turgenev, Orel, 302026 Russia*
[b] *University of Oulu, Oulu, Finland*
[c] *LAZMA Science and Production Enterprise, Moscow, 125252 Russia*
[d] *Priorov Central Research Institute of Traumatology and Orthopedics, Moscow, 127299 Russia*
[e] *Orel Regional Clinical Hospital, Orel, Orel oblast, 302028 Russia*
**e-mail: potapova_ev_ogu@mail.ru*

Received August 26, 2016

Abstract—Immunoinflammatory reactions affecting the state of the microvasculature play the key role in the genesis of rheumatic diseases. Therefore, it is important to develop new methods for the early detection of microcirculatory disorders. The purpose of this study was to assess the possibilities of diffuse reflectance spectroscopy used to identify microcirculatory disturbances in patients with rheumatic diseases by measuring skin blood supply and oxygenation rate and their relationship with the varying degrees of inflammatory activity. A total of 36 patients with rheumatic diseases and 31 healthy volunteers took part in the study. We analyzed the skin diffuse reflectance spectra recorded on the palmar side of the distal phalange of the right middle finger using a FLAME spectrometer. The erythema index and saturation rate were calculated to quantify the content of hemoglobin and oxygen saturation of tissues in both groups. The differences in the parameters under study between the groups were found to be statistically significant. The average value of erythema index was twofold higher in patients with rheumatic diseases with the second degree of inflammatory activity and about 2.5-fold higher in patients with the third degree of inflammatory activity, compared to the control group. This fact indicates impaired blood circulation with increased blood flow caused by inflammatory processes. Thus, diffuse reflectance spectroscopy can be used as an additional non-invasive diagnostic test for assessing the severity of microcirculatory disturbances and the activity of inflammation in rheumatic diseases.

Keywords: non-invasive diagnostics, diffuse reflectance spectroscopy, oxygenation, erythema index, rheumatic diseases, inflammatory activity

DOI: 10.1134/S036211971702013X

In all countries of the world, rheumatic diseases (RD) occupy a significant place in the structure of the total morbidity of population. They undoubtedly are socially and economically significant and exert a negative effect on society due to their increasing occurrence, early disability, high cost of therapy, noticeable decrease in life quality, great labor and economic losses [1, 2].

The clinical manifestations of RD depend on inflammatory process activity (IPA). According to the recommendations of EULAR (European League Against Rheumatism), the strategy of treating RD in each particular case depends first of all on the level of disease activity [3]. IPA determines the frequency of examinations of a patient, the selection of antirheumatic drugs, and the necessity of correcting the therapy. The timely detection of minimal activity of the process and anti-inflammatory therapy contribute to a considerable reduction of the number of complications and improvement of prognosis for the disease [4].

At present, most scientists believe [5–7] that immunoinflammatory reactions affecting the state of the microvascular bed play a key role in rheumatic pathology. In RD, the permeability of vascular walls increases and immune complexes are deposited in the walls; as a result, the vascular lumen becomes narrower and the capillary bloodstream and vascular sensitivity to sympathetic stimulation are reduced. Rheumatoid vasculitis (immunopathological inflammation of blood vessels) causes fibrinoid modifications in vascular walls, proliferation of endothelial and adventitial

cells, and thrombosis. The extent of microcirculatory disorder determines the severity of pathological processes in the joints of rheumatic patients and is interrelated with the duration and activity of inflammatory process [8]. The diagnostics of microcirculatory disorders in RD patients increases the accuracy of IPA detection and contributes to accurate prediction of the clinical course and precise assessment of therapeutic efficiency [9, 10].

The microcirculatory disorders in rheumatic patients are most often assessed by the methods of nailfold capillaroscopy [11], biomicroscopy of bulbar conjunctiva [12], and laser Doppler flowmetry (LDF) [13–15]. In addition, the clinical practice of rheumatologists involves using thermometry and thermal imaging, indirectly suggesting the presence of microcirculatory disorders on the basis of the changes in body surface temperature in the projection of affected microvessels [16].

Diffuse reflectance spectroscopy (DRS) is a promising technique for studying the microvasculature bed in rheumatic patients. DRS has all the advantages of optical noninvasive diagnostics: painless procedures, quick results, the absence of expensive reagents and consumables, and the minimal effect on an object and its properties [17–19]. The study of tissue oxygenation and blood engorgement by DRS is based on the difference between absorption spectra of the major tissue chromophores, oxyhemoglobin (HbO_2) and deoxyhemoglobin (Hb) [20]. The recorded diffuse reflectance spectra show the levels of blood engorgement and oxygen saturation of tissues in terms of different mathematical models or derived empirical ratios for the relationship between the reflection coefficient and the concentrations of these chromophores [21–23].

It is known that microcirculatory disorders caused by rheumatic diseases lead to the development of tissue hypoxia and impairment of blood supply [8, 24–26]. These states result in alterations in the spectral characteristics of tissue due to the changes in blood engorgement and concentrations of the main chromophores of the skin, oxyhemoglobin and deoxyhemoglobin, so that they can be noninvasively diagnosed by DRS. The study [27] shows that the diffusion reflectance spectra of healthy and inflamed tissues are different and can be quantitatively assessed by erythema index. Erythema is an indicator of increased blood level in the surface dermal vascular plexus and may characterize the level of activity of inflammatory process. Tissue saturation can be determined by the ratio of blood absorbance in the isobestic and nonisobestic points of oxy- and deoxyhemoglobin [28].

In this context, the aim of this work was to assess the possibilities of diffuse reflectance spectroscopy in detection of microcirculatory disorders in rheumatic patients by analyzing the calculated parameters of blood engorgement and oxygenation both in patients with different level of activity of inflammatory process and in conventionally healthy volunteers.

METHODS

The skin reflectance of the finger was recorded and assessed in the spectral range from 400 to 800 nm.

The experimental facility is shown schematically in Fig. 1a. An R400-7 fiberglass probe (Ocean Optics, United States) was used for radiation delivery from a HL-2000-HP-232R broad-band tungsten halogen light source (Ocean Optics, United States) and collection of reflected signal. The probe has 7 fibers: 6 illumination fibers around one read fiber. The reflected signal was analyzed with a portable FLAME spectrometer (Ocean Optics, United States). A personal computer and the Ocean View specialized software (Ocean Optics) supplied together with the spectrometer were used for data storage and reproduction.

The initial calibration was performed before recording diffusion reflectance spectra. The reflectance spectra were calculated by the equation:

$$R(\lambda) = \frac{R_t(\lambda) - R_b(\lambda)}{R_{PTFE}(\lambda) - R_b(\lambda)}, \quad (1)$$

where $R_t(\lambda)$ is the measured diffuse reflectance coefficient (DRC) of biological tissue;

$R_{PTFE}(\lambda)$ is the measured DRC of diffusely reflecting surface of white fluoroplastics (*PTFE*) sheet;

$R_b(\lambda)$ is the background spectrum obtained with the light source turned off.

Normalization makes it possible to eliminate the effect of light source intensity and receiver sensitivity on the measurement of spectral characteristics of biological tissues.

Experimental studies involved 36 patients (31 women and 5 men, 55 ± 13 years old) of the Department of Rheumatology at the Orel Regional Clinical Hospital (Orel, Russia). The patients were diagnosed with atrophic arthritis (22 subjects), systemic sclerosis (2 subjects), systemic lupus erythematosus (5 subjects), psoriatic arthritis (2 subjects), ankylosing spondylitis (Bechterew's disease) (1 subject), idiopathic dermatopolymyositis (1 subject), bilateral gonarthrosis (2 subjects), seronegative spondyloarthritis (1 subject). The patients with acute exacerbations of cardiovascular, bronchopulmonary and neuroendocrine diseases, gastrointestinal, liver and renal diseases, blood disorders, and any other serious chronic diseases that could influence diagnostic results were excluded from the study, as well as the patients with anamnestic alcohol abuse, drug addiction and drug abuse. The main clinical and laboratory parameters of rheumatic patients are given in Table 1.

The patients were divided into two groups: patients with the second-degree activity of inflammatory process (IPA 2, 28 subjects) and patients with the third-

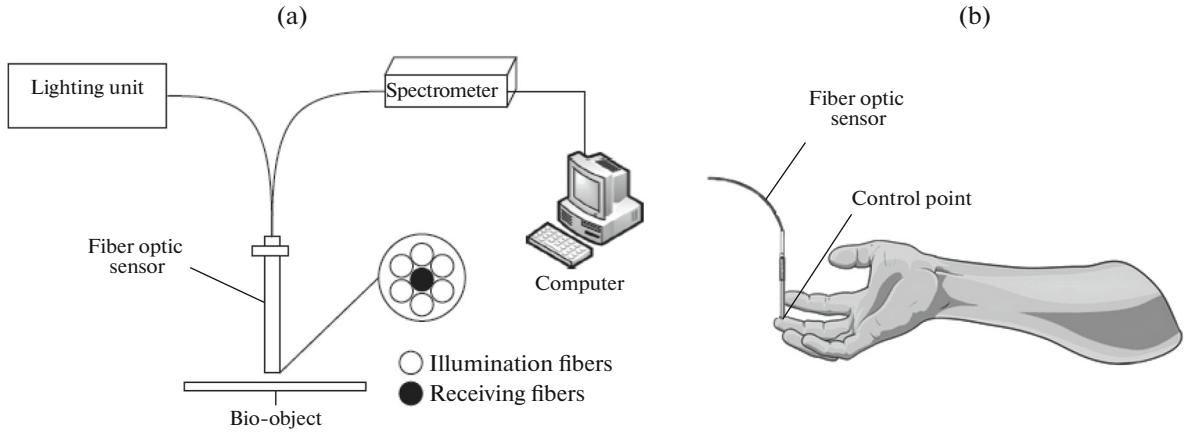

Fig. 1. The scheme of the experimental facility (a) and the optical fiber probe arrangement during the studies (b).

degree activity of inflammatory process (IPA 3, 8 subjects). ESR, C-reactive protein concentration and the level of rheumatoid factor (RF) in blood serum are considered as the main markers of inflammatory process activity. The IPA degree was assessed in each case individually on the basis of combinations of the above markers, external examination of the patients, and additional X-ray analysis in accordance with recommendations for laboratory diagnostics of rheumatic diseases [29, 30] and assessment of IPA degree [4].

The control group included 31 conventionally healthy volunteers, 8 women and 23 men with an average age of 46 ± 13 years having no diagnosed cardiovascular and musculoskeletal disorders and connective tissue diseases. All participants of experimental studies signed the informed consent form, with indication of their readiness to participate in the measurements.

During the studies, the diffuse reflectance spectra were recorded at the control point localized on the palmar surface of the distal phalanx of the right hand middle finger. The subjects were in the state of physical and mental rest and had been pre-adapted to the room temperature varying within a range of 21–25°C. The measurements were made no earlier than 2 h after the meal, while sitting with the right forearm laid on the table at heart level (the optical fiber probe arrangement during the studies is shown in Fig. 1b).

Data processing included the analysis of the measured curves of diffuse reflectance spectra, the calculation and analysis of erythema coefficient. Erythema is determined integrally in skin vessels, both in the capillaries and beyond the nutritional vascular bed, probably with the prevalence of non-nutritional component.

We have used the known technique for assessing blood engorgement and blood oxygenation by the erythema index proposed by Dawson et al. [31]. This technique is based on estimation of the area under the curve of optical density of skin in the spectral region of 510–610 nm. This approach allows the quantitative assessment of hemoglobin in skin tissue and is widely used by researchers. For example, in the work [27] it is proposed to use the erythema index for detecting hyperemia of the middle ear caused by infection. The same principle underlies the method of diagnosing otitis proposed by the researchers [32]. In [33], the authors describe the work of EMM-01 (erythema/melaninometer) designed by the principle of measuring the erythema index, which is used for objective assessment of vascular disorders, e.g., hemangiomas.

Table 1. The major clinical and laboratory indices of rheumatic patients

	Indices	Patients	
		patients with the 2nd degree of activity of inflammatory process (28)	patients with the 3rd degree of activity of inflammatory process (8)
1	ESR, mm/h	23.8 (2–60)	28.1 (18–45)
2	Concentration of C-reactive protein (CRP), mg/L	30.1 (0.8–192)	55.6 (0.8–96)
3	Level of rheumatoid factor (RF) in blood serum, MU/mL	67.7 (5–256)	142.8 (5–512)

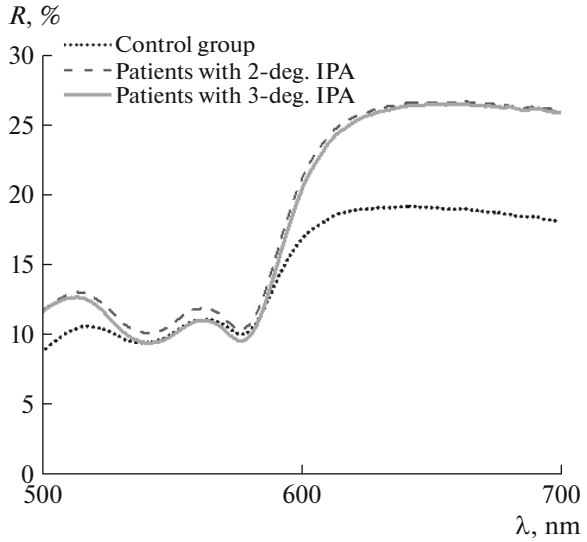

Fig. 2. The averaged diffuse reflectance spectra in the control point on the palmar surface of the distal phalanx of the right hand middle finger for rheumatic patients with second- and third-degree IPA and for conventionally healthy volunteers.

There are several approaches to the calculation of erythema index, which is most often estimated by the equation:

$$E = 100 \times [OD_{560} + 1.5 \times (OD_{545} + OD_{575}) - 2.0 \times (OD_{510} + OD_{610})], \quad (2)$$

where $OD = \log(1/R)$ is the optical density being a quantitative characteristic of skin absorption and the inferior indices denote the wavelength (nm), at which optical density is measured.

Optical density is measured in the range of wavelengths, where blood absorption is high (510–610 nm); the erythema index calculated thereby does not depend on the degree of blood saturation with hemoglobin [31].

The degree of blood saturation with oxygen in tissue (tissue saturation) can be determined using reflection coefficients at the wavelengths corresponding to the isobestic and nonisobestic points of oxy- and deoxyhemoglobin by the expression proposed by Spott et al. [28]:

$$SO_2 = \frac{\mu_{Hb}(\lambda_1) - \mu_{Hb}(\lambda_2)\dfrac{R(\lambda_2)}{R(\lambda_1)}}{\mu_{Hb}(\lambda_1) - \mu_{HbO_2}(\lambda_1)}, \quad (3)$$

where $R(\lambda)$ is the measured diffuse reflection coefficient (DRC) at the chosen wavelength;

μ_{Hb} and μ_{HbO_2} are the absorption coefficients of deoxygenated and oxygen-saturated blood, respectively [34];

λ_1 and λ_2 are the wavelengths of nonisobestic and isobestic points, respectively.

In the general case, the recorded saturation is a value averaged for the entire diagnosed volume, and the saturation of mixed blood or tissue saturation with oxyhemoglobin (S_tO_2) are suggested [35, 36]. The degree of oxygenation can be calculated by using several combinations of nonisobestic and isobestic points, which makes it possible to obtain information from different skin layers by selecting the respective wavelengths. For wavelengths of the blue and green ranges, due to low depth of penetration, the calculated value will represent the degree of tissue saturation with oxygen in the more superficial layer of the skin [23, 37]. In this study, $\lambda_1 = 560$ nm and $\lambda_2 = 545$ nm in the green region were chosen as a nonisobestic and isobestic point, respectively.

The experimental data were statistically analyzed. The results were checked for normal distribution by the Kolmogorov–Smirnov test and for homogeneity of variance by the Levene's test. The significance of statistical differences between the samples was assessed by one-way ANOVA.

RESULTS AND DISCUSSION

The possibilities of the DRS method for assessment of inflammatory process activity and microvascular disorders were analyzed with calculating all parameters and characteristics separately for the two groups of patients with the second- and third-degree IPA and for the control group of conventionally healthy volunteers.

Figure 2 shows the averaged diffuse reflectance spectra for the patients of the Department of Rheumatology and for the control group of conventionally healthy volunteers. As Fig. 2 shows, the spectra have the characteristic oxyhemoglobin (540 and 578 nm) and deoxyhemoglobin (555 nm) absorption bands.

The analysis of Fig. 2 shows that the averaged diffuse reflectance spectra recorded in the control point (on the palmar surface of the distal phalanx of the right hand middle finger) of rheumatic patients are located much higher than the spectra in the control point of conventionally healthy volunteers. It may be accounted for by the fact that the higher DRC values in patients compared to healthy volunteers were most probably caused by inflammatory processes in the upper limbs, because the most of subjects (22 patients) were diagnosed with rheumatoid arthritis. In the overwhelming majority of cases, this disease is accompanied by inflammation and swelling of metacarpophalangeal articulations of the index and long fingers. In the group under study, 5 patients were diagnosed with systemic lupus erythematosus accompanied, as is known [38], by polyarthritis with preferential affection of small joints of hands. Other patients also had inflammatory processes in joints of different genesis

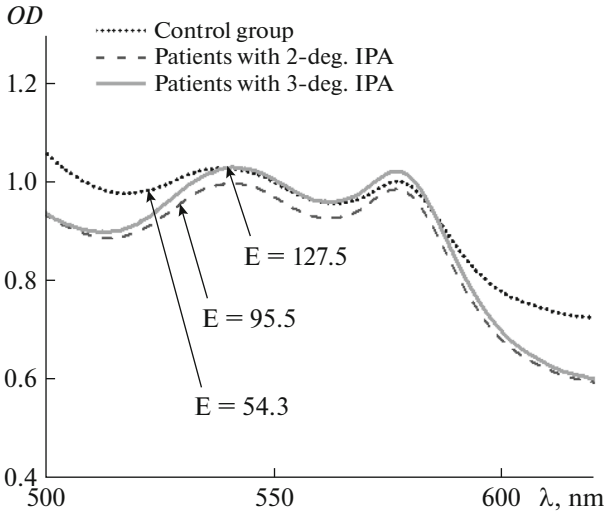

Fig. 3. The averaged spectra of optical density of skin at the control point (on the palmar surface of the distal phalanx of the right hand middle finger) for rheumatic patients with second- and third-degree IPA and for conventionally healthy volunteers.

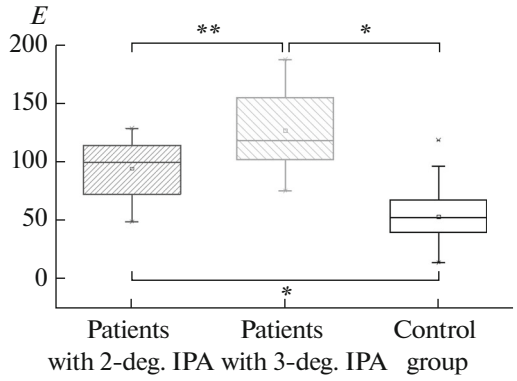

Fig. 4. The diagram of erythema index spread for 3 groups: the central line is a median, the box edges are the lower and higher quartiles (25th and 75th). Other symbols are as in Table 2.

(Bechterew's disease, psoriatic arthritis, systemic sclerosis).

However, it should be noted that the spectra of patients with the second-degree IPA are different in the region of hemoglobin absorption bands from the spectra of patients with the third-degree IPA. The quantitative difference between diffuse reflectance spectra obtained in the control point for rheumatic patients with inflammatory process of different degree and for conventionally healthy volunteers can be determined by using the erythema index, which characterizes the content of hemoglobin in skin tissue and is proportional to the area under the curve of optical density of skin (Fig. 3) in the spectral range of 510–610 nm.

The results of calculation of erythema index for patients of the Department of Rheumatology and for conventionally healthy volunteers in the control point are summarized in Table 2. This stage of experimental data processing showed that rheumatic patients had the higher values of erythema index and that the calculated index depended on the degree of activity of inflammatory process. Table 2 presents the results of calculation of erythema index for rheumatic patients and for conventionally healthy volunteers. It gives the mean values of erythema index and the calculated RMSD. In Figure 4, the results of statistical data processing are illustrated by the diagram of erythema index spread for 3 groups. The central line on the diagrams is a median and the box edges are the lower and higher quartiles (25th and 75th).

In addition, we calculated the degree of blood saturation with oxygen in tissue (tissue saturation) for the green region of wavelengths, S_tO_2. The results of calculating saturation for rheumatic patients with second-degree IPA and conventionally healthy volunteers are presented in Table 3 and in Fig. 5. Statistical processing was performed by analogy with the erythema index data processing.

The results of erhythema index calculation show that the mean value of this parameter, compared to the control group, is twofold higher for rheumatic patients with the second-degree IPA and almost 2.5-fold higher than erythema for rheumatic patients with the third-degree IPA, which makes it possible to state circulatory failures with enhanced blood engorgement caused by inflammatory processes.

The analysis of the calculated tissue saturation shows that rheumatic patients have a great spread of saturation data, with deviations upwards and downwards from the mean, which (in particular, at higher values of the parameter) may be indirect evidence of hypoxic states; however, it needs more detailed study and comparison of the results with other parameters obtained by different methods of noninvasive spectro-

Table 2. The results of calculation of erythema index for rheumatic patients and for conventionally healthy volunteers

Erythema index for rheumatic patients with second-degree IPA	Erythema index for rheumatic patients with third-degree IPA	Erythema index for conventionally healthy volunteers
95.5 ± 24.7*(**)	127.5 ± 36.5*	54.3 ± 23.1

* Statistical significance of differences relative to conventionally healthy volunteers with a probability of $p < 0.01$; ** statistical significance of differences relative to the group of rheumatic patients with the third-degree IPA with a probability of $p < 0.01$.

Table 3. The results of calculation of the extent of blood saturation with oxygen (tissue saturation) for rheumatic patients and for conventionally healthy volunteers

Tissue saturation for rheumatic patients with second-degree IPA, %	Tissue saturation for rheumatic patients with third-degree IPA, %	Tissue saturation for conventionally healthy volunteers, %
48.3 ± 10.1	49.2 ± 14.6	51.3 ± 21.1

photometric diagnostics, e.g., light tissue oximetry and pulse oximetry.

Thus, the statistically significant difference between the calculated erythema indices for the groups of rheumatic patients and conventionally healthy volunteers can be used to assess the degree and nature of rheumatoid inflammation, which may enhance the reliability of diagnostics of the activity and severity of inflammatory process. In case of long-term observation of patients, this parameter can be used for prognosis and assessment of the dynamics and efficiency of therapy.

CONCLUSIONS

The findings demonstrate that diffuse reflectance spectroscopy can be used for diagnosing microcirculatory disorders in rheumatic patients. Recommendations for the treatment of rheumatologic diseases can be developed only on the basis of quantitative assessment of disease activity. The immunoinflammatory process, which accompanies almost all RDs, causes microcirculatory disorders and changes in blood engorgement of tissues and concentrations of the main types of hemoglobin. These changes are clearly manifested in diffuse reflectance spectra. The observed relationship between the erythema index and the degree of IPA allows noninvasive and early detection of microvasculatory disorders, which favors the timely correction of therapy and improvement of prognosis for the disease.

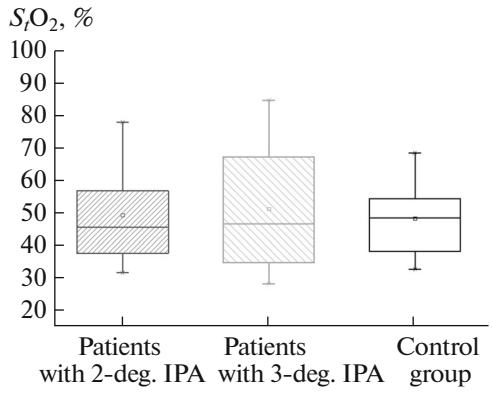

Fig. 5. The diagram of tissue saturation spread for 3 groups: the line is a median, the box edges are the lower and higher quartiles (25th and 75th).

Thus, diffuse reflectance spectroscopy is a promising method of additional diagnostics of the degree of activity of inflammatory process in rheumatic diseases, and its availability, simplicity, short duration of measurement (several tens of seconds), noninvasiveness and safety allow us to recommend it for broad application in clinical practice.

ACKNOWLEDGMENTS

This research was carried out in the framework of the basic part of the State Contract of the Ministry of Education and Science of the Russian Federation with Turgenev Orel State University for 2017–2019 and supported by the Grant of the President of the Russian Federation for federal support of young Russian candidates of sciences, project no. MK-7168.2016.8.

REFERENCES

1. Balabanova, R.M. and Erdes, Sh.F., The prevalence of rheumatic diseases in Russia during 2012–2013, *Nauchno-Prakt. Revmatol.*, 2015, vol. 53, no. 2, p. 120.
2. Folomeeva, O.M., Galushko, E.A., and Erdes, Sh.F., Prevalence of rheumatic diseases in adult populations of Russia and the USA, *Nauchno-Prakt. Revmatol.*, 2008, no. 4, p. 4.
3. Smolen, J.S., Landewé, R., Breedveld, F.C., et al., EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs, *Ann. Rheum. Dis.*, 2010, vol. 69, no. 6, p. 964.
4. Olyunin, Yu.A., Estimation of the disease activity at rheumatoid arthritis: Recommendations and practice, *Sovrem. Revmatol.*, 2014, no. 2, p. 4.
5. Nasonova, V.A. and Astapenko, M.G., *Klinicheskaya revmatologiya. Rukovodstvo dlya vrachei* (Clinical Rheumatology. Handbook for Doctors), Moscow, 1989.
6. Mach, E.S., Features of vessel lesions in rheumatoid arthritis: Effects of age, disease course, *Klin. Revmatol.*, 1994, no. 2, p. 19.
7. Blaginina, I.I., Dependence of microcirculation system affection on inflammatory process activity in patients with rheumatoid arthritis, *Ukr. Revmatol. Zh.*, 2008, no. 3 (33), p. 30.
8. Zapryagaeva, M.E. and Mach, E.S., Functional status of endothelium and its role in pathogenesis of some rheumatic diseases, *Nauchno-Prakt. Revmatol.*, 2003, no. 3, p. 60.
9. Guseva, N.G., Nevskaya, T.A., and Starovoitova, M.N., The problem of activity in systemic scleroderma, *Sovrem. Revmatol.*, 2013, no. 2, p. 18.

10. Werner, S.G., Langer, H.E., Ohrndorf, S., et al., Inflammation assessment in patients with arthritis using a novel in vivo fluorescence optical imaging technology, *Ann. Rheum. Dis.*, 2012, vol. 71, no. 4, p. 504.
11. Kuryliszyn-Moskal, A., Kita, J., and Hryniewicz, A., Raynaud's phenomenon: New aspects of pathogenesis and the role of nailfold videocapillaroscopy, *Reumatologia*, 2015, vol. 53, no. 2, p. 87.
12. Shilkina, N.P., Butusova, S.V., and Dryazhenkova, I.V., System of microcirculation, markers of vascular wall damage, and systematicity of the process in rheumatic diseases, *Angiol. Sosudistaya Khir.*, 2014, no. 1, p. 27.
13. Zherebtsova, A.I., Zherebtsov, E.A., Dunaev, A.V., et al., Study of the functional state of peripheral vessels in fingers of rheumatological patients by means of laser Doppler flowmetry and cutaneous thermometry measurements, *Proc. SPIE – Int. Soc. Opt. Eng.*, 2016, vol. 9917, p. 99170M.
14. Novikova, I.N., Dunaev, A.V., Sidorov, V.V., and Krupatkin, A.I., Functional status of microcirculatory-tissue systems during the cold pressor test, *Hum. Physiol.*, 2015, vol. 41, no. 6, p. 652.
15. Andrienko, A.V., Lychev, V.G., and Bublikov, D.S., The prospects of studying the features of vegetative regulation of blood circulation system activity in patients with rheumatoid arthritis by means of laser Doppler flowmetry, *Sib. Med. Zh.*, 2014, vol. 124, no. 1, p. 32.
16. Snekhalatha, U., Anburajan, M., Sowmiya, V., et al., Automated hand thermal image segmentation and feature extraction in the evaluation of rheumatoid arthritis, *Proc. Inst. Mech. Eng., Part H*, 2015, vol. 229, no. 4, p. 319.
17. Dremin, V.V., Zherebtsov, E.A., Rafailov, I.E., et al., The development of attenuation compensation models of fluorescence spectroscopy signals, *Proc. SPIE – Int. Soc. Opt. Eng.*, 2016, vol. 9917, p. 99170Y.
18. Tuchin, V.V., *Opticheskaya biomeditsinskaya diagnostika* (Handbook of Optical Biomedical Diagnostics), Moscow: FIZMATLIT, 2007, vols. 2.
19. Feather, J.W., Hajizadeh-Saffar, M., Leslie, G., and Dawson, J.B., A portable scanning reflectance spectrophotometer using visible wavelengths for the rapid measurement of skin pigments, *Phys. Med. Biol.*, 1989, vol. 34, no. 7, p. 807.
20. Lister, T., Wright, P.A., and Chappell, P.H., Optical properties of human skin, *J. Biomed. Opt.*, 2012, vol. 17, no. 9, p. 90901.
21. Shmyreva, V.F., Petrov, S.Yu., Antonov, A.A., et al., Method of evaluation of subconjunctival vascular bed with reflected light spectroscopy (experimental study), *Glaukoma*, 2008, no. 2, p. 9.
22. Sujatha, N., Suresh, Anand B.S., Bala, Nivetha K., et al., Assessment of microcirculatory hemoglobin levels in normal and diabetic subjects using diffuse reflectance spectroscopy in the visible region—a pilot study, *J. Appl. Spectrosc.*, 2015, vol. 82, no. 3, p. 432.
23. Randeberg, L.L., Haugen, O.A., Haaverstad, R., and Svaasand, L.O., A novel approach to age determination of traumatic injuries by reflectance spectroscopy, *Lasers Surg. Med.*, 2006, vol. 38, no. 4, p. 277.
24. Karyakina, E.V. and Belova, S.V., Peculiarities of pathogenic mechanisms of endogenous intoxication in patients with rheumatoid arthritis, *Nauchno-Prakt. Revmatol.*, 2001, no. 1, p. 21.
25. Muz, B., Larsen, H., Madden, L., et al., Prolyl hydroxylase domain enzyme 2 is the major player in regulating hypoxic responses in rheumatoid arthritis, *Arthritis Rheum.*, 2012, vol. 64, no. 9, p. 2856.
26. Hitchon, C.A. and El-Gabalawy, H.S., Oxidation in rheumatoid arthritis, *Arthritis Res. Ther.*, 2004, vol. 6, no. 6, p. 265.
27. Zhang, H., Huang, J., Li, T., Svanberg, S., et al., Optical detection of middle ear infection using spectroscopic techniques: Phantom experiments, *J. Biomed. Opt.*, 2015, vol. 20, no. 5, p. 57001.
28. Spott, T., Svaasand, L.O., Anderson, R.E., and Schmedling, P.F., Application of optical diffusion theory to transcutaneous bilirubinometry, *Proc. SPIE – Int. Soc. Opt. Eng.*, 1998, vol. 3195, p. 234.
29. Aleksandrova, E.N., Novikov, A.A., and Nasonov, E.L., The 2015 guidelines for the laboratory diagnosis of rheumatic diseases by the All-Russian Public Organization "Association of Rheumatology of Russia", *Sovrem. Revmatol.*, 2015, vol. 9, no. 4, p. 25.
30. *Bolezni sustavov: rukovodstvo dlya vrachei* (Diseases of Joints: Handbook for Doctors), Mazurov, V.I., Ed., St. Petersburg: Spetslit, 2008.
31. Dawson, J.B., Barker, D.J., Elliset, D.J., et al., A theoretical and experimental study of light absorption and scattering by in vivo skin, *Phys. Med. Biol.*, 1980, vol. 25, no. 4, p. 695.
32. Sundberg, M., Peebo, M., Oberg, P.A., et al., Diffuse reflectance spectroscopy of the human tympanic membrane in otitis media, *Physiol. Meas.*, 2004, vol. 25, no. 6, p. 1473.
33. Dolotov, L.E., Sinichkin, Y.P., Tuchin, V.V., et al., Design and evaluation of a novel portable erythema-melanin-meter, *Lasers Surg. Med.*, 2004, vol. 34, no. 2, p. 127.
34. Bosschaart, N., Edelman, G.J., Aalders, M.C., et al., A literature review and novel theoretical approach on the optical properties of whole blood, *Lasers Med. Sci.*, 2014, vol. 29, no. 2, p. 453.
35. Podbregar, M. and Mozina, H., Skeletal muscle oxygen saturation does not estimate mixed venous oxygen saturation in patients with severe left heart failure and additional severe sepsis or septic shock, *Crit. Care*, 2007, vol. 11, no. 1, p. R6.
36. Thorn, C.E., Matcher, S.J., Meglinski, I.V., and Shore, A.C., Is mean blood saturation a useful marker of tissue oxygenation?, *Am. J. Physiol.: Heart Circ. Physiol.*, 2009, vol. 296, no. 5, p. H1289.
37. Denstedt, M., Pukstad, B.S., Paluchowski, L.A., et al., Hyperspectral imaging as a diagnostic tool for chronic skin ulcers, *Proc. SPIE – Int. Soc. Opt. Eng.*, 2013, vol. 8565, p. 85650N.
38. Klyukvina, N.G. and Nasonov, E.L., The clinical and laboratory manifestations of systemic lupus erythematosus, *Sovrem. Revmatol.*, 2012, no. 4, p. 40.

Translated by E. Makeeva