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Features of Neurogenic Disorders and Endothelial Mechanisms of Vasoregulation in Patients with Neuropathic and Neuroischemic Forms of Diabetic Foot

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Abstract: The state of neurogenic and endothelial mechanisms of vasoregulation of microvasculature in patients with diabetic foot syndrome, depending on the nature of the main blood flow and form of necrotic lesions of feet was studied. To assess violations of regulatory mechanisms of vasoregulation and identification of adaptive reserves of microvasculature of the lower extremities precision thermometry with indirect cold test and wavelet analysis of the oscillation amplitude of skin temperature in neurogenic (0.02 - 0.05 Hz) and endothelial (0.0095 - 0.02 Hz) frequency ranges was used. The sequence of neurogenic violations and the endothelial regulatory mechanisms of vasomotion function of the microvasculature, depending on the form of diabetic angiopathy of the lower extremities were established. Investigation of skin temperature in patients with diabetic foot syndrome is a diagnostic method of diabetic polyneuropathy symptoms, endothelial dysfunction and can be used to assess treatment efficacy.

Key words: Diabetic foot % Precision thermometry with indirect cold test % Wavelet analysis % Neurogenic and endothelial mechanisms of vasoregulation of microvasculature

INTRODUCTION

Occlusive-stenotic arterial disease is the most common pathology of the lower limbs that combines the main lesion of blood flow and microvasculature, presenting a direct threat to the development of necrotic processes and gangrene of foot [1, 2]. Diabetes affects about 4-5% of the world population, the number of patients in Russia is 6% [3]. From 30 to 50% of patients have signs of peripheral arterial disease of varying severity by the time of diagnosis of type 2 diabetes. They develop atherosclerosis of the lower extremities that proceeds more malignant 10 years earlier than persons of general population [4]. Hyperglycemia and diabetic microangiopathy trigger a cascade of biochemical reactions that lead to neuropathy and endothelial dysfunction. Diabetic neuropathy contributes to bypass surgery of blood flow through arteriovenous anastomoses, bypassing the capillary bed, which exacerbates the severity of injury and leads to the manifestation of diabetic foot [3]. Progressive thickening of the arterial wall of medium caliber in patients with type 2 diabetes leads to their rigidity and dilatation, diabetic macroangiopathy formation. Vasodilation of the distal capillary bed and autonomic neuropathy entail intravascular platelet activation, reduced antiplatelet activity of the vascular wall, leading to the appearance of platelet agents in the bloodstream, compounding microcirculation [5]. The combination of diabetic micro-macroangiopathy, atherosclerotic vascular bed lead to the cessation or reduction of peripheral blood flow and the development of critical ischemia of tissues of the foot, the appearance of necrotic lesions of the lower extremities.

The purpose of the study. To assess the state of neurogenic and endothelial mechanisms of vasoregulation of microvasculature in patients with neuropathic and neuroischemic forms of diabetic angiopathy of the lower extremities complicated by necrotic lesions of feet.

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Clinical material. The study involved 14 healthy people (7 men and 7 women) aged between 41 and 60 years (56.1 ± 0.8 years) and 55 patients with diabetic foot syndrome (18 men and 38 women), aged from 51 to 74 years (65.3 ± 1.8 years). Five groups of surveyed were distinguished:

The first group consisted of 14 healthy people (7 men and 7 women) aged between 41 and 60 years (56.1 ± 0.8 years).

The second group consisted of 5 patients (3 men and 2 women) with a form of neuropathic diabetic foot syndrome complicated by ulcerative lesions of feet, at the age of 52 to 74 years (62.0 ± 1.0 years) with duration of disease 11.2 ± 0.1 year. Before hospitalization 4 patients received oral hypoglycemic agents, 1 patient was on insulin therapy. The third group consisted of 5 patients (2 males and 3 females) with a form of neuropathic diabetic angiopathy of the lower extremities complicated by necrosis of feet. Their age ranged from 52 to 58 years (54.1 ± 0.2 years), duration of disease was 10.5 ± 0.3 years. All patients received short and longer-acting insulin. The exclusion criteria for patients of the 2nd and 3rd groups were: the presence of different length and hemodynamic significance of stenosis and occlusions of the great vessels of the lower extremities caused by atherosclerotic plaques, confirmed by the results of angiography.

Group 4 included 22 patients (19 males and 3 females) with neuroischemic form of diabetic foot syndrome, complicated by ulcerative lesions of feet, aged from 54 to 72 years (62.5 ± 0.5 years).All patients received insulin and were diabetic for 10.7 ± 0.5 years.

Group 5 was represented by 23 patients (9 men and 14 women), aged between 54 and 73 years (66.4 ± 0.7 years) with neuroischemic form of diabetic angiopathy complicated by necrosis of feet. All received insulin and treated for diabetes for 10.0 ± 1.2 years.

MATERIALS AND METHODS

To assess the state of regulatory mechanisms and identify adaptation reserves of microcirculation of the lower extremities was done by precision thermometry with indirect cold breakdown in neurogenic (0.02-0.05 Hz) and endothelial (0.0095-0.02 Hz) frequency ranges with wavelet analysis of fluctuations of skin temperature [6]. During the examination, the patient was lying on his back, the room temperature was 20 - 24°C. The surveyed was applied a sensor on the palmar surface of the distal phalanx of the second finger of his right hand and connected with the device "Termodat" (produced by NPP "control systems", Perm, Russia, RU.S. 32.001. A certificate number 18321). Temperature was registered within 5 minutes after insertion of the finger into a cell with a low thermal conductivity. Temperature measurement was performed at rest for 10 minutes, during which the indirect cold test with the left hand immersion into a bath of water-ice mixture at a temperature of 0°C for 3 minutes and 10 minutes after the functional test [6]. Patency of the arteries of the lower extremities was determined by selective radiopaque coronary arteriography by the complex *****Innova 3100, General Electrix**+** according to standard procedures and Seldinger access.

To reveal significant differences in these groups the methods of nonparametric statistics were used - the criteria of Wald-Wolfowitz Runs Test, Mann-Whitney U Test and the Kolmogorov-Smirnov test (the comparison of quantitative traits in different groups) and Wilcoxon sign (comparison of quantitative traits in a single group in different periods of time).

RESULTS AND DISCUSSION

In healthy individuals the level of oscillation amplitude of skin temperatures in neurogenic and endothelial frequency range during cold test decreased (from 0.00899 to 0.00322 Hz and 0.00302 to 0.00152 Hz, respectively ($p<0.05$) and then starting from the third minute of the functional load it increased (from 0.00700 to 0.01285 Hz and 0.00222 to 0.00247 Hz, respectively ($p<0.05$), it reached the level of initial values by the 10th minute of studies in neurogenic frequencies (0.01285 Hz) and was below the level of endothelial range (0.00247 Hz; $p=0.035$).

In patients of the 2nd group oscillation amplitude of skin temperature in the neurogenic frequency range during the pressor tests was significantly reduced without changing up to 3 minutes after its completion and increased after 10 minutes of functional load reaching initial values (Table 1).

In endothelial frequency range oscillation amplitude of skin temperature during the cold test was decreasing, it was smoothly increasing after the pressor test and by the 10th minute it corresponded to the level of the initial values (Table 2).

In patients of the 3rd group neurogenic response of frequency range of oscillation amplitudes to cold skin temperature test and its changes at 3 and 10 minutes after the functional load were absent.

Table 1: Dynamics of changes of oscillation amplitude of skin temperature during cold pressor test in the neurogenic frequency range

	Groups Research time			
Groups Research	Time before test (1)	During test (2)	3 minutes after test (3)	10 minutes after test (4)
Group 2	0.00209±0.0001	0.00130±0.0001 p_{1-2}=0.043	0.00141±0.0001 p_{1-3}=0.043	0.00376±0.0005 p_{2-4}=0.043 p_{3-4}=0.043
Group 3	0.00240±0.0003	0.00247±0.0001	0.00213±0.0003	0.00226±0.0003
Group 4	0.00231±0.0002	0.00152±0.0001 p_{1-2}=0.045	0.00228±0.0002 p_{2-3}=0.015	0.00267±0.0002 p_{2-4}=0.007
Group 5	0.00523±0.0001	0.00694±0.0001 p_{1-2}=0.045	0.00339±0.0001 p_{1-3}=0.036 p_{2-3}=0.026	0.00286±0.0005 p_{2-4}=0.046

Table 2: Dynamics of changes of oscillation amplitude of skin temperature during cold pressor test in endothelial frequency range

	Groups Research time			
Groups Research	Time before test (1)	During test (2)	3 minutes after test (3)	10 minutes after test (4)
Group 2	0.00379±0.0003	0.00257±0.0002 p_{1-2}=0.046	0.00320±0.0002 p_{1-3}=0.043 p_{2-3}=0.043	0.00460±0.0004 p_{3-4}=0.043
Group 3	0.00501±0.0003	0.00521±0.0005	0.00396±0.0004 p_{1-3}=0.043	0.00387±0.0003 p_{1-4}=0.043 p_{2-4}=0.043
Group 4	0.00676±0.0008	0.00436±0.0012 p_{1-2}=0.045	0.00543±0.0008 p_{2-3}=0.043	0.00494±0.0008
Group 5	0.01334±0.0014	0.01369±0.0011	0.00643±0.0005 p_{1-3}=0.028 p_{2-3}=0.012	0.00624±0.0005 p_{1-4}=0.012 p_{2-4}=0.005

Table 3: Patency of arteries of the lower extremities in patients with a neuropathic form of diabetic foot

	Feet ulcers		Necrosis of feet	
Arteries	The degree of stenosis from the right side (%)	The degree of stenosis from the left side (%)	The degree of stenosis from the right side (%)	The degree of stenosis from the left side (%)
Superficial Femoral artery	12.0 ± 3.5	12.0 ± 3.3	24.0 ± 2.7*	28.0 ± 1.5*
Popliteal artery	17.0 ± 4.6	16.0 ± 4.3	34.0 ± 1.3*	35.6 ± 2.1*
Anterior tibial artery	47.2 ± 1.0	45.8 ± 1.3	43.6 ± 1.5	42.6 ± 2.2
Posterior tibial artery	52.4 ± 1.1	49.0 ± 0.8	51.0 ± 0.8	50.6 ± 2.3

Note: *- difference is significant (p<0.05) in comparison with the indices of patients with a neuropathic form of diabetic foot complicated by ulcers of feet.

Table 4: Patency of the arteries of the lower extremities in patients with neuroischemic form of diabetic foot syndrome complicated by necrosis of feet

	Feet ulcers		Necrosis of feet	
Arteries	The degree of stenosis from the right side (%)	The degree of stenosis from the left side (%)	The degree of stenosis from the right side (%)	The degree of stenosis from the left side (%)
Superficial Femoral artery	35.8 ± 3.1	42.0 ± 3.1	56.7 ± 2.3*	59.2 ± 1.7*
Popliteal artery	48.0 ± 3.0	51.1 ± 2.7	51.8 ± 1.6*	63.1 ± 1.1*
Anterior tibial artery	63.3 ± 2.8	62.1 ± 2.8	71.3 ± 2.2	80.7 ± 2.2
Posterior tibial artery	88.2 ± 2.1	71.9 ± 2.7	78.4 ±2.1	81.8 ± 2.1

Note: * - the difference was significantly (p<0.05) in comparison with indicators in patients with neuroischemic form of diabetic foot syndrome complicated by the feet ulcers

In endothelial frequency range, as a response to pressor test, oscillation amplitude of skin temperature remained at initial values and decreased to the 3d minute after the cold test, remained unchanged until the end of the study.

On angiography of the lower extremities it was found that in patients with a neuropathic form of diabetic foot complicated by ulcers and necrosis of feet trunk blood flow was saved to the periphery on both sides (Table 3).

Patients with neuroischemic form of diabetic angiopathy of the lower extremities complicated by foot ulcers (group 4), the oscillation amplitudes of skin temperature in the neurogenic frequency range during pressor test decreased and beginning from the 3d minute after the cold test gradually increased, reaching to the end of the study the initial values. During the cold test (p=0.029) and by the 3d minute after it (p=0.036) the oscillation amplitude of this frequency range was much higher than in persons of the 2d group. In the endothelial frequency range the oscillation amplitude of skin temperature during cold test decreased (p=0.045) and it increased by the 3d minute after the pressor test, it did not change until the end of the study. The values of the oscillation amplitude of skin temperature after 3 minutes of functional load was higher than those of Group 2 patients (p=0.046). In patients with neuroischemic form of diabetic foot syndrome, complicated by necrosis of feet (Group 5), the oscillation amplitude of skin temperature in

neurogenic frequency range during the cold test increased and in the next 3 minutes declined sharply and continued to fall until the end of the study. The oscillation amplitude of the skin temperature at the beginning of the study and (p=0.045) during the cold sample was higher than in Group 3 patients (p=0.043). In endothelial frequency range during pressor test oscillation amplitude of skin temperature did not change and, having declined down in 3 minutes after functional loading, remained unchanged until the end of the study. The values of the oscillation amplitude of skin temperature at the beginning of the study and (p=0.023) during cold test (p=0.027) were higher than in Group 3 patients.

In patients with neuroischemic form of diabetic foot syndrome complicated by feet ulcers, hemodynamically significant stenosis at the level of popliteal-tibial segment was found. The development of feet necrosis occurred against the background of the femoropopliteal lesions and popliteal-tibial segments of the vascular bed (Table 4).

The study showed that in healthy persons reaction to the cold test showed vasoconstriction, accompanied by a decrease in the oscillation amplitude of skin temperature in the neurogenic and endothelial frequency range. After completion of pressor test oscillation amplitude of skin temperature in these frequency ranges restored to the initial level [6, 8].

The development of ulcerous feet defects in patients with neuropathic form of diabetic foot syndrome was based on infringements of microcirculatory blood flow caused by autonomic neuropathy, which was manifested by impaired regulation of vascular tone of the parasympathetic and sympathetic nervous system and was consistent with the data of other authors [5, 7].

The progression of type 2 diabetes is associated with deterioration of endothelial function and the development of diabetic polyneuropathy [9]. Both of these factors contribute to the vasodilation of the distal capillary bed entail intravascular platelet activation and reduction of antiplatelet activity of the vascular wall. This leads to the appearance platelet agents in the bloodstream, compounding the microcirculatory disorders and it is confirmed by the disappearance of the reaction of oscillation amplitudes of skin temperature in the neurogenic and endothelial frequency ranges to cold pressor test. The development of critical limb ischemia and the formation of necrotic tissue lesions of feet occurs when the stored blood flows to the periphery [5, 10].

In patients with a neuroischemic form of diabetic angiopathy of the lower limbs trophic ulcers of feet arise from disorders of the main flow in combination with endothelial dysfunction [4]. This was manifested by the lack of an adequate restore of the oscillation amplitude of skin temperature in the frequency range of the endothelial conducted after pressor test. Progression of the disease leads to diabetic neuropathy, which manifests as abnormal microvascular response to local hypothermia in neurogenic frequency range (higher level of the oscillation amplitude of skin temperature during pressor test), which does not contradict with the data of other authors [5]. The disappearance of the response of the oscillation amplitude of skin temperature in the endothelial frequency range to cold test indicates a simultaneous worsening of endothelial dysfunction.

CONCLUSIONS

- Neuropathic form of diabetic foot syndrome complicated by feet ulcers, characterized by disorders of neurogenic mechanism of vazoregulation against the stored main blood flow, further accession of endothelial dysfunction involves the progression of trophic disorders.
- The severity of necrotizing ulcerative complications of neuroischemic forms of diabetic foot syndrome, is caused by the degree of reduction of the main flow and the severity of subsequent disturbances of neurogenic and endothelial regulatory system of vascular tone.
- The study of oscillation amplitudes of skin temperature with wavelet analysis and cold test in patients with diabetic foot syndrome is a method of monitoring the state of neurogenic and endothelial mechanisms regulating vascular tone of the microvasculature and can be used to assess the treatment efficacy.

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