

## Endothelium Dysfunction as the Predictor of Oral Lichen Planus

Irina V. Firsova<sup>1</sup>, Julia A. Makedonova<sup>2</sup>, Alexandra N. Popova<sup>3</sup>,  
Sergey V. Krajnov<sup>4</sup>, Yuliya M. Fedotova<sup>5</sup>

1. Professor and Chair, DDS PhD, Volgograd State Medical University, Department of Therapeutic Dentistry/Russia.
2. M.D., associate professor of the Department of Therapeutic Dentistry Volgograd State Medical University; Senior Researcher of the Pathology Laboratory of the Volgograd Medical Scientific Center/Russia.
3. Assoc. Prof, DDS, PhD Volgograd State Medical University, Department of Therapeutic Dentistry/Russia.
4. Assoc. Prof, DDS, PhD Volgograd State Medical University, Department of Therapeutic Dentistry/Russia.
5. Assist. Prof. Volgograd State Medical University, Department of Therapeutic Dentistry/Russia.

### Abstract

Lichen planus is a common disease among pathologies of the oral mucosa. The polygenic nature of this illness causes different approaches to its treatment. Numerous disturbances, including microvasculature disorders, occur in case of inflammatory-destructive process. Oral cavity microcirculation abnormalities of patients with lichen planus were investigated guided by the Laser doppler flowmetry at term before treatment and 12 months after it. The conventional treatment was administered for all patients, including local application of Tizol with L-arginine, systemic treatment consisted of endothelium protective action drug prescription. The basal bloodstream estimation and the amplitude frequency response analysis (using method of wavelet decomposition) were carried out. The attained results were compared with the indices of normal healthy control middle age subjects. Administration of Tizol with L-arginine application and Vazoton increased the vasomotor activity of vessels, the contribution of low-frequency flux motions and the local blood velocity.

**Clinical article (J Int Dent Med Res 2019; 12(3): 997-1003)**

**Keywords:** Laser doppler flowmetry, lichen planus, oral cavity, microcirculation

**Received date:** 16 January 2019

**Accept date:** 27 March 2019

### Introduction

At the present time the problem of ethiology and pathogenesis of oral lichen planus (OLP) remains to be uninvestigated and essential, because in the setting of prevalence rate increasing, the conventional treatment resistance, the growth of complicated disease occurrence and its abnormalities, the risk of neoplastic transformation and the involvement not only skin, but also the oral mucosa, gastrointestinal mucosa and the mucosa of genitourinary tract were registered.<sup>1,2</sup>

In recent times in dental practice more and more attention is given to investigation of the oral cavity capillary blood flow, because the role of claudication in pathogenesis of oral mucosa inflammatory-destructive diseases and its appendage is sufficiently high.<sup>3</sup>

Most probably, that individual typological features of the capillary blood flow, as a genetically determined factor, predispose the contraction of an oral mucosa disease or the particularity of the disease progression in some patients, what serves as weighty argument about the necessity of local microcirculation examination and its disturbances in oral cavity tissues. The microcirculatory system is one of those important systems where various illnesses manifest themselves at the initial stages of development.<sup>4,5</sup> Herewith, the cause-and-effect relationship, in which the disturbances of the capillary blood flow can be the primary stage in the development of many pathological conditions, determining the further disease outcome, and not being only their result.<sup>5</sup> A vast number of elderly patients diseases associate with those or other disturbances, which are expressed in the change of basal blood flow and the contribution of active and passive factors providing intravascular oscillations.<sup>6</sup>

Functional and morbid conditions lead to disturbances of capillary blood flow, manifested by the changes in myogenic, neurogenic and endothelial activities of arterioles and precapillaries (the distribution unit of microvasculature), resulting

#### \*Corresponding author:

Julia A. Makedonova

Department of Therapeutic Dentistry Volgograd State Medical University, Pathology Laboratory of the Volgograd Medical Scientific Center / Russia.

E-mail: mihai-m@yandex.ru

in the luminal occlusion or vascular distensibility, in arteriovenular quotient (of their diameters) and, on the back of, in the decrease or increase of the number of functioning capillaries. Structural changes in the microvessels are noted in conditions of significant functional loads and in pathological disorders in the body.<sup>7</sup>

The clinical research of capillary blood flow is a rather difficult task, because a dentist's choice of ancillary diagnostic techniques is sufficiently restricted from behind the small number of harmless examination methods. Also, in the process of diagnosis and at the end of the study, the findings are very difficult for interpretation, it takes from a doctor a lot of domain knowledge and high qualification.<sup>8</sup>

There are a lot of research references in scientific literature with a focus on oral mucosa microcirculation.<sup>9,10</sup> All researches about the oral cavity microvessels are divisible into investigation of oral mucosa microcirculation as a peripheral part of the vascular system inclusive of harmful factor influence, physiological status, as well as microvessels responses on the back of systemic diseases and medication intake, when the oral mucosa serves as accessible region for examination of the body microcirculation systemic disturbances all of a lump.<sup>11</sup>

The development of inflammatory reaction is coupled with microcirculation disturbances, resulting in hypoxia and, on the back of, in solution of epithelium continuity. It is necessary to reveal such components of microcirculation pathogenesis, the intervention on which will reduce the level of capillary disorders, increase the synthesis of NO in the body, and, thus, restore the nutrition of the oral mucosa.<sup>12</sup>

To take a comparative assessment of oral mucosa microcirculation functional status of patients with erosive-ulcerous form of oral lichen planus against healthy control subjects as well as follow-up treatment, verified with the help of Laser doppler flowmetry.

### Materials and methods

LDF measurement of patients aged 45-59 years was realized in the dental chair in a sitting position. To register blood flow in the oral mucosa, a Russian LAKK-OP device (a laser analyzer of capillary blood flow, which was quantity-built by the scientific-production enterprise "LAZMA") was used. After the

registration of LDF-grams, the monitor shows signal magnitude indices at the output of the device: the value of the average perfusion flow of blood –  $M$  in over the range of recording time, (measured in perfusion units (pf.ed)), the parameter  $\sigma$  ("flax") is the average variance of perfusion toward the average blood flow  $M$ , it has a dimension in perfusion units and an integral indicator of variations -  $Kv$  of the process. All these design parameters allow for the conclusion about the hemomicrocirculation condition (calculated in percent, %). The calculated parameters  $M$ ,  $\sigma$  and  $Kv$  make a general assessment of blood microcirculation state. A more detailed analysis of the microcirculation functioning was carried out at the second stage of data treatment of the basal bloodstream LDF-grams while investigating of the blood perfusion oscillating rhythms structure. At the second stage of investigation, the amplitude frequency analysis (AFA) of perfusion oscillations was performed by the Wavelet transform method. The values of the bloodstream oscillations rhythm fluctuations in the microcirculation were estimated by following indices:  $VLF$ ,  $LF_H$ ,  $LF_M$ ,  $HF$ ,  $CF$ . This experimental study was approved of by the Commission on Study Ethics of the Volgograd State Medical University (№2036-2017 16.10.2017).

All patients with erosive-ulcerous form of oral lichen planus were administered the conventional treatment, including local application of Tizol with L-arginine. The systemic treatment consisted of following medicaments: immunomodulator "Imudon" 8 tablets per day during 10 days, fast-disintegrating, the stretch between medication taking should not be less than 1 hour; the vasodepressor with endothelium protective action "Vasoton" with food, 2 caps (180 mg) three times a day; antianxiety agent "Tenoten" 1 tablet twice a day in the course of a month.

The function test of microcirculation was carried out in a group of healthy control subjects (control group) – 20 persons, as well as in the group of patients with erosive-ulcerous form of OLP (30 persons) within the following time period: before treatment and long-term period of monitoring (12 months).

Statistical analysis of the data included determination of the means, standard error, and statistical significance using a Student  $t$  test (Statistica 6, TIBCO Software; Excel 2000 for

Windows, Microsoft). Differences between groups in the parameters being compared were regarded to be significant at  $P < 0.01$ ;  $t \geq 2$ .

## Results

Based on the data obtained during the Laser Doppler flowmetry, it was established that the parameters of patients with OLP basal bloodstream and their amplitude-frequency variety stands out from healthy control subjects. Thus, while calculating the mean values of changes in perfusion ( $M$ ,  $\sigma$  and  $Kv$ ), a significant difference was obtained towards the control group (healthy individuals in this age group). Thus, the  $M$  parameter was statistically valid higher by a factor of 1,4 over this figure in the control group ( $22.81 \pm 0.51$  perf units) and was  $31.68 \pm 0.55$  perf units in the region of erosions and ulcers and it was  $31.37 \pm 0.1$  perf units on the symmetrical side ( $p < 0.05$ ). The level of the "flax" ( $\sigma$  or RMS) was 2,8 times less then in the control group ( $5.24 \pm 0.34$  perf. units.), equaled  $1.87 \pm 0.03$  perf. units in the pathological area and it was 2,5 times less on the symmetrical side ( $2.06 \pm 0.03$  perf. units). The variation coefficient in the control group was  $23.0 \pm 0.1$  perf. units, that was 4.2 times higher than in the erosive-ulcerous region ( $5.5 \pm 0.17$  perf. units) and it was 3.5 times higher relative to the data obtained in a symmetrical region (Table 1).

The averaged distribution of bloodstream rhythm amplitudes accomplished with the help of amplitude frequency variety assessment revealed that low-frequency oscillations prevailed in the group of healthy control subjects. The vasomotor rhythm was dominant: VLF – oscillations – 25%;  $LF_H$  – oscillations – 21%;  $LF_M$  – 39%; HF – 12%; CF – 3%. The amplitude-frequency spectrum analysis in patients with OLP in symmetric points of oral mucosa and in the affected area showed a high degree of asymmetry, the statistical analysis of LDF data didn't identify any significant differences ( $p > 0.05$ ). Thus, in the region of erosive and ulcerated lesions, the amplitude of low-frequency oscillations decreased, and as a result, the intensification in a greater degree of the pulse wave amplitude contribution was detected: the amplitude of the  $LF_H$  – oscillations was – 17%;  $LF_M$  – 18%, VLF – 26.5%; HF – and CF – oscillations – 17,5% and 21% respectively. In such a manner, there is a decrease of vasomotor

mechanism (reduction of endothelial, neurogenic and myogenic oscillations), vasoconstriction (reduction of basal bloodstream parameters) in patients with OLP. It should be noted that in the microcirculation the frequency interval of endothelium secretory activity and of the NO synthesis are coincided, which characterizes the functional link presence between the data of nitric oxide synthesis and the flux motions of the endothelial genesis and indicates the development of endothelial dysfunction.

The active factor which controlled precapillaries muscle tone condition, regulating blood flow into the nutritional channel, predominated in the group of healthy control subjects. The contribution of the passive factor (amplitude of the respiratory and pulse waves) was minimal. In patients with OLP, conversely, the contribution of the respiratory and cardiac rhythms flux motions prevailed over myogenic, endothelial and neurogenic oscillations, which were low-grade under rest conditions of healthy trial subjects. It is obvious that microcirculatory disorders in the oral cavity occur in equal measures both in the region of erosive lesions, and on the symmetrical side without apparent pathological manifestations.

A favourable evolution, characterizing microcirculatory changes in oral cavity, was registered in the course of the treatment after 12 months. Thus, the vasomotor activity of microvessels significantly changed relative to the analogous index, obtained before treatment and substantially approached to the control group values (Table 2).

The nature of the changes in the value of the average blood flow, the parameter  $M$ , characterizing the increase or decrease of perfusion, without the flax level, does not seem possible to assess. The flax level significantly increased by 58.1% after 12 months of monitoring against the indicator before treatment, however, the mean square deviation in the pathological area was 62.7% and 23.9% less on the symmetry side in comparison with the control group. In the symmetric region, a high value of vessels vasomotor activity was noted, the variation coefficient was not significantly different from this figure in the group of healthy subjects ( $p > 0.05$ ). In the area of erosive-ulcerative lesions, there was also a significant increase in vasomotor vascular activity by 2.8 times against the initial value ( $p < 0.05$ ).

Indices	M, perf. units	$\sigma$ , perf. units	Kv, %
The control	22.81±0.51*	5.24±0.34*	23.0±0.1*
Pathological condition	31.68±0.55*	1.87±0.03*	5.5±0.17*
Symmetry	31.37±0.1*	2.06±0.04*	6.57±0.14*

**Table 1.** Measurements of basal bloodstream. Annotation: statistical significance in reference to the control group:\* - p< 0.05

00	M, perf. units	$\sigma$ , perf. units	Kv, %
The control	22.81±0.51	5.24±0.34*	23.0±0.1*
II group, pathology	19.33±1.44	3.22±0.32*	15.49±0.5*
II group, symmetry	21.78±1.093	4.23±0.04*	21.26±1.26

**Table 2.** Local blood flow speed dynamics in microvasculature vessels of oral mucosa after a year of treatment onset. Annotation: statistical significance in reference to the control group:\* - p< 0.05

Frequency range	VLF	LFH	LFM	HF	CF
A	1.175±0.2	1.735±0.04	0.76±0.01	0.685±0.069	0.59±0.04
F	0.019±0.0001	0.028±0.001	0.139±0.007	0.335±0.02	1.005±0.02
A/3q	17.124±0.02	13.6±0.2	6.033±0.16	5.57±0.6	4.59±0.3
A/M	10.95±0.66	8.9±0.64	3.67±0.12	2.89±0.17	3.275±0.37

**Table 3.** Correlation between frequencies and oscillatory amplitude

After 12 months of monitoring, the analysis of the amplitude-frequency spectrum by the Wavelet transform method revealed that the oscillatory amplitudes predominated in the endothelial range (Table 3).

The redistribution of oral mucosa microvascular tone regulation, especially, the enhancement of endothelial activity occurred in the setting of decrease in the passive oscillations factor. It was found that the contribution of the pulse and respiratory waves oscillatory amplitude significantly decreased, amounting to 12% and 10%, respectively. Herewith the contribution of low-frequency flux motions was increasing, probably at a time when taking Vazoton, which was a powerful vasodilator and endothelioprotector, providing a material for NO synthesis by endotheliocytes. Local application of Tysol with L – arginine also increased the vasomotor activity of the vessels, the contribution of low - frequency flaxemias and the blood velocity. Perhaps this was due to the ability of arginine to increase the synthesis of NO in the body. This phenomenon, known as the “arginine paradox”, occurs when there are certain concentrations of free asymmetric dimethylarginine (ADMA) in cells that, in vivo, compete with

arginine at the level of the Y + either or both NO-synthases. With a high level of ADMA, endothelial NO-synthases is inhibited, but the administration of L-arginine restores its activity, normalizes endothelial function and vascular tone. NO, being a highly reactive and unstable compound, is a universal regulator of physiological functions and a powerful vasodilator. Based on the data of the authors Ravaeva M.Yu., Chuyan E.N. and others (2013) that the frequency interval of endothelium secretory activity and the synthesis of nitrogen oxide coincide, it can be assumed that an increase in the synthesis of nitric oxide occurs against a background of increased endothelial oscillations amplitudes.<sup>13</sup>

An increase in the regulation of the active microcirculatory system control factors occurred against the background of a decrease in the amplitude of aperiodic flux motions.

The use of spectral analysis of the bloodstream rhythmic components had allowed to establish that on the pathology area and on the symmetrical side, the ratio of active (LF, VLF) and passive (HF, CF) components of tissue bloodstream oscillation was disrupted. The spectrum power of LF-oscillations of the bloodstream, estimated by its contribution to the general spectrum of the flux motions, progressively decreases in the lesion, which characterizes the precapillaries muscle tone state, regulating the blood flow into the nutritional stream. In patients with an erosive-ulcerous form of oral lichen planus, according to laser Doppler flowmetry, vasomotor vascular activity decreased, as with the bloodstream deceleration, vasoconstriction and a significant decrease in the low-frequency oscillations amplitudes, that was accompanied by the development of endothelial dysfunction in the oral cavity. The oral cavity microcirculation disturbances were sufficiently monotonous both in the lesion site and on the symmetrical healthy side. In the oral cavity, the local spasm of arteriolar vessels was registered, as well as hypoxia in microvasculature and a decrease in the intensity and speed of bloodstream in the capillaries. It should be noted that disorders of microcirculation in the oral cavity could not be uniquely compared with any one concrete form. The main trends in the changes of LDF parameters corresponded to the vasospastic form. The microcirculation index was higher than normal, the flax was lowered, the amplitude of

the vasomotor waves was lowered, and the amplitude of the respiratory and especially pulse waves was significantly increased, the variation coefficient was below normal. The monotonic type of LDF – grams with high perfusion (hyperemic) was characterized by a high perfusion index and monotonous tissue bloodstream oscillations, caused by low indexes of the flaks and Kv. Herewith a significant contribution of respiratory and pulse components, along with a reduced vasomotor tone oscillations indicated the fractional attenuation of sympathetic influences.

### Discussion

Oral lichen planus (OLP) is relating to pluricausal, inflammatory and destructive diseases, in which the oral mucosa is involved in the pathological process.<sup>12</sup> One of the most important component of the oral mucosa diseases pathogenesis is a disorder of microcirculation, determining the intensity of reparative regeneration. The laser Doppler flowmetry is a modern diagnostic technique of the state of local system of microcirculation which allows the effective and noninvasive assessment of blood microcirculation indices in the diagnosis of various diseases, when selecting the local therapy and the control of providing treatment of gerontostomatological patients.<sup>10</sup>

Functional and pathological conditions lead to capillary bloodstream disturbances, manifested by changes in the myogenic, neurogenic and endothelial activity of arterioles and precapillaries (the distributing element of microcirculatory bloodstream), which is expressed in the arctationing or widening of their lumens, changes in the arteriovenous ratio (by their diameters) and, as a consequence, in decrease or increase in the number of functioning capillaries.<sup>4,5</sup> Structural changes in microvessels are noted under conditions of significant functional loads and pathological disturbances in the body.<sup>7</sup>

In the research articles of Sabantseva E. G. (2006) it was proved that in the pathogenesis of microcirculatory disorders in inflammatory-destructive diseases of the oral mucosa, structural and functional disorders of microvessels occurred, as well as blood rheological properties changes and barrier function of microvessels were observed, which

were accompanied by changes in bloodstream intensity (1,5-2 times), which was due to suppression of the vasomotor mechanism and compensatory increase in pulse oscillations. The severity of microcirculatory disorders in the lesion site correlated with the degree of destructive changes in the oral cavity.<sup>3</sup>

According to the data of a number of authors, the pathological process with lichen planus proceeds affected by the microcirculatory changes, however, it is not known whether these changes are the cause or consequence of the pathological process in the oral cavity.<sup>14,15</sup>

Thus, the most crucial tasks that need a solution of the problem are the determination of new pathogenesis components, determining the possibility of therapeutic intervention on the manifestations of OPL, as well as the development of pathogenetic treatment of OLP (especially its complicated forms (erosive-ulcerative)), having a complex character, combining high therapeutic efficiency at the minimum medicinal load, providing stimulation of tissues regenerative potential, reductioning of treatment duration and increasing the period of remission. The solution of these tasks will increase not only the effectiveness of dental care, but also the life quality of this category of patients.

Laser Doppler flowmetry is carried out using instruments designed for these purposes. In Russia, the most frequently used different modifications of the device "LAKK" - a laser analyzer for the evaluation of blood microcirculation. As a sensor in LAKK devices, the light probe made of three monofilaments is used. The one of fibers is used to deliver laser radiation from the device to the researchable object, the other two fibers are receiving for the laser radiation diffused into the tissue.<sup>16</sup> The diffused radiation delivered through the fibers is detected by a two-channel photo-integrated device. The electrical signals from the photo-integrated device enter the analyzer processing unit, where a Doppler frequency shift is detected in the registered signal. After the analog processing, an output signal is formed, proportional to the product of the multiplicand: the average velocity of the erythrocytes kinetics and their concentration in the probed region of the tissue.

Based on the data obtained with the help of LDF measurement, it is possible to analyze the

conditions and disorders of the microcirculation system, to detect various diseases at earlier stages of their development, to create a basis for a keen understanding of the pathogenesis of emerging microcirculation disorders, and to carry out objective control over the administering treatment activities and individual selection of pharmacological agents.

### Conclusion

The degree of mycrocirculatory changes depends on the intensity of the process. A high degree of severity of microcirculation disorders is observed in the region of the lesion of labial and buccal mucosa. These changes in the rhythmic structure of the flux motions expressed so much the more than the deeper the disorders of bloodstream and microcirculation. It means, that while the contribution of vasomotions to the active modulation of microcirculatory hemodynamics decreases, the compensatory role of other regulatory mechanisms increases. With the oral mucosa inflammation, vascular disturbances of the microvasculature occur early on, manifested in increased venostasis, a decrease in metabolic processes, a decrease in the vasomotor activity of the vessels, and a decrease in the rate of local bloodstream.

Capillary blood flow data reflect intensity of clinical implications in oral cavity. The more intense and stronger the inflammatory process, the higher the shifts in functional disorders of microcirculatory disorders and also the other way around.

Particularly it should be noted that in OPL reversible changes in hemodynamics are observed, which corresponds to compensated disorders, in other words, in the early detection of this pathology and early treatment, structural and hemodynamic disorders can be leveled and approximated to the indices of healthy people of this age group. Thus, the data of LDF - metria in patients with erosive-ulcerous form of oral lichen planus allows to correct existent pathogenetic and symptomatic treatment regimen, reflecting the severity of clinical manifestations of the oral mucosa in patients with erosive-ulcerous form of OPL. So far as with oral lichen planus together with structural and functional disorders of the oral mucosa, microcirculatory changes in the oral cavity play an important role, which makes it possible to identify vascular and metabolic

disturbances as the leading component in the pathogenesis of OLP.

### Acknowledgements

The authors thank, the local authorities (Volgograd State Medical University) for their support and contributes in this study.

### Declaration of Interest

The authors report no conflicts of interest pertaining to any of the products or companies discussed in this article.

### References

1. Lukins LM, Tiunova NV. Optimization of treatment of red flat lichen of the oral mucosa [in Russian] // *Maestro Dentistry*. 2009; 4: 79-81.
2. Roeykens H. Use of laser Doppler flowmetry in dentistry / H. Roeykens, S. Nammour, R. De Moor // *Rev Beige Med Dent*. 2009; 64 (3): 114-128.
3. Sabantseva EG. Pathophysiological characteristics of microcirculation disorders in inflammatory and destructive diseases of the oral mucosa / EG Sabantseva [in Russian] // *Regional blood circulation and microcirculation*. 2006; 5 (1): 30-36.
4. Barkhatov I.V. The use of laser Doppler flowmetry to assess violations of the human blood microcirculation system [in Russian] // *Kazan Medical Journal*. 2014; 1. (95): 63-69.
5. Kozlov V.I., Azizov G.A., Ibragim R.Kh. et al. Individually-typological features of microcirculation in humans [in Russian] // *Regional blood circulation and microcirculation*. 2005; 1: 77-78.
6. Severina T. V. Changing the condition of the capillary blood flow of the oral mucosa in chronic recurrent aphthous stomatitis [in Russian] // *Kuban Scientific Medical Journal*. 2009; 1: 112-115
7. Kozlov V.I., Gurova O.A., Litvin F.B. Disorders of tissue blood flow, their pathogenesis and classification [in Russian] // *Regional blood circulation and microcirculation*. 2007; 1: 75-76.
8. Firsova I.V., Makedonova Iu.A., Mikhailchenko D.V., Poroiskii S.V., Sirak S.V. Clinical and experimental study of the regenerative features of oral mucosa under autohemotherapy // *Research Journal of Pharmaceutical, Biological and Chemical Sciences*. 2015; 6(6): 1711-1716.
9. Laser Doppler flowmetry in assessing the mechanisms of regulation of tooth pulp microcirculation [Text] / S.N. Ermoliev, A.P. Sheriev, Yu.S. Tulip. [in Russian] // *Bulletin of the Scientific Center for Cardiovascular Surgery. A.N. Bakulev RAMS "Cardiovascular diseases."* Application. 2008; 9 (6): 155.
10. Maksimovskaya L.N. The state of the gum tissue microcirculation system in patients with inflammatory periodontal diseases against the background of different stages of GERD [Text] / L.N. Maksimovskaya, ETC. Dzhambaldinova, M.A. Sokolova [in Russian] // *Dentistry for all*. 2011; 1: p. 14-17.
11. Makedonova Iu.A., Firsova I.V., Temkin E.S., Poroiski S.V. and Mikhailchenko D.V. Justification of the Effectiveness of PlasmoliftingTM Procedure in Treatment of Patients with Erosive and Ulcerative Lesions of the Oral Cavity // *Research Journal of Medical Sciences*. 2016; 10 (3): 64-68.
12. Petrova L.V. Clinic, pathogenesis and treatment of red flat lichen of the oral mucosa: author. dis. ... Dr. med Sciences: 14.00.11 [dissertation] [in Russian]. Moscow, Central Research Institute of Dermatovenerologic Institute. 2002: 27.

13. . Ravaeva M. Yu., Chuyan E. N., Drevvetnyak N. A. The role of nitric oxide in the development of endothelial dysfunction [in Russian] // Uchenye zapiski Tavricheskogo Natsionalnogo Universiteta im. V.I. Vernadsky. 2013; 26 (65) No. 4: 147-157.
14. Jafarzadeh H. Laser Doppler flowmetry in endodontics: a review [Текст] / H. Jafarzadeh // IntEndod J. - 2009. - Vol. 42, № 6. – P.476-490.
15. Humeau A., Steenbergen W., Nilsson H., Stromberg T. Laser Doppler perfusion monitoring and imaging: novel approaches // Med. Biol. Eng. Comput. — 2007. — Vol. 45. — P. 421–435.
16. Rossi M., Ricco R., Carpi A. Spectral analysis of skin laser Doppler blood perfusion signal during cutaneous hyperemia in response to acetylcholine iontophoresis and ischemia in normal subjects // Clin. Hemorheol. Microcirc.2004; 31:303–310.