ANATOMICAL-FUNCTIONAL STATE OF SURFACE LYMPHATIC SYSTEM OF LOWER EXTREMITIES IN CHRONIC VEIN DISEASES ACCORDING TO FLUORESCENCE LYMPHOGRAPHY

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Abstract

Despite the large arsenal of diagnostic methods for studying the lymphatic system, there are isolated works on its morpho-functional state in chronic venous insufficiency. The purpose of the study was to study the anatomical and physiological state of the surface lymphatic system of the lower extremities in persons with different clinical classes of chronic vein diseases using fluorescence lifography. The study was conducted in 105 patients divided into six groups according to the clinical class of chronic diseases of the veins of the lower extremities according to the CEAP classification. We used fluorescent lymphography using sodium fluorescein to study the anatomical and functional capabilities of the lymphotone. The study revealed that morphofunctional changes in superficial lymphatic vessels in chronic lower extremity vein diseases depend on venous system decompensation. With an increase in the clinical class of chronic diseases of the veins of the lower extremities, the rate of lymph flow through the superficial lymphatic vessels is statistically significantly reduced. At the same time, the antegrade lymph cell is completely absent in C5-C6, with the appearance of retrograde outflow and discharge of the lymph into the deep lymph vessels. Thus, the progression of chronic venous insufficiency leads to proportional progression of morphofunctional changes in the superficial lymphatic system, which leads to the formation of lymphovenous insufficiency.

Keywords: varicose veins, chronic diseases of veins of lower extremities, chronic venous insufficiency, lymphatic vessels, lymphography, fluorescent lymphography, lymph cell.

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АНАТОМО-ФУНКЦИОНАЛЬНОЕ СОСТОЯНИЕ ПОВЕРХНОСТНОЙ ЛИМФАТИЧЕСКОЙ СЕТИ НИЖНИХ КОНЕЧНОСТЕЙ ПРИ ХРОНИЧЕСКИХ ЗАБОЛЕВАНИЯХ ВЕН ПО ДАННЫМ ФЛУОРЕСЦЕНТНОЙ ЛИМФОГРАФИИ

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Резюме

Несмотря на большой арсенал диагностических методов исследования лимфатической системы, имеются единичные работы, посвящённые морфофункциональному ее состоянию при хронической венозной недостаточности. Целью исследования явилось изучение анатомо-физиологического состояния поверхностной лимфатической сети нижних конечностей у лиц с разными клиническими классами хронических заболеваний вен при помощи флуоресцентной лимфографии. В исследование включены 105 пациентов, распределённых на шесть групп согласно клиническому классу хронических заболеваний вен нижних конечностей по классификации CEAP. Для исследования анатомо-функциональных возможностей лимфооттока нами использована методика флуоресцентной лимфографии с применением флуоресцеина натрия. При исследовании выявлено, что морфофункциональные изменения поверхностных лимфатических сосудов при хронических заболеваниях вен нижних конечностей зависят от декомпенсации венозной системы. При возрастании клинического класса хронических заболеваний вен нижних конечностей статистически достоверно уменьшается скорость лимфооттока по поверхностным лимфатическим сосудам. При этом антеградный лимфооттток полностью отсутствует у пациентов с классом хронических заболеваний вен нижних конечностей по классификации CEAP C5-C6, с появлением ретроградного оттока и сброса лимфы в глубокие лимфатические сосуды. Таким образом, прогрессирование хронической венозной недостаточности приводит к пропорциональному прогрессированию морфофункциональных изменений в поверхностной лимфатической системе, что вызывает формирование лимфовенозной недостаточности.

Ключевые слова: варикозная болезнь, хронические заболевания вен нижних конечностей, хроническая венозная недостаточность, лимфатические сосуды, лимфография, флуоресцентная лимфография, лимфооттток.

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Introduction

Chronic venous diseases of the lower extremities are one of the urgent problems in modern medicine. According to a number of authors, 80% of the population of industrialized countries suffers from these diseases, up to 50% of them have signs of chronic venous insufficiency (CVI), and up to 10% have trophic disorders of the lower extremities [1, 2, 3, 4, 5]. When venous outflow from the lower limb basin is disturbed, as some authors note, the function of the lymphatic system is also disturbed, which proves the close interrelation of these two systems. At pathological processes in the vein system of the lower limbs a vicious circle is created, which represents secondary compensatory morphofunctional changes in the lymphatic system, which subsequently take irreversible character [6].

To date, many techniques for studying the morphofunctional state of the lymphatic system has been developed. Back in the beginning of the last century, russian scientists A.S. Zolotukhin and M.G. Prives developed a technique of lifetime study of the lymphatic system – indirect lymphography. With the development of technologies the study of the lymphatic system was improved. Various ways of studying the lymphatic system with the help of radiation methods were introduced into medical practice [7, 8, 9]. Modern diagnostic methods allow to give morphofunctional characterization of the studied objects, but at the same time these methods are rather expensive and often invasive.

Today, various methods of lymphography, including fluorescence lymphography, are used worldwide. Most researchers point to the effectiveness of this method in patients with lymphedema to identify the causes of lymphatic channel dysfunction [10, 11, 12, 13, 14, 15]. At the same time, there are few studies in the literature, which are aimed at studying the lymphatic system in chronic venous insufficiency.

The aim of our study was to investigate the anatomo-physiological state of the superficial lymphatic network of the lower extremities in individuals with different clinical classes of chronic venous diseases using fluorescence lithography.

Materials and Methods

The study was approved by the independent ethics committee of the Moscow Clinical Research and Practice Center named after A.S. Loginov, Department of Public Health, Moscow (protocol No. 6/2021 of 23.06.2021). 105 patients were examined. There were 48 women and 57 men among the patients. Preliminarily, all patients underwent ultrasound duplex examination of the lower limb vessels to study the morphologic and functional status of both veins and arteries. Complaints and anamnesis were analyzed. Patients with oncological diseases, patients who had undergone occlusive thrombosis of deep veins of the lower extremities, as well as patients with diabetes mellitus and stenotic atherosclerosis of the arteries of the lower extremities were not included in the study. Depending on the clinical class of chronic vein diseases of the lower limbs according to the CEAP classification, the patients were categorized into six groups (Table 1).

To study the anatomy of superficial lymphatic vessels and functional capabilities of lymphatic outflow in real

Таблица 1
Распределение пациентов с разными клиническими классами хроническими заболеваниями вен (ХЗВ) по CEAP

Table 1
Distribution of patients with different clinical classes of chronic vein diseases (CVD) by CEAP

№ группы № group	CEAP	Количество пациентов Number of patients	Пол		Возраст Age
			M Male	Ж Female	
1	C-0; C-1	30	18	12	68 [64–72]
2	C-2	15	7	8	67 [61-73]
3	C-3	15	7	8	66 [63-74]
4	C-4	15	10	5	67 [59-72]
5	C-5	15	9	6	67 [64-72]
6	C-6	15	6	9	69 [63-73]
Всего Total		105	57	48	68 [63-73]

time, we applied the technique of fluorescence lymphography with the use of sodium fluorescein [16, 17].

The CEAP classification was adopted at the American phlebological forum in 1994. Later it was widely spread in Europe and Asia. Today this classification is widely used by the majority of phlebologists in Russia.

In our study we applied fluorescent lymphography using fluorescein preparation ("Novartis"), the active substance of which is diagnostic dye fluorescein sodium (Fig. 1). In the horizontal position of the patient, 2 ml of fluorescein sodium diluted 10 times in physiological solution was injected into the area of the first and second interfinger spaces and the area of the right and left ankle. After subcutaneous injection of the drug, an examination was performed using a light source with a blue spectrum of radiation (wavelength – 480 nm), stimulation of which leads to yellow-green fluorescence with a wavelength of 520 to 530 nm. After 5, 10, 15, 15, 30, 45, 60 min in dark room conditions using a light source with 480 nm wavelength, staining of superficial lymphatic vessels was assessed, followed by documentation with a digital camera. The number of visualized vessels, their topography, straightness of direction, as well as the width of luminescence and the direction of lymph flow through lymphatic vessels were evaluated (Fig. 2).

Using a stopwatch and a ruler, the lymph flow velocity along the superficial lymphatic vessels was measured, for which the length of the stained vessel and the time elapsed after fluorescein injection was measured in each of the specified time intervals. To calculate the lymph flow velocity the formula V=S/T was applied, where S is the length of the stained vessel, T is the time after the drug injection.

The Shapiro-Wilk method was used to determine the type of quantitative features. A sign was considered normally distributed at p>0.05. Quantitative data are presented as median and interquartile range (25% and 75%). Statistical analysis was performed using non-parametric statistical methods. The Kraskell-Wallis method (ANOVA) was used to compare the six groups. The sign was considered reliably different in the groups at p<0.05. When this condition was met, the Mann-Whitney method for pairwise comparisons with Bonferroni correction (k=0.05/15=0.0033) was further used.

Рис. 1. Флуоресцеин натрия и фонарь с излучением синего спектра.
Fig. 1. Fluorescein sodium and Blue Light.

Рис. 2. Оценка степени лимфатической недостаточности после введения флуоресцеина натрия.
Fig. 2. Assessment of the degree of lymphatic insufficiency after fluorescein sodium injection.

Results and Discussion

Preliminary ultrasound examination showed that patients with clinical class 0 and 1 had no signs of valve insufficiency and varicose transformation of the lower limb veins. At the same time, clinically there were only signs of telangiectasias or reticular vein dilatation. The listed clinical and instrumental data and further investigation of lymphatic vessels by fluorescence lymphography showed that in group 1 patients the superficial lymphatic network consisted of rectilinear and uniform in diameter numerous drainage collectors.

After sodium fluorescein injection there was a clear fluorescence with the image of lymphatic vessels course, and during further 30-50 min there was a clear staining of superficial lymphatic network. In the first group of patients we noted that 1-2 min after the drug injection the injection site took a proximal elongated shape (Fig. 3). The velocity indices of lymph flow through superficial lymphatic vessels in the patients of the first group were the highest and amounted to 11.3 [10.9-11.5] cm/min (Table 3). When studying morphometric parameters in patients of this group the following data were obtained: vessel luminal width was equal to 2 [1.5-2.0] mm (Table 2).

Further study showed that in group 2 patients suffering from varicose veins without clinical signs of CVI, such as edema or trophic disorders, superficial lymphatic vessels took a tortuous shape. At the same time, the width of lymphatic vessels in patients of this group was 2 [2-2.5] mm, which was significantly greater compared to the parameters of group 1 patients (p=0.0016). In patients of the 2nd group three groups of direction of superficial collector lymphatic vessels, as well as the multiplicity of diverting collector lymphatic vessels were preserved in the tibia region. The functional state of the superficial lymphatic network in patients with CEAP class 2 was significantly lower than in group 1 patients, as indicated by a decrease in lymphatic outflow velocity to 8.3 [8.2-8.5] cm/min (p<0.0001 compared with group 1).

In patients with varicose disease with clinical manifestation in the form of lower limb edema without trophic disorders, the same number of superficial vessels in the lower leg area was preserved as in patients of groups 1 and 2. The course of the superficial lymphatic vessels was not straight, in the tibia region there was noted a tortuosity of their direction. At the same time it was revealed that in group 3 patients with the appearance of edema, which characterizes the beginning of venous insufficiency, the width of superficial lymphatic vessels luminescence increases, indicating morphological changes in lymphatic vessels. Thus, the luminal width in group 3 was the maximum, amounting to 3.5 [3.5-3.5] mm (p<0.001 compared with the values of groups 1 and 2). Parallel to the increase in the width of lymphatic vessels in patients of group 3, their functional state also deteriorated, which was indicated by a decrease in the antegrade lymph

Рис. 3. Флуоресцентная лимфография у пациентки с 1-м клиническим классом ХЗВ по CEAP. Через 5 мин после введения флуоресцеина натрия окрашены лимфатические сосуды тыла правой стопы.
Fig. 3. Fluorescent lymphography in a patient with CVD Class 1 according to CEAP. 5 min after the injection of fluorescein sodium, lymph vessels of the rear of the right foot were stained.

Таблица 2
Морфологическая характеристика поверхностных лимфатических сосудов при различных клинических классах ХЗВ по CEAP

Table 2
Morphological characterization of superficial lymphatic vessels in different clinical CVD classes according to CEAP

Группы Groups	Ширина свечения сосуда (мм) Vessel glow width (mm)	P-value p<0,0001
1 (n-30)	2 [1,5-2,0]	P1-2 p=0,0016; P1-3 p<0,0001; P1-4 p<0,0001; P1-5 p=0,0044; P1-6 p<0,0001
2 (n-15)	2 [2-2,5]	P2-3 p<0,0001; P2-4 p<0,0001; P2-5 p=0,001; P2-6 p<0,0001
3 (n-15)	3,5 [3,5-3,5]	P3-4 p=0,0013; P3-5 p<0,0001; P3-6 p<0,0001
4 (n-15)	3,0 [3,0-3,5]	P4-5 p<0,0001; P4-6 p<0,0001
5 (n-15)	1,0 [0,5-2,0]	P5-6 p=0,23
6 (n-15)	1,0 [0,5-1,5]	

*Для сравнения шести групп применяли метод Краскела-Уоллиса. Признак считали достоверно отличным в группах при p<0,05, При выполнении этого условия далее использовали метод Манна-Уитни для парных сравнений с поправкой Бонферрони (k=0,05/15=0,0033)
*The Kraskel-Wallis method was used to compare the six groups. The sign was considered significantly different in groups at p < 0,05, Under this condition, the Mann-Whitney method was further used for Bonferroni-corrected pairwise comparisons (k = 0,05/15 = 0,0033)

Таблица 3
Функциональная характеристика поверхностных лимфатических сосудов при различных клинических классах ХЗВ по CEAP

Table 3
Functional characteristics of superficial lymphatic vessels in different clinical CVD classes according to CEAP

Группы Groups	Скорость лимфотока (см/мин) Lymph flow rate (cm/min)	P-value p<0,0001
1 (n-30)	11,3 [10,9-11,5]	P1-2, P1-3, P1-4, P1-5, P1-6 p<0,0001
2 (n-15)	8,3 [8,2-8,5]	P2-3, P2-4, P2-5, P2-6 p<0,0001
3 (n-15)	4,7 [4,6-5,7]	P3-4, P3-5, P3-6 p<0,0001
4 (n-15)	1,3 [1-1,6]	P4-5, P4-6 p<0,0001
5 (n-15)	0,6 [0,4-0,8]	P5-6 p=0,19
6 (n-15)	0,5 [0-0,6]	

flow rate to 4.7 [4.6-5.7] cm/min (p<0.0001 compared to groups 1 and 2).

Patients included in group 4 had edema of varying severity and trophic disorders in the form of indurative changes of the skin and subcutaneous tissue or lipodermatosclerosis. Trophic disorders in the majority of patients in this group had a circular character. The study revealed that in this group of patients the width of vessels was uneven, along the course of vessels their dilation and constriction, as well as tortuosity of lymphatic vessels on the foot were noted (Fig. 4). The luminescence width of superficial lymphatic collectors in this group of patients was 3.0 [3.0-3.5] mm (p<0.0001 compared to the values of patients in the previous groups). At fluorescence lymphography in the area of trophic disorders, the contrast of superficial lymphatic vessels was not not observed. At the same time, patients with the 4th clinical class showed pronounced disorders of the functional state of the lymphatic network of the lower limbs, which was indicated by a significant decrease in the antegrade lymph flow rate to 1.3 [1.0-1.6] cm/min (p<0.0001 compared to the previous groups). When sodium fluorescein was injected into the ankle region, the staining of lymphatic vessels in this group of patients occurred in a retrograde direction. The established retrograde current of sodium fluorescein from the ankles was at a rate of 2.9 [1.5-3.1] cm/min.

Patients with a history of trophic ulcers on the background of CVI were included in group 5, and patients with open trophic ulcers in the shin area – in group 6. During the examination it was revealed that patients of groups 5 and 6 also had uneven diameter of superficial lymphatic vessels on the background of trophic disorders (as well as patients of groups 3 and 4). The width of vessels was narrowed, and their course was not straight on the back of the foot in the form of tortuosity of the vascular network. The luminal width of vessels in patients of groups 5-6 was statistically significantly (p<0.0033 with Bonferroni correction) smaller compared to the values of patients of groups 1-4, amounting to 1.0 [0.5-2.0] mm and 1.0 [0.5-1.5] mm, respectively. It should be noted that no fluorescence of lymphatic vessels was detected in the area of pronounced indurative changes and trophic ulcers when performing lymphography, which indicated sclerosing of lymphatic vessels against the background of scarring changes of soft tissues. At the same time in patients of these groups against the background of expressed trophic disorders there was a significant decrease of lymph flow velocity along the superficial lymphatic vessels (Table 3). The lymph flow velocity was equal to 0.6 [0.4-0.8] cm/min, and 0.5 [0.0-0.6] cm/min, respectively. When

Рис. 4. Флуоресцентная лимфография у пациента с 4-м клиническим классом ХЗВ по CEAP. Через 15 мин после введения флуоресцеина натрия окрашены лимфатические сосуды тыла стопы, переходящие в медиальную группу коллекторов.
Fig. 4. Fluorescence lymphography in a patient with CVD class 4 according to CEAP. 15 min after the injection of fluorescein sodium, the lymph vessels of the rear of the foot were stained, passing into the medial group of collectors.

Рис. 5. Флуоресцентная лимфография у пациента с 6-м клиническим классом ХЗВ по CEAP. Через 5 мин после введения флуоресцеина натрия происходит окрашивание в ретроградном направлении.
Fig. 5. Fluorescence lymphography in a patient with CVD 6 clinical class according to CEAP. 5 min after the injection of fluorescein sodium, retrograde staining occurs.

sodium fluorescein was administered, it was observed that staining of lymphatic vessels occurred in the retrograde direction, and the lymphatic current velocity was 1.5 [1.2-1.7] cm/min, 1.2 [1.1-1.7] cm/min in the retrograde direction, respectively (Figure 5).

There are single works in the literature, which are devoted to the study of the functional state of the lymphatic network of patients with chronic venous insufficiency of the lower extremities [18, 19]. Using functional lymphography with the use of superfluid oil lipidol preparation and lymphoscintigraphy, G.V. Chepelenko a violation of drainage and transport function of lymphatic capillaries was established from the edges of the ulcer, at the level of withdrawing (from the skin to the collector), collecting (from the foot to the regional nodes) vessels [18]. We have developed and patented the technique of fluorescent lymphography [16, 17, 19], which was used to study superficial lymphatic vessels in individuals with different clinical classes of CVD according to CEAP classification. On the basis of the performed study using fluorescent lymphography a close relationship between secondary changes in the lymphatic channel of the lower limbs and the severity of trophic disorders on the background of chronic venous insufficiency was revealed. It was found out that the antegrade lymph flow rate through superficial lymphatic vessels decreases in proportion to the increase of clinical class according to CEAP and is completely absent at C5-C6, which is explained by retrograde flow and lymph discharge into deep lymphatic vessels. The course of varicose veins is manifested by deterioration of functional state of lymphatic vessels, which leads to decompensated state of lymphatic outflow.

Conclusion

Thus, the progression of chronic venous insufficiency leads to proportional deterioration of the morphofunctional state of the superficial lymphatic system, which leads to the formation of lymphovenous insufficiency.

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