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CLINICAL SAFETY OF THE USAGE OF MATERIALS FOR IMPLANTATION SURGERY BASED ON TITANIUM AND ITS ALLOYS ACCORDING TO THE BIOCOMPATIBILITY INDEXES

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SUMMARY
Biocompatibility is one of the most important characteristics of materials for implantation. It has been scientifically confirmed that the physical and chemical properties of the surface of metal implants or their elements can have an impact on clinical safety. The structure of the material (porosity, smoothness, geometry) can influence its incorporation into surrounding tissues. This requires conducting experiments with a longer contact interval of the tested materials under in vivo conditions.

KEYWORDS: *titanium, VT6, embryotoxicity, biocompatibility, chicken embryos.*

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КЛИНИЧЕСКАЯ БЕЗОПАСНОСТЬ ИСПОЛЬЗОВАНИЯ МАТЕРИАЛОВ ДЛЯ ИМПЛАНТАЦИОННОЙ ХИРУРГИИ НА ОСНОВЕ ТИТАНА И ЕГО СПЛАВОВ ПО ДАННЫМ ПОКАЗАТЕЛЕЙ БИОСОВМЕСТИМОСТИ

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РЕЗЮМЕ
Биосовместимость выступает одной из важнейших характеристик материалов для имплантации. Научно подтверждено, что физические и химические свойства поверхности металлических имплантатов или их элементов могут оказывать влияние на клиническую безопасность. Структура материала (пористость, гладкость, геометрия) может оказывать влияние на его включение в окружающие ткани. Это требует проведения экспериментов при более длительном интервале контакта тестируемых материалов в условиях in vivo.

КЛЮЧЕВЫЕ СЛОВА: титан, ВТ6, эмбриотоксичность, биосовместимость, куриные эмбрионы.

КОНФЛИКТ ИНТЕРЕСОВ. *Авторы заявляют об отсутствии конфликта интересов.*
Источник финансирования. *Работа выполнена за счет гранта Российского научного фонда (Грант № 24-69-00074). https://rscf.ru/project/24-69-00074/.*

Introduction

Medical materials science includes the development and research of materials that are used in medicine, created to compensate for the loss of organs or tissues. The subject of inorganic medical materials science are metals or metal alloys in the form of load-bearing structures or diagnostic preparations; materials of inert metals, oxide materials intended for the treatment of bone tissue defects or the cultivation of cell cultures when applied to appropriate metal surfaces [2, 8].

The biomaterial should be biocompatible and can be biodegradable [1, 9]. Biocompatible materials are materials that have a nonbiological origin and are used in medicine to achieve interaction with a biological system. They have the ability to function with the appropriate reaction of the host body in a particular case of use, without causing inflammation or necrosis of the surrounding tissues [3, 4, 7]. Biocompatible materials and devices act or function harmoniously and coherently when in contact or inside a living body, without causing serious diseases or complications.

The biocompatibility of materials includes:

1. immunological compatibility, which is mainly related to the selection of antigen-compatible tissues, cells, and bioengineered structures;
2. morphofunctional compatibility (embedding, integration with surrounding tissues);
3. biomechanical compatibility (the ability to withstand mechanical, hydrodynamic and other types of loads) [2, 10].

Biocompatibility is a complex selective property of an organism, in which the possibility of coexistence of a biomaterial and a biosystem is mediated with the preservation of all tissue functions and its ability to regenerate [6]. The use of biomaterials becomes vital due to their special effect on the quality and duration of human life. Implants should not cause a local inflammatory reaction, systemic pathological processes, exacerbate complications, and must preserve the declared properties during their service life, thus confirming their clinical safety while using [5].

Materials and methods of research

The studied samples were titanium washers of the Ti VT 6 brand, similar to Ti-6Al-4V, with a diameter of 6 mm and a thickness of 1.5 mm with a functional coating. The film was pure titanium (Ti) and zirconium (Zr), as well as titanium oxides (TiO_2) and zirconium (ZrO_2). The thickness of the functional film was 3 microns. The coating was applied by the vacuum arc plasma-assisted method on the vacuum experimental installation "QUINTA" [11], which is included in the list of unique installations "UNIQUUM" (https://ckp-rf.ru/catalog/usu/434216/). The samples were mounted in special equipment, which allows covering > 98% of the surface area of the sample.

The biocompatibility of the product samples was studied using the chorioallantoid membrane (CAM) model of a chicken embryo in accordance with the method described in [7, 9]. For the experiment, fertilized eggs were treated with 70% ethanol and incubated in an automatic incubator Rcom Maru Deluxe Max 380 (AUTOELEX CO., LTD, Korea). On the 3rd day of incubation, 3 ml of protein was aspirated from the sharp pole of the egg through a drilled hole. The hole was sealed with sterile paraffin. On the 8th day of incubation, a square window measuring ≈2.5 cm^2 was cut out in the shell and sterile products of four variants (n = 8) were inserted into the CAM, one sample per egg. Sterile round cover glasses of a similar diameter (5 mm) based on silicate glass were used as a control. The hole in the shell was sealed with transparent tape to prevent dehydration, and the eggs were incubated for another 6 days.

All manipulations with the CAM of the chicken embryo were performed in a box of abacterial air medium BAVnp-01-"Laminar-S"-1.5 (LORICA, CJSC "Laminar Systems", Russia). The experiment included eight embryos per group. On day 14, the embryos were euthanized in a gas chamber (70% CO_2, 30 minutes). The sealing tape was removed, the eggs were opened, the implantable products were excised with the surrounding areas of CAM tissue. Macroscopic assessment of CAM areas in contact with implantable products was performed using an Axio ZOOM.V16 macroscope equipped with the AxioCam MRc5 image visualization system and the Zen 2 Pro software package (Carl Zeiss Microscopy, Oberkochen, Germany). CAM tissues in contact with product samples were carefully separated and fixed in a buffered solution of 10% formalin for subsequent histological analysis.

Assessment of the condition and visualization of CAM blood vessels in dynamics 5 minutes after applying the test solutions to CAM was performed using an ARSTEK SZ0850 stereo microscope (China) and image fixation using a digital camera (38 MP Samega V6) and the S-EYE2.0 program (YOUNG WIN Technology Co., Ltd.).

All quantitative data were analyzed using univariate analysis of variance. The Biostat software package (version 4.03) was used. The differences were considered statistically significant at $p < 0.05$.

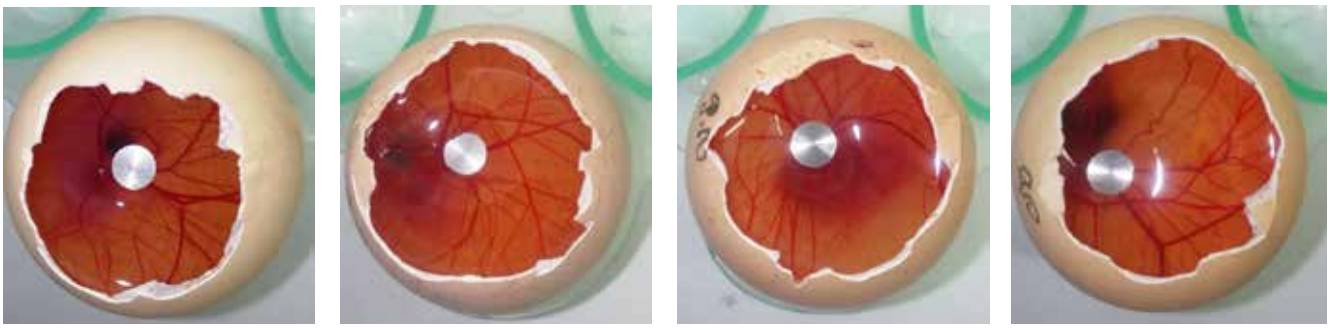
Results and discussion

The chemical composition, structure and texture of the surface of a material usually determine its main characteristics. The interaction of these properties in vivo is difficult to predict, so the final results can only be obtained empirically.

Among CAM's in vivo experiments, analysis is a fairly fast, simple, reproducible and practical method for studying the primary biocompatibility reaction of materials. The CAM system and the developing chicken embryo are recognized as a useful tool for assessing the toxic properties of engineering structures in vivo. The absence/presence of inflammatory and other reactions at the implantation site, as well as the mortality of the chicken embryo, are accepted as a method for assessing the biocompatibility of implants.

Biocompatibility is one of the most important characteristics of implantation materials. It has been scientifically confirmed that the physical and chemical properties of the surface of metal implants or their components can affect clinical safety. The structure of the material (porosity, smoothness, geometry) can affect its incorporation into surrounding tissues. This requires conducting experiments with a longer contact interval of the tested materials under in vivo conditions.

Considering the proven similarity of tissue reactions (vascular permeability, acute and chronic inflammation, granulation tissue formation and fibrosis) CAM and mammalian biocompatibility of the tested products *in vivo* was studied by implanting the products on the CAM of a chicken embryo (Figure 1).



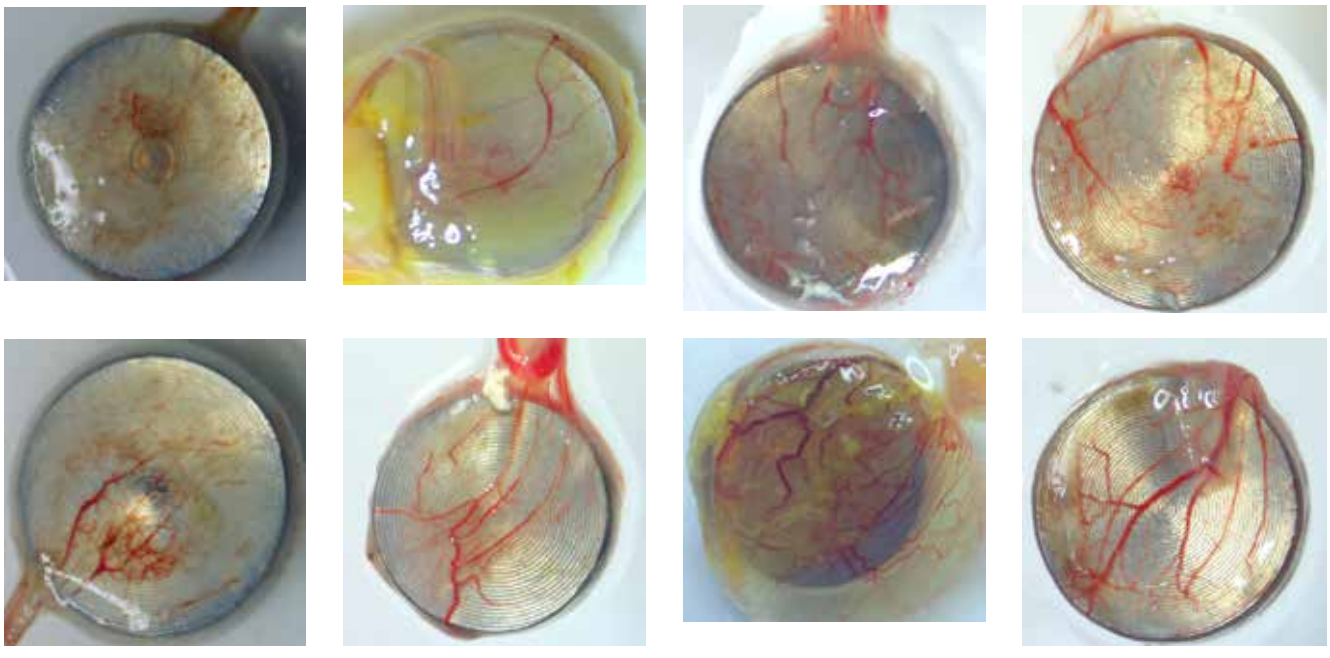
VT6 VT6+Ti VT6+TiO_2 VT6+ZrO_2

Fig. 1. Implantation of test products on the CAM of a chicken embryo on the 8th day of incubation

As in experiment of other researchers [4], because of their weight, the products placed on the CAM gradually dropped within an hour after implantation. Flooding of the implants was accompanied by their complete confinement in the CAM tissue. As a result, all the surfaces of the implanted product were in contact with the vascular network of the CAM (Figure 2).

Fig. 2. Immersion of the implanted product in CAM tissues

Macroscopic assessment of CAM tissues in contact with samples of metal products was performed after excision on the 14th day of incubation. Images of implanted articles and adjacent CAM sites for macroscopic assessment of the vasoproliferative response were made for each sample (Figure 3).



VT6 VT6+Ti VT6+TiO_2 VT6+ZrO_2

Fig. 3. Appearance of metal structures extracted from CAM 6 days after implantation

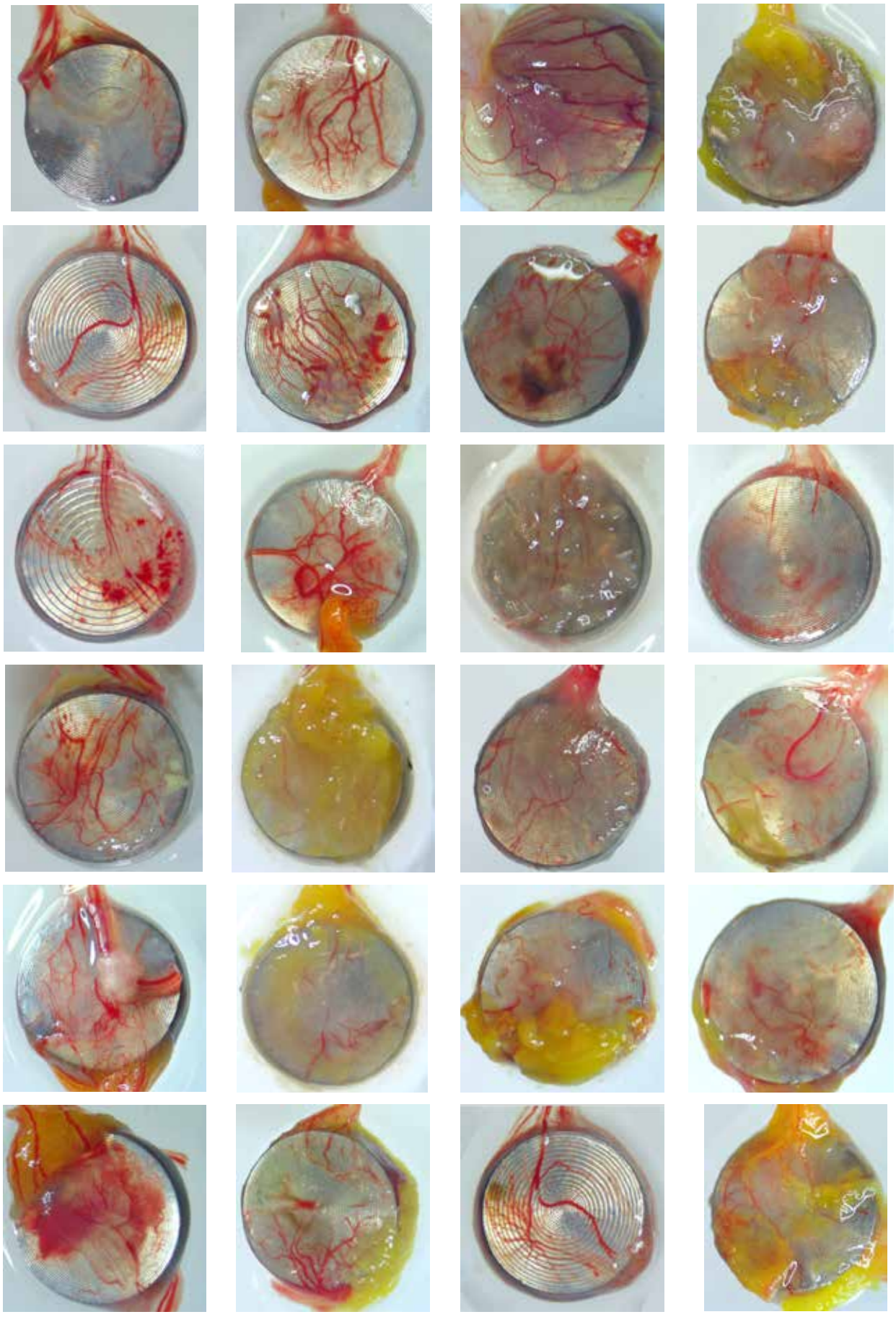


Fig. 3 (cont.). Appearance of metal structures extracted from CAM 6 days after implantation

Toxic substances can cause pronounced morphological and vascular changes in the CAM. Implantation of a material with toxic properties can be accompanied by coagulation, hemorrhage, discoloration of the contacting CAM tissues, the appearance of ghost vessels, and embryo mortality. Implantation of VT6, VT6+Ti, VT6+TiO_2, VT6+ZrO_2 samples on CAM did not critically affect the survival of embryos up to 14 days of development. In these groups and in the control group, the percentage of embryo mortality did not exceed 15%, which is not out of the reference range for the conditions of conducting such experiments and, presumably, is associated with manipulations with the incubation egg, rather than with the toxicity of implanted materials.

Macroscopic visualization of the extracted implants clearly shows vascularization and proliferation of contacting tissues around the products, which confirms their biocompatibility under CAM conditions. It was visually noted that the samples VT6+TiO_2, VT6+ZrO_2 were characterized by the highest rate of capsule formation from CAM tissues around the implanted products VT6+TiO_2, VT6+ZrO_2.

According to the presence of signs of vascular lysis, which is one of the signs of a toxic reaction, the implant samples were distributed in the order of its decrease as follows:

1. VT6;
2. VT6 + ZrO_2;
3. VT6 + Ti = VT6 + TiO_2.

Signs of CAM hemorrhage were also recorded for all product groups. To reduce the appearance of signs of hemorrhage, the samples were arranged as follows:

1. VT6;
2. VT6 + Ti = VT6 + ZrO_2;
3. VT6 + TiO_2.

It should be borne in mind that registered hemorrhages of CAM in contact with samples can be regarded not so much as a consequence of the toxic effect of the products, but rather as a result of mechanical injury and stretching of the CAM vessels. This fact is described in some works [9] and logically confirmed by the recorded hemorrhages in the control group (Figure 4).

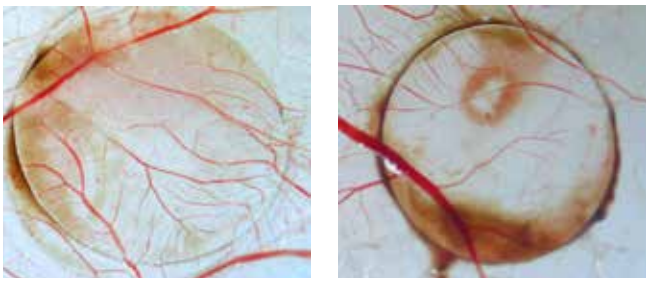


Fig. 4. Appearance of CAM and silicate glass samples (control) implanted on CAM after treatment on the 14th day of incubation

Conclusion

Summarizing the results of the evaluation of biocompatibility of coatings based on titanium, zirconium and their alloys deposited on implants using vacuum-arc sputtering with plasma assistance, we can conclude the following.

A series of experiments conducted to assess the biocompatibility of the tested products under the conditions of the CAM model of a chicken embryo confirmed the adequacy of its application. The size and weight of the studied samples were accompanied by subsidence deep into the CAM and their complete confinement in the tissue. As a result, all the surfaces of the implanted product were in contact with the vascular network of the CAM, which ensured the same conditions and the validity of conducting a comparative analysis of the tested samples. Mechanical action during implantation of the studied products on the surface of CAM did not affect the viability of chicken embryos up to 14 days of embryogenesis. Observations made at this stage of the study using specific in vivo techniques showed that the studied samples of products were compatible with the biological environment of CAM and did not show pronounced irritating, angiotoxic properties.

However, it should be borne in mind that this study has some limitations. The model of a developing chicken embryo and the CAM system may not always fully reflect the picture of the real clinical situation and act primarily as a preliminary screening test. The CAM model is mainly used for short-term studies due to the relatively short incubation period. In addition, substances introduced into the air chamber of the incubation egg may not correspond to the amount absorbed by the embryo, as they can spread to other egg structures. Therefore, to study the long-term effect and interaction, in some cases, it is obvious that it is advisable to expand the range of studies of the tested materials in mammalian models.

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DIASTOLIC DYSFUNCTION OF THE LEFT VENTRICLE IN HIV–INFECTED PATIENTS, CLINICAL AND PROGNOSTIC RELATIONSHIPS

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SUMMARY

Diastolic dysfunction in HIV-infected patients is a common problem, the pathway of which is based on chronic low-intensity inflammation, and whose consequences are associated with progression of chronic heart failure (CHF) and death. The aim of the study was to evaluate clinical, echocardiographic and laboratory data of patients with diastolic left ventricular myocardial dysfunction infected with HIV and to present new prognostic relationships. Within the framework of a one-stage, screening, clinical study in the conditions of a multidisciplinary clinic, 240 patients with HIV infection were examined, and 136 of them showed signs of diastolic dysfunction. The development of diastolic dysfunction in HIV-infected patients is a factor provoking the development and progression of CVD, ventricular rhythm disturbances, ischemic heart disease, and anemia. Diastolic dysfunction in HIV-infected patients increases the risks of death within 2 years by 1.46 times. Increase of NT-proBNP concentration in plasma of HIV-infected patients ≥ 185.7 pg/mL is associated with the development of diastolic dysfunction in them.

KEYWORDS: *HIV infection, diastolic dysfunction, chronic heart failure.*

CONFLICT OF INTEREST. The authors declare no conflict of interest.

ДИАСТОЛИЧЕСКАЯ ДИСФУНКЦИЯ ЛЕВОГО ЖЕЛУДОЧКА У ВИЧ–ИНФИЦИРОВАННЫХ ПАЦИЕНТОВ, КЛИНИЧЕСКИЕ И ПРОГНОСТИЧЕСКИЕ ВЗАИМОСВЯЗИ

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РЕЗЮМЕ

Диастолическая дисфункция у ВИЧ-инфицированных пациентов является распространенной проблемой, в основе которой лежит хроническое воспаление низкой интенсивности и последствия которого связаны с прогрессированием хронической сердечной недостаточности (ХСН) и смертью. Целью исследования была оценка клинических, эхокардиографических и лабораторных данных пациентов с диастолической дисфункцией миокарда левого желудочка, инфицированных ВИЧ, и представление новых прогностических зависимостей. В рамках одноэтапного, скринингового, клинического исследования в условиях многопрофильной клиники было обследовано 240 пациентов с ВИЧ-инфекцией, и у 136 из них были выявлены признаки диастолической дисфункции. Развитие диастолической дисфункции у ВИЧ-инфицированных пациентов является фактором, провоцирующим развитие и прогрессирование сердечно-сосудистых заболеваний, желудочковых нарушений ритма, ишемической болезни сердца и анемии. Диастолическая дисфункция у ВИЧ-инфицированных пациентов увеличивает риск смерти в течение 2 лет в 1,46 раза. Повышение концентрации NT-proBNP в плазме крови ВИЧ-инфицированных пациентов ≥ 185,7 пг/мл связано с развитием у них диастолической дисфункции.

КЛЮЧЕВЫЕ СЛОВА: ВИЧ-инфекция, диастолическая дисфункция, хроническая сердечная недостаточность.

КОНФЛИКТ ИНТЕРЕСОВ. *Авторы заявляют об отсутствии конфликта интересов.*

Introduction

The prevalence of diastolic dysfunction in HIV-infected patients is of concern, because there is a clear association between the development of diastolic dysfunction, chronic heart failure (CHF) and mortality, and the age of patients with first diagnosed diastolic dysfunction is getting younger [1]. The leading role in the pathogenesis of diastolic dysfunction in HIV infection belongs to chronic low-intensity inflammation against the background of constant immune activation [2, 3, 4]. Inflammatory markers remain elevated despite viral load suppression, and the progression of diastolic dysfunction is accompanied by myocardial and arterial stiffness in HIV-infected patients [5], with myocardial inflammation and diffuse myocardial fibrosis clearly identified on cardiac MRI [6, 7]. The aim of the study was to evaluate clinical, echocardiographic and laboratory data of patients with diastolic left ventricular myocardial dysfunction infected with HIV and to present new prognostic relationships.

Materials and methods

In the conditions of a multidisciplinary city hospital, 240 HIV-infected patients with different therapeutic pathology after compensation of the disease that led to hospitalization were examined during four years; signs of diastolic dysfunction were detected in 136 of them. The study is single-stage, clinical, screening and complies with GCP and Declaration of Helsinki criteria. Inclusion criteria were the presence of HIV infection confirmed by immunoblot, signed voluntary consent to participate in the study. Exclusion criteria were patient refusal to participate in the study, oncopathology, and deviant behavior, acute decompensation of CHF or acute heart failure. The author personally performed echocardiography in each patient according to the methodology prescribed in the guidelines for quantitative assessment of the structure and function of heart chambers recommended by the American Echocardiographic Society and the European Echocardiographic Association. All patients were examined physically to detect symptoms and signs of CHF, the severity of detected CHF was assessed using the kinic state assessment scale modified by V.Y. Mareev and the six-minute walk test.

Diastolic dysfunction was determined in accordance with the recommendations for visualization of left ventricular diastolic function on echocardiography proposed by the American Society of Echocardiography and the European Association of Cardiovascular Imaging in 2016 [8], and Tei index was determined by pulsed-wave Doppler peaks. In addition to traditional clinical analyses, the patients underwent: determination of brain natriuretic propeptide (NT-proBNP) concentration in blood plasma by Vector Best reagent sets (Russia), serum levels of transferrin, ferritin, serum iron by RANDOX reagent sets (Great Britain), lipocaine-2 (NGAL) by reagent sets of Sanlong Biotech Co. Ltd (China), C-reactive protein (CRP) by Vector Best reagent kits (Russia). Verification of alcohol dependence was performed by questioning patients with AUDIT questionnaire with ≥ 20 points.

Statistical processing was performed in SPSS 26 and Statistika 13.0 programs. After determining the normality of the distribution of signs according to Kolmogorov – Smirnov and Shapiro – Wilk, signs with normal distribution were prescribed in the form of arithmetic mean and standard deviation (M±SD), signs with irregular distribution – in the form of median, first and third quartiles (Me [LQ; UQ]). Categorical traits were prescribed as absolute value and frequency of occurrence in percentage (n (%)). A statistical significance level of $p<0.050$ was recognized as critical. Mann – Whitney, Kraskell – Wallis, Student's t-criterion, quadratic conjugation tables, odds ratio and risk ratio were used in pairwise comparison of traits.

Results of the study

Table 1 presents the main data characterizing the clinical course of diastolic dysfunction in patients with HIV infection.

Table 1

The main indicators characterizing the clinical features of the course of diastolic dysfunction in HIV-infected people

Sign	Diastolic dysfunction present, n=136	Diastolic dysfunction not determined, n=104	p
Male gender, n (%)	78 (57)	67 (64)	0,267
Age, years	38,00 [34,00; 42,00]	36,00 [32,00; 40,00]	0,114
TSW, m	400 [300; 450]	450 [400; 500]	0,004*
SACC, points	5,0 [4,0; 8,0]	2,5 [1,0; 5,0]	<0,001*
Smoking, n (%)	94 (69)	66 (63)	0,357
Probable alcohol dependence, n (%)	83 (61)	42 (40)	0,001*
Drug usage, n (%)	109 (80)	73 (70)	0,074
IHD, n (%)	31 (23)	7 (7)	<0,001*
History of myocardial infarction, n (%)	4 (3)	0 (0)	0,077
Diabetes mellitus, n (%)	7 (5)	6 (6)	0,832
Atrial fibrillation, n (%)	5 (4)	0 (0)	0,048*
VA, n (%)	50 (37)	14 (13)	<0,001*
Stroke in anamnesis, n (%)	3 (2)	2 (2)	0,879
CABG, PCI in anamnesis, n (%)	1 (0,6)	0 (0)	0,380
Chronic virus hepatitis C, n (%)	97 (71)	69 (66)	0,408
Ascites, n (%)	30 (22)	12 (11)	0,033*
Liver cirrhosis, n(%)	30 (22)	12 (11)	0,033*
Hydropericardium, n(%)	10 (7,35)	4 (4)	0,250
Hydrothorax, n (%)	23 (17)	13 (12)	0,342
ART, n (%)	25 (18)	13 (12)	0,216
BMI, kg/m^2	20,0 [17,7; 21,9]	20,2 [18,4; 22,0]	0,409
Low body weight, n (%)	26 (19)	18 (17)	0,839
Valve defects, n (%)	36 (26)	18 (17)	0,092
Esophageal candidiasis, n (%)	12 (9)	5 (5)	0,229
Unsuppressed viral load	130 (95,59)	6 (5,77)	<0,001
Death within 2 years	22 (16,17)	6 (5,77)	0,012*

Abbreviations: * – differences in indicators are statistically significant (p <0.05); TSW – six-minute walk test; SACC – scale for assessing the clinical condition of patients with CHF, modified by V.Yu. Mareev; VA – Ventricular arrhythmias; CABG – coronary artery bypass grafting; PCI – percutaneous coronary intervention; ART – antiretroviral therapy; BMI – body mass index.

According to the data obtained, against the background of the development of diastolic dysfunction, tolerance to physical activity is significantly reduced, which is expressed in a decrease in the results of the six-minute walk test (SMT). Patients with diastolic dysfunction have higher scores on the scale for assessing the clinical condition of patients with CHF as modified by V.Yu. Mareeva. In addition, patients with diastolic dysfunction were more likely to suffer from alcohol dependence. The anamnesis of cardiovascular events in patients with diastolic dysfunction is more aggravated by cases of detection of coronary heart disease (CHD), atrial fibrillation, and various specified ventricular arrhythmias. Unsuppressed viral load was more common in the group of patients with diastolic dysfunction. Liver cirrhosis and ascites were more often detected in the group of patients with diastolic dysfunction.

Table 2 presents the main indicators obtained when the author conducted an echocardiographic study of all patients with HIV infection, depending on the presence of diastolic dysfunction. The data obtained indicate significant differences between the groups in the slowdown time of early diastolic filling flow (DFF), LV isovolumic relaxation time (IVRT), and Tei index. Left ventricular hypertrophy (LVH), along with the value of left ventricular myocardial mass index (LVMMI) significantly prevailed in the group of patients with diastolic dysfunction. Left ventricular end-diastolic vo-lume (LV end-diastolic volume) and its ratio to body surface area (BSA) had higher values in the group of patients with diastolic dysfunction. Left atrial volume (LAV) and the number of patients with increased left atrium volume significantly prevailed in the group of patients with identified diastolic dysfunction. The number of patients with pulmonary arterial hypertension and the level of mean pressure in the pulmonary artery significantly prevailed in the group of patients with diastolic dysfunction. High diagnostic compliance for determining diastolic dysfunction was demonstrated by the Tei index and the ratio of the maximum velocity of early filling of the left ventricle to the early diastolic velocity of the annulus fibrosus (E/e') >14.

Table 2

Main indicators characterizing echocardiographic features of diastolic dysfunction in HIV-infected patients

Sign	Diastolic dysfunction present, n=136	Diastolic dysfunction not determined, n=104	p
LVEF, %	55,3 [48,0; 65,0]	55,5 [50,0; 63,0]	0,803
E/A LV	1,18 [0,87; 1,80]	1,3 [1,08; 1,5]	0,180
DT,ms	100,0 [64,0; 120,0]	126,0 [86,5; 181,5]	0,031*
IVRT, ms	68,0 [52,0; 100,0]	88,5 [76,0; 112,0]	<0,001*
Tei Index	0,55 [0,48; 0,70]	0,21 [0,15; 0,33]	<0,001*
LVMI, g/m^2	132,0 [103,0; 177,6]	115,9 [89,0; 131,0]	0,027*
LVH, n (%)	73 (54)	31	<0,001*
LV EDV	97,0 [79,0; 114,0]	88,0 [67,0; 110,0]	0,014*
LV ESR	40,0 [25,5; 54,0]	39,5 [22,0; 51,0]	0,285
OLP index, ml/m^2	36,5 [29,5; 54,0]	27,8 [20,7; 35,4]	0,015*
Increased OLP, n (%)	65 (48)	30 (29)	0,003*
PAH, n (%)	79 (58)	25 (24)	<0,001*
MPAP, mm Hg	29,0 [16,0; 41,3]	16,0 [12,0; 25,0]	<0,001*
EDV LV/PPT	55,83 [45,05; 70,80]	50,0 [40,49; 51,5]	0,046*
ESR LV/PPT	21,67 [16,83; 30,68]	21,3 [14,66; 27,97]	0,431
E/e'	17,3 [13,8; 19,0]	5,8 [4,46; 6,91]	<0,001*

Abbreviations: * – differences in indicators are statistically significant (p <0.05); LVEF% – left ventricular ejection fraction as a percentage; E/A - ratio of the peaks of the maximum speed of early and late filling; DT – flow deceleration time of early diastolic filling; IVRT – LV isovolumic relaxation time; DD – diastolic dysfunction; LVMI – left ventricular myocardial mass index; LVH – left ventricular hypertrophy; LV EDV – end diastolic volume of the left ventricle; LV ESV – left ventricular end-systolic volume; OLP – left atrium volume; PAH – pulmonary arterial hypertension; MPAP – mean pulmonary artery pressure; BSA – body surface area; E/e' – the ratio of the maximum speed of early filling of the left ventricle to the early diastolic speed of movement of the fibrous ring.

The data obtained indicate significant differences between the groups in the slowdown time of early diastolic filling flow (DT), LV isovolumic relaxation time (IVRT), and Tei index. Left ventricular hypertrophy (LVH), along with the value of left ventricular myocardial mass index (LVMI) significantly prevailed in the group of patients with diastolic dysfunction. Left ventricular end-diastolic volume (LV end-diastolic volume) and its ratio to body surface area (BSA) had higher values in the group of patients with diastolic dysfunction. Left atrial volume (LAV) and the number of patients with increased left atrium volume significantly prevailed in the group of patients with identified diastolic dysfunction. The number of patients with pulmonary arterial hypertension and the level of mean pressure in the pulmonary artery significantly prevailed in the group of patients with diastolic dysfunction. High diagnostic compliance for determining diastolic dysfunction was demonstrated by the Tei index and the ratio of the maximum velocity of early filling of the left ventricle to the early diastolic velocity of the annulus fibrosus (E/e') >14. Of course, the disadvantage of this study is the lack of speckle tracking options on hospital ultrasound machines, however, the use of a combination of pulse wave, color and tissue Doppler indicators allows for effective and timely identification of signs of diastolic dysfunction. There are presents the main laboratory changes in HIV-infected patients, depending on the presence of diastolic dysfunction in Table 3.

Table 3

Basic laboratory parameters characterizing the features of diastolic dysfunction in HIV-infected patients

Sign	Diastolic dysfunction present, n=136	No diastolic dysfunction, n=104	p
Serum NT-proBNP, pg/ml	581,2 [261,5; 1474,6]	83,7 [25,2; 206,7]	<0,001*
Cholesterol, mmol/l	3,8 [3,65; 4,55]	3,64 [3,45;5,0]	0,543
Transferrin, mg/dl	92,0 [50,2; 125,7]	113,0 [60,0;161,7]	0,022*
Ferritin, mcg/l	129,25 [61,0; 320,0]	141,0 [73,0; 429,8]	0,460
Serum iron, mcmol/l	2,3 [1,2; 4,7]	2,4 [1,1; 5,9]	0,588
Hemoglobin, g/l	92,0 [74,5; 113,0]	120,0 [99,0; 132,0]	<0,001*
Anemia, n (%)	110 (81)	48 (46)	<0,001*
Severe anemia, n (%)	29 (21)	6 (6)	<0,001*
Mild anemia, n (%)	45 (33)	27 (26)	0,232
Moderate anemia, n (%)	36 (26)	14 (13)	0,013*
Platelets, cells ·10^9/l	164,0 [100,0 ; 261,0]	194,0 [119,0; 269,0]	
Thrombocytopenia,n (%)	60 (44)	39 (37)	0,302
Erythrocytes, cells •10^{12}/l	3,2 [3,0; 3,6]	3,8 [3,3; 4,2]	0,019*
Leukocytes, cells •10^9/l	5,9[4,0; 9,3]	7,3 [6,1; 13,5]	0,056
Lymphocytes, %	16,0 [9,0;23,0]	25,0 [20,0; 30,0]	0,009*
Fibrinogen, g/l	4,0 [3,0; 4,5]	3,5 [3,0; 4,5]	0,361
CD4 T-lymphocytes,	200,0 [41,00; 350,00]	240,0 [76,0; 500]	0,088
Urea	5,7 [4,2; 13,6]	4,7 [3,7; 6,6]	0,011*
NGAL, pg/ml	69,6 [46,1; 267,9]	28,2 [23,0; 130,4]	0,045*
Creatinine, mcmol/l	98,0 [79,0; 148,0]	87,0 [69,0; 105,0]	0,002*
GFR, ml/min/1.73m^2	75,0 [41,0; 97,0]	89,0 [70,0; 113,0]	0,001*
CKD, n (%)	37 (27)	9 (9)	<0,001
ALT, units/l	27,0 [17,0; 60,0]	32,0 [20,5; 55,0]	0,123
AST, units/l	41 [27,0; 86,0]	51,5 [31,5; 79,0]	0,210
Glucose, mmol/l	5,1[4,4; 6,0]	5,0 [4,4; 6,0]	0,691
ESR, mm/h	41,0 [21,0;60,5]	32,0 [15,0; 44,0]	0,007*
Serum CRP, mg/l	23,50 [12,0; 84,0]	28,0 [7,0; 69,0]	0,533
Urine SRP, mg/l	0,8 [0,1; 1,0]	0,0 [0,0; 0,1]	0,027*
Sodium, mmol/l	142,0 [138,0; 144,0]	142,0 [137,0; 146,0]	0,279
Potassium, mmol/l	4,1 [3,6; 4,5]	4,1 [3,8; 4,5]	0,434
Total protein, g/l	68,0 [62,0; 74,5]	69,0 [64,00; 78,00]	0,176
Uric acid, mcmol/l	104,6 [52,8; 207,9]	138,35 [43,2; 163,5]	0,326

Abbreviations: * – differences in indicators are statistically significant (p <0.05); NT-proBNP – N-terminal brain natriuretic propeptide; LDL – low density lipoproteins; CD4 – level of CD4 T-lymphocytes; NGAL, human neutrophil gelatinase-associated lipocalin; GFR – glomerular filtration rate; CKD – chronic kidney disease; ESR – erythrocyte sedimentation rate; CRP – C-reactive protein.

An increase in the concentration of NT-proBNP in diastolic dysfunction is due to manifestations of CHF. There are significant differences between groups of patients associated with the presence of anemia and impaired renal function. Thus, the levels of transferrin and hemoglobin decrease with diastolic dysfunction, which indicates the leading role of anemia in the development of CHF in HIV-infected patients, while the number of patients with severe anemia significantly prevailed in the group with diastolic dysfunction. Glomerular filtration rate in diastolic dysfunction was lower, and serum creatinine and urea concentrations were higher in the group of patients with diastolic dysfunction. The value of human lipocalin associated with neutrophil gelatinase in the group of patients with diastolic dysfunction was almost 3 times higher than the level in patients without diastolic dysfunction. It is known that lipocaine associated with neutrophil gelatinase (lipocaine-2) is a sensitive marker of acute kidney injury and/or an early and very sensitive marker of the development of chronic kidney disease [18]. Serum C-reactive protein (CRP) did not differ significantly between groups, however, the concentration of urinary CRP was significantly higher in the group of patients with diastolic dysfunction, and in patients without diastolic dysfunction in the urine it was practically not detectable. The latter indicates the role of the inflammatory process in the kidneys in the development of diastolic dysfunction. Additionally, the role of inflammation in the formation of diastolic dysfunction is indicated by a significant increase in erythrocyte sedimentation rate. The level of lymphocytes in patients with diastolic dysfunction was significantly lower, which can be explained by the worsening of immunodeficiency in these patients. At the same time, the level of CD4 lymphocytes was reduced in both groups of patients and did not differ significantly. An analysis of the chances and risks for the development of diastolic dysfunction in patients with HIV infection was carried out. The results are presented in Table 4.

Table 4

Results of the analysis of the chances and risks of developing diastolic dysfunction

Index	p	OR and 95%CI	RR and 95%CI
Anemia	<0,001	4,76 (2,67–8,48)	2,14 (1,52–2,98)
Death within 2 years	0,014	3,14 (1,22–8,08)	1,46 (1,15–1,84)
Ventricular arrhythmias	<0,001	3,48 (1,77–6.82)	1,54 (1,26–1,89)
Cardiac ischemia	0,002	3,79 (1,59–9,02)	1,51 (1,24–1,85)
Chronic heart failure	<0,001	13,03 (6,68–25,43)	3,94 (2,47–6,25)
Low transferrin	0,001	4,36 (1,37–13,82)	2,43 (1,02–5,78)
Unsuppressed viral load	<0,001	4,58 (2,5–8,15)	2,10 (1,51–2,93)

When comparing the incidence of diastolic dysfunction depending on the presence of anemia, cytolysis, ventricular arrhythmias, CHF, low transferrin levels and death within 2 years after hospitalization in patients with HIV infection, statistically significant differences were obtained ($p<0.050$). The chances of developing diastolic dysfunction in the presence of anemia increase by 4.76 times (95% CI 2.67–8.48), in the presence of ventricular arrhythmias – by 3.48 times (95% CI 1.77–6.82), with detected ischemic heart disease – 3.79 times (95% CI 1.59–9.02), when detecting a reduced level of transferrin – 4.36 times (95% CI 1.37–13.82). The presence of CHF increases the chances of developing diastolic dysfunction by 13.03 times (95% CI 6.68–25.43). Unsuppressed viral load increases the odds of developing diastolic dysfunction by 4.58 times (95% CI 2.5–8.15). Detected diastolic dysfunction in HIV-infected people increases the chances of developing anemia by 2.14 times (95% CI 1.52–2.98), death within years – by 1.46 times (95% CI 1.15–1.84), ventricular arrhythmias by 1.54 times (95% CI 1.26–1.89), coronary heart disease – by 1.51 times (95% CI 1.24–1.85), CHF – by 3.94 times (95% CI 2.47–6.25), reduced transferrin by 2.43 times (95% CI 1.02–5.78). An inverse relationship was revealed between the development of diastolic dysfunction and taking angiotensin receptor antagonists, so the chances of developing diastolic dysfunction are reduced by 3.45 times when taking sartans (OR = 0.29, 95% CI 0.11–0.75).

Figure 1 shows an ROC curve describing the prognosis of the development of diastolic dysfunction in patients with HIV infection depending on the level of NT-proBNP in the blood plasma. The area under the ROC curve corresponding to the relationship between the prognosis of diastolic dysfunction depending on the level of NT-proBNP in the blood plasma was 0.860±0.024 with a 95% CI of 0.813–0.907. The resulting model turned out to be statistically significant ($p<0.001$). The threshold value of NT-proBNP at the cut-off point was 185.7 pg/ml. If the plasma NT-proBP value is ≥ 185.7 pg/ml, a high risk of developing diastolic dysfunction is predicted. The sensitivity of the method was 80.1%, specificity – 72.5%.

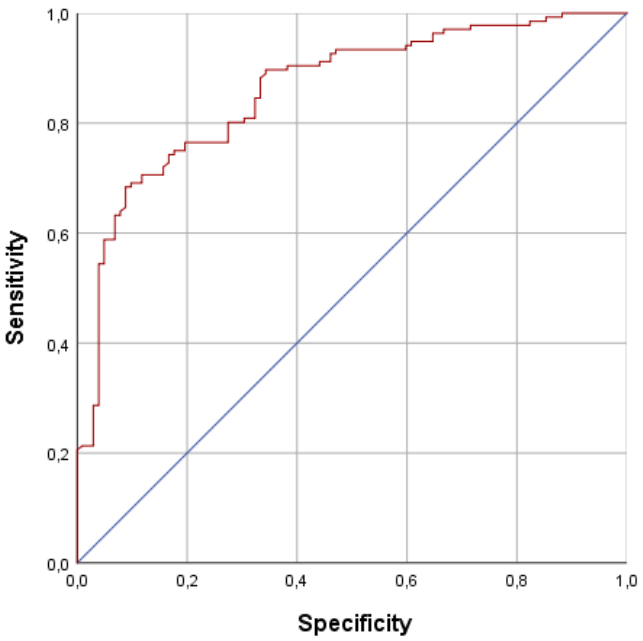

Fig. 1. ROC curve of the relationship between the prognosis of diastolic dysfunction and the value of plasma NT-proBNP in HIV-infected patients

Discussion

Diastolic dysfunction in HIV infection must be diagnosed promptly in order to prevent further worsening of the development of CHF and target organ damage. Against the background of the development of diastolic dysfunction in HIV-infected patients, in our study, tolerance to physical activity significantly decreased, which was evident in a decrease in the results of the six-minute walk test (SWT), symptoms and signs of CHF, noted in the scale for assessing the clinical condition of patients with CHF in modification B, appeared more often .YU. Mareev, which is natural for the development of CHF with preserved EF [1]. Possible alcohol dependence was more often diagnosed in people with diastolic dysfunction, which causes even more intense immunodeficiency in HIV-infected people, aggravates the chronic inflammatory process and oxidative stress; against this background, patients more often refuse antiretroviral therapy and more often suffer from comorbid diseases [9].

Diastolic dysfunction in HIV-infected patients is often asymptomatic, and clinical signs of CHF begin to appear already in the case of the formation of HIV-associated cardiomyopathy with dilatation of the heart cavities, diffuse inflammatory process in the myocardium and diffuse myocardial fibrosis, therefore, in our study, the history of cardiovascular events of patients with diastolic dysfunction is burdened by more frequent cases of detection of chronic coronary heart disease (CHD), atrial fibrillation, and various specified ventricular arrhythmias [1, 10, 11].The inflammatory model of diastolic dysfunction occupies one of the leading places in the pathogenesis of this clinical condition in HIV-infected patients and is based on the fact that many chronic diseases, such as anemia, COPD, chronic kidney disease, diabetes mellitus and others are accompanied by microvascular low-intensity inflammation, which leads to the formation of free radicals and reduces the bioavailability of nitric oxide [15]. Left ventricular hypertrophy (LVH) is a common component of diastolic dysfunction and CHF in HIV-infected patients, as in the work of Okeke NL et al. [11] indicated that LVH is more pronounced in individuals with suppressed immunity and unsuppressed viral load. The risk of developing CHF with preserved ejection fraction is especially high

in HIV-infected people with a viral load of 2,100,000 copies/ml and a CD4 T-lymphocyte level of 200 cells/μl or less, which raises the understanding that immune processes significantly model the risks of developing CHF in HIV-infected people [1]. Our work also revealed the dependence of the development of diastolic dysfunction on the unsuppressed viral load, and also in the group of patients with diastolic dysfunction there were higher values of the left ventricular myocardial mass index and a larger number of patients with its hypertrophy, and the unsuppressed viral load increased the chances of developing diastolic dysfunction by 4.58 times (95% CI 2.5–8.15).Despite the fact that the traditional factors for the development of LVH and increased LVMI, respectively, are male gender, older age and arterial hypertension, HIV infection is the same factor for increased LVMI and the development of LVH [11, 12]. The chances of developing diastolic dysfunction in patients with HIV infection in our study in the presence of ventricular arrhythmias increased by 3.48 times (95% CI 1.77–6.82), with a history of coronary artery disease – by 3.79 times (95% CI 1.59–9.02).

Volume parameters of the left ventricle and left atrium on ultrasound examination had higher values in the group of patients with diastolic dysfunction, which is explained by the development of HIV-associated cardiomyopathy [13].

The number of patients with pulmonary arterial hypertension and the level of mean pressure in the pulmonary artery significantly prevailed in the group of patients with diastolic dysfunction. The literature describes the predominance of pulmonary arterial hypertension in HIV-infected patients in comparison with patients without HIV, associated with the development of CHF [14]. The transformation of diastolic dysfunction into the clinical picture of CHF with the development of shortness of breath, weakness, and fatigue occurs through a weakening of the outflow of blood from the pulmonary veins into the overfilled left atrium with the development of first venous and then mixed pulmonary hypertension [15].

The history of gastrointestinal diseases with diastolic dysfunction is more aggravated by the development of liver cirrhosis and ascites. It is known that fatty liver disease, even in patients without obesity, is accompanied by the development of diastolic dysfunction due to a low-intensity chronic inflammatory process [16]. The prevalence of left ventricular diastolic dysfunction in patients with liver cirrhosis ranges from 25.7% to 81.4% according to various studies and often correlates with the severity of liver failure [17]. Cirrhotic cardiomyopathy, as a complication of liver cirrhosis of any etiology, is often manifested by the development of diastolic dysfunction of the left ventricle with the development of myocardial fibrosis, hypertrophy and subendothelial edema, often accompanied by ascites, and subsequently progresses to systolic dysfunction [18].

In our study, against the background of diastolic dysfunction, the concentration of NT-proBNP in blood plasma increases significantly. The literature describes a close relationship between the concentration of plasma brain natriuretic peptide in HIV-infected patients and the mass of the left ventricular myocardium [12]. Our study revealed a threshold value of NT-proBNP at the cut-off point equal to 185.7 pg/ml; accordingly, with a plasma NT-proBP value ≥185.7 pg/ml, a high risk of developing diastolic dysfunction is predicted. The sensitivity of the method was 80.1%, specificity – 72.5%.

Serum transferrin concentrations and peripheral blood hemoglobin levels were lower in our patients with diastolic dysfunction. There were more patients with anemia, and especially severe anemia with a hemoglobin level ≤70 g/l, in the group with diastolic dysfunction. There is literature data on the secondary development of diastolic dysfunction and its aggravation in individuals with iron deficiency and iron deficiency anemia, and a decrease in the concentration of transferrin, in addition to the formation of iron deficiency, may be due to the intensification of free radical oxidation [17]. The chances of developing diastolic dysfunction in patients with HIV infection in our study in the presence of anemia increased by 4.76 times (95% CI 2.67–8.48), and when a decreased level of transferrin was detected – by 4.36 times (95% CI 1.37–13.82).

Serum creatinine, urea and lipocaine-2 levels in patients with diastolic dysfunction in our study increased significantly, and glomerular filtration rate decreased. The presence of HIV infection in itself is already a risk factor for the development of chronic kidney disease (CKD), occurring against the background of HIV-associated nephropathy, membranous nephropathy against the background of co-infection with hepatitis B and C, membranoproliferative glomerulonephritis, more often associated with contagion with hepatitis C, mixed cryoglobulinemia – all of these diseases, as well as diastolic dysfunction in HIV, are associated with a chronic inflammatory process [19]. Therefore, the erythrocyte sedimentation rate was significantly higher in patients with diastolic dysfunction, and the concentration of C-reactive protein in the urine was also significantly higher.

Patients with diastolic dysfunction were more likely to take angiotensin receptor antagonists (ARA) and proton pump inhibitors. Patients with diastolic dysfunction took significantly more antiretroviral therapy drugs, namely nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors. Effective combination antiretroviral therapy is associated with changes in the nature of CHF in HIV from a phenotype with predominantly systolic dysfunction of the left ventricle to diastolic dysfunction [1]. The role of antiretroviral therapy drugs in the development and aggravation of diastolic dysfunction is also described in the literature, especially for the group of protease inhibitors [20].

The formation of diastolic dysfunction in HIV-infected patients is associated with the development of target organ damage that occurs with CHF, as well as other multiple organ pathologies. The results of our study prove that diastolic dysfunction in HIV-infected people increases the risk of developing anemia by 2.14 times (95% CI 1.52–2.98), death within two years by 1.46 times (95% CI 1 .15–1.84), ventricular arrhythmias – 1.54 times (95% CI 1.26–1.89), coronary heart disease – 1.51 times (95% CI 1.24–1.85), CHF – 3.94 times (95% CI 2.47–6.25), reduction in transferrin level – 2.43 times (95%CI 1.02–5.78). An inverse relationship was revealed between the development of diastolic dysfunction and taking sartans, so the chances of developing diastolic dysfunction are reduced by 3.45 times when taking angiotensin receptor antagonists (OR = 0.29, 95% CI 0.11-0.75).

Conclusion

The development of diastolic dysfunction in HIV-infected patients is a factor that provokes the development and progression of CHF, ventricular arrhythmias, coronary heart disease, and anemia. Diastolic dysfunction in HIV-infected people increases the risk of death by 1.46 times within 2 years. An increase in the concentration of NT-proBNP in the blood plasma of patients with HIV infection ≥ 185.7 pg/ml is associated with the development of diastolic dysfunction in them.

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EXPLORING THE IMPACT OF NANOMEMBRANE–BASED LOW VOLUME PLASMA EXCHANGE ON GUT BARRIER INTEGRITY IN METABOLIC SYNDROME: A PROSPECTIVE STUDY

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SUMMARY

A comprehensive understanding of the human intestine and its structural-functional unit, the "gut barrier," implies an intricate cross-talk between epithelial cells and the underlying immune system to coordinate the surveillance of intestinal luminal contents. Disruption of this barrier leads to an increased passage of antigens and macromolecules from the external environment into the host, triggering local or systemic inflammation and immune activation, commonly referred to as "leaky gut." In recent times, increased intestinal permeability has been recognized as a key factor or pivotal pathogenic component in chronic inflammatory diseases, including metabolic disorders. Metabolic syndrome (MetSy) encompasses a cluster of metabolic disorders associated with an elevated risk of cardiovascular diseases, despite lifestyle modifications and medications. Zonulin, among the non-invasive markers of intestinal permeability, stands out due to its sensitivity. Nanomembrane-based low-volume plasma exchange (LVPE) is an innovative approach to blood purification designed to remove toxic and inflammatory blood components. This safe and minimally invasive procedure involves a device that pumps and filters the patient's blood through nanopores in a multi-membrane layout. ***Objective.*** *This study aims to investigate the impact of nanomembrane-based LVPE on the intestinal barrier in individuals with MetSy, elucidating its potential therapeutic role in chronic inflammatory diseases.* ***Materials and methods.*** *In this prospective study, 48 outpatient participants (31.3% female, 68.7% male) with an average age of 50 years underwent four cycles of nanomembrane-based LVPE, conducted every other day. Each cycle involved the removal of 30% of circulating plasma, replaced with a saline solution. Serum samples were collected before the first and after the fourth LVPE cycle, measuring markers including Zonulin, C-reactive protein (CRP), high-sensitive CRP, Interleukin-6 (IL6), vitamin D3, and cardiometabolic parameters. Additionally, these markers were measured in plasma samples obtained after each LVPE cycle.* ***Results.*** *After four cycles of LVPE, there was a significant decrease in the concentrations of vitamin D3 ($p<0.001$), CRP ($p<0.02$), glucose ($p<0.0001$), total cholesterol ($p<0.0001$), triglycerides ($p<0.011$), and HDL-C ($p<0.006$). Before the first cycle, Zonulin was significantly associated with HDL-C ($\beta=1.406$; $p=0.002$), LDL-C ($\beta=-1.263$; $p=0.012$), and hsCRP ($\beta=0.302$; $p=0.046$). After the fourth cycle, significant associations were obtained for HbA1c ($\beta=0.342$; $p=0.025$) and total cholesterol ($\beta=0.570$; $p=0.001$).* ***Conclusion.*** *Our study advocates for the use of nanomembrane-based LVPE as a targeted method to enhance gut barrier permeability in individuals with MetSy. Through four LVPE cycles, our research validates the efficacy of this approach in correcting carbohydrate and lipid metabolism. Notably, our investigation reveals LVPE's potential immunomodulatory effect on inflammatory pathways.*

KEYWORDS: *gut barrier, metabolic syndrome, Zonulin, low-volume plasma exchange.*

CONFLICT OF INTEREST. The authors declare no conflict of interest.

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ИЗУЧЕНИЕ ВЛИЯНИЯ НИЗКООБЪЕМНОГО ПЛАЗМООБМЕНА НА ОСНОВЕ НАНОМЕМБРАН НА ЦЕЛОСТНОСТЬ КИШЕЧНОГО БАРЬЕРА ПРИ МЕТАБОЛИЧЕСКОМ СИНДРОМЕ: ПРОСПЕКТИВНОЕ ИССЛЕДОВАНИЕ

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РЕЗЮМЕ

Всестороннее понимание работы кишечника человека и его структурно-функциональной единицы, «кишечного барьера», подразумевает сложную взаимосвязь между эпителиальными клетками и лежащей в их основе иммунной системой для координации контроля содержимого просвета кишечника. Нарушение этого барьера приводит к усиленному проникновению антигенов и макромолекул из внешней среды в организм хозяина, вызывая местное или системное воспаление и активацию иммунитета, обычно назы-

ваемое «дырявым кишечником». В последнее время повышенная проницаемость кишечника была признана ключевым фактором или основным патогенетическим компонентом хронических воспалительных заболеваний, включая нарушения обмена веществ. Метаболический синдром (MetSy) включает в себя группу метаболических нарушений, связанных с повышенным риском сердечно-сосудистых заболеваний, несмотря на изменение образа жизни и медикаментозное лечение. Зонулин, один из неинвазивных маркеров проницаемости кишечника, выделяется своей чувствительностью. Малообъемный плазмообмен на основе наномембран (МОПН) – это инновационный подход к очистке крови, предназначенный для удаления токсичных и воспалительных компонентов крови. Эта безопасная и малоинвазивная процедура включает в себя устройство, которое прокачивает и фильтрует кровь пациента через нанопоры в виде мультимембраны. ***Цель.*** *Это исследование направлено на изучение влияния LVPE на основе наномембран на кишечный барьер у людей с MetSy, выяснение его потенциальной терапевтической роли при хронических воспалительных заболеваниях.* ***Материалы и методы.*** *В этом проспективном исследовании 48 амбулаторных участников (31,3% женщин, 68,7% мужчин), средний возраст которых составлял 50 лет, прошли четыре цикла МОПН на основе наномембран, которые проводились через день. Каждый цикл включал удаление 30% циркулирующей плазмы, которая заменялась физиологическим раствором. Образцы сыворотки были взяты до первого и после четвертого цикла МОПН, для определения таких маркеров, как зонулин, С-реактивный белок (СРБ), высокочувствительный СРБ, интерлейкин-6 (IL6), витамин D3 и кардиометаболические параметры. Кроме того, эти маркеры были измерены в образцах плазмы, полученных после каждого цикла МОПН.* ***Результаты.*** *После четырех циклов МОПН наблюдалось значительное снижение концентраций витамина D3 (p < 0,001), СРБ (p < 0,02), глюкозы (p < 0,0001), общего холестерина (p < 0,0001), триглицеридов (p < 0,011) и хс-ЛПВП (p<0,011).0,006). Перед первым циклом зонулин был достоверно связан с уровнем Хс-ЛПВП (β = 1,406; p=0,002), ХС-ЛПНП (β = -1,263; p=0,012) и hsCRP (β=0,302; p=0,046). После четвертого цикла были получены значимые ассоциации для уровня HbA1c (β=0,342; p=0,025) и общего холестерина (β=0,570; p=0,001).* ***Выводы.*** *В нашем исследовании мы выступаем за использование МОПН на основе наномембран в качестве целенаправленного метода повышения проницаемости кишечного барьера у людей с MetSy. Проведя четыре цикла МОПН, мы подтвердили эффективность этого подхода в коррекции углеводного и липидного обмена. Примечательно, что наше исследование выявило потенциальный иммуномодулирующий эффект МОПН на воспалительные процессы.*

КЛЮЧЕВЫЕ СЛОВА: кишечный барьер, метаболический синдром, зонулин, малообъемный плазмообмен.

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Introduction

Twenty-five hundred years ago, Hippocrates stated that "All diseases begin in the gut" [1]. Today, we recognize the human intestine as the largest and most exposed biological interface, spanning an area of 200 m², serving not only for nutrient absorption and fluid exchange but also playing a crucial role in allowing various environmental antigens from the intestinal lumen into the body [2, 3]. This structural-functional unit, known as the "Gut Barrier" (GB), encompasses the epithelial/intestinal mucosal barrier, the gut microbiota, the intestinal mucus layer, and the complex immune system associated with the gut mucosa, including the intestinal vascular/lymphatic system and the intestinal endocrine and neuroenteric system [4]. The intricate arrangement of the GB suggests an intimate cross talk between epithelial cells and the underlying immune system for coordinated surveillance of intestinal luminal contents [5]. Disruption of the GB results in increased passage of antigens and macromolecules from the external environment into the host, triggering local or systemic inflammation and immune activation, known as "leaky gut," significantly affecting tolerance and immunity [6].

The transport mechanism through the epithelial/intestinal barrier (EB) involves two pathways: the transcellular and the paracellular pathways. Roughly, 90% of antigens use the selective transcellular pathway, involving lysosomal degradation into small, non-immunogenic peptides. The remaining 10% cross the EB through the less selective paracellular pathway as intact proteins or partially digested peptides, crucial for antigenic tolerance [7, 3]. The EB comprises a single layer of specialized epithelial cells called enterocytes. These cells' junctions are regulated by adherens junctions (AJs) and tight junctions (TJs), forming a physical barrier impermeable to bacteria or other substances [8]. TJs, the main apical junctional multiprotein complex, consist of over 150 proteins, including occludin, claudins, junctional adhesion molecules, and tricellulin connecting neighboring epithelial and endothelial cells [9, 10, 11, 12]. These transmembrane proteins' intracellular domains interact with cytosolic scaffold proteins like zonula occludens (ZO) proteins, anchoring them to the actin cytoskeleton [13]. The interplay between TJs and the actin cytoskeleton is fundamental in maintaining TJ structure, regulating the paracellular pathway, and maintaining barrier homeostasis, crucial for both transcellular and paracellular transport [5, 14, 15]. The discovery of Zonulin, an analog to Vibrio cholerae zonula occludens toxin, is considered the only known physiological intestinal modulator, affecting small intestinal permeability through reversible actin polymerization [16, 17]. Zon, a 47 kDa protein in the haptoglobin family, serves as a precursor of haptoglobin-2 (HP2), involved in various protective and modulatory activities [18, 19]. Recent studies propose increased intestinal permeability as a key factor in chronic inflammatory diseases (CID), including metabolic diseases [20, 15].

Impaired GB is now considered a pivotal pathogenic component in several CIDs [21, 22]. MetSy encompasses a cluster of metabolic disorders associated with an increased risk of cardiovascular diseases, despite lifestyle modifications and medications [23, 24].

Innovative methods like nanomembrane-based therapeutic plasma exchange, known as low volume plasma exchange (LVPE), offer a non-selective approach to blood purification by removing toxic and inflammatory blood components through nanopores [25, 26]. This minimally invasive procedure is utilized in treating over 75 diseases and syndromes, including MetSy [27], replacing plasma with solutions like albumin, saline, or artificial plasma [28]. Nanomembrane-based LVPE efficiently removes small molecules like cytokines and toxins while preserving essential blood components [25, 26]. Despite its promising role in CID management, its effects on GB and EB remain unexplored.

This study aims to investigate the impact of nanomembrane-based LVPE on the intestinal barrier in MetSy individuals, elucidating its potential therapeutic role in CID.

Materials and Methods

Participants:

A prospective study enrolled 48 participants who met the criteria for MetSy. Inclusion criteria required the presence of three out of the five risk factors defined by the National Cholesterol Education Programs Adult Treatment Panel III (NCEP: ATP III) [29]. Exclusion criteria included recent acute infection, injury, surgical treatment, individuals under 18 years old, and pregnant women. Informed consent was obtained from all participants in accordance with the Declaration of Helsinki. The study received approval from the Ethical Committee of the Faculty of Medicine, University of Montenegro (No. 778/3/2020).

Protocol of LVPE

The LVPE protocol consisted of four cycles of LVPE performed every other day using the Hemofenix device (Trackpore Technology Company, Russia). Approved by the American Society for Apheresis (ASFA) in 2013 [30], the minimally invasive and safe procedure employed the following specifications:

- Utilization of a one-needle procedure with small catheters in the peripheral vein in the arm.
- Application of a small volume (65–70 ml) for filling the extracorporeal contour to maintain cardiovascular system stability and circulating blood volume.
- Use of a nanotech membrane (PFM 500 filter; ZAO Plasmafilter, Russia), requiring only 15–20 ml of blood.
- Incorporation of a pump for extracorporeal circulation functioning on the systole-diastole principle.
- Infusion of sodium citrate (ACD-A, Fresenius Kabi, Germany) as an anticoagulant for the extracorporeal circulation.
- Removal of 30% of circulating plasma or 1% of body weight, replaced with a usual isotonic sodium chloride solution via constant infusion for four cycles, removing up to 1.5 times the circulating plasma volume.

Clinical Assessments

Before the initiation of the first cycle of LVPE, a comprehensive set of clinical assessments were conducted to gather baseline data on the participants.

- *Anthropometric Measurements*

Participants were instructed to wear light clothes and be barefoot during anthropometric measurements, which included assessments of body height, weight, body mass index (BMI), waist circumference (Wc), and hip circumference (Hc). The measurements were performed using the Vaga Seka SE 711 equipment from Germany, ensuring accuracy and standardization.

- *Medical Examination*

A qualified Endocrinologist conducted a thorough medical examination of each participant. This examination aimed to assess overall health, identify any pre-existing conditions, and ensure participants were fit for the LVPE procedure. Before each cycle of LVPE, blood pressure (BP) and heart rate (HR) were measured to monitor cardiovascular parameters. An automatic digital blood pressure monitor (M6 Comfort, Omron Healthcare Co, Japan) was used for accurate and efficient readings. This allowed for the continuous evaluation of cardiovascular stability throughout the LVPE cycles.

Hematological and Biochemical Measurements

Hematological parameters were evaluated with a complete blood count (CBC) analyzer (Celltak α, Nihon-Kohden, Japan). Sedimentation rate (SE) was measured both before the first cycle and after the fourth cycle.

Serum concentrations of various biomarkers were determined before the first cycle and after the fourth cycle using an automatic biochemistry analyzer (A15, Biosystems, Spain) for glucose, triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), C-reactive protein (CRP), high-sensitive CRP (hsCRP), glycosylated hemoglobin (HbA1c), Interleukin-6 (IL-6) (Cobas e 801, Switzerland), and vitamin D3 (Vit D3) (Alinity, Abbott, USA). Plasma samples, totaling four (one after each cycle of LVPE), were analyzed for the same set of biochemical parameters.

Biomarker of Intestinal Permeability

Zonulin concentrations were assessed using the Human Zonulin ELISA kit (Immunodiagnostik AG, Germany) and enzyme-linked immunosorbent assay techniques (Rayto 2100-C, ELISA reader, China). The kit has a sensitivity limit of 34 ng/ml and a detection range of 3.03–40.25 ng/ml. Measurements were conducted in serum samples obtained immediately before the first cycle and after the fourth cycle. Additionally, Zonulin concentrations were measured in plasma samples collected after each LVPE cycle, totaling four plasma samples.

Statistical analyses were conducted using IBM SPSS Statistics, version 26. Descriptive statistics were employed for quantitative variables with a normal distribution, reporting mean values and standard deviations. Frequencies were calculated for qualitative variables. Student's t-tests were utilized to compare paired samples of quantitative variables. One-way ANOVA was employed to compare means across one or more variables based on repeated observations. Mul-

tiple linear regression models were used to assess the interaction between applied LVPE and analyzed biomarkers. Interactional models were applied to evaluate the relationship between Zonulin concentration and various parameters. The statistical significance threshold was set at $p < 0.05$.

Results

Participants and Anthropometric Characteristics

The study involved 48 participants diagnosed with MetSy, comprising 68.7% men and 31.3% women, with an average age of 50 years. The research included the calculation of blood and plasma volumes (BV; PV) for the subjects, considering that 7% of body mass constitutes blood volume (Nadler 1962). Anthropometric characteristics were analyzed to compare physical attributes and blood volumes between male and female participants (Table 1).

Table 1
Anthropometric Characteristics of Participants with MetSy by sex (mean±SD)

Variables	Total (n=48)	Men (n=33)	Women (n=15)	p Value
Age (years)	50.38±9.41	51.27±9.87	48.40±8.27	0.332
Height (cm)	91.55±16.82	98.85±12.31	75.48±14.16	<0.001
Weight (kg)	182.38±8.96	186.55±5.96	173.20±7.57	<0.001
BMI (kg/m^2)	27.44±4.04	28.43±3.30	25.26±4.74	<0.010
Wc (cm)	99.13±13.28	104.39±10.86	87.53±10.62	<0.001
Hc (cm)	105.42±10.09	106.30±10.19	103.47±9.94	0.373
BV (ml)	6409.17±1177.30	6920.79±861.44	5283.60±991.22	<0.001
PV (ml)	2884.44±528.15	3113.64±387.88	2380.20±443.08	<0.001

BMI – body mass index, Wc – waist circuference, Hc – hip circuference, BV – blood volume, PV – plasma volume.

Men demonstrated significant differences in physical attributes compared to women, indicating distinctive physical disparities between genders in the MetSy group.

LVPE Cycle Parameters

The LVPE cycle protocol assessed its impact on cardiovascular and circulatory measures, monitoring various parameters (Table 2).

Table 2
Protocol Parameters and Hemodynamic Measures During LVPE Cycles (mean±SD)

Variables	I cycle	II cycle	III cycle	IV cycle	p Values
SBP (mmHg)	131.60±19.60	126.90±16.94	125.52±15.53	122.69±15.65	<0.0001
DBP (mmHg)	86.65±10.34	82.19±9.96	81.08±10.10	80.81±10.75	<0.0001
HR (/min)	79.04±12.07	77.65±11.96	77.52±11.43	78.15±12.32	0.816
CL (min)	76.23±27.90	70.38±24.14	76.48±25.04	75.23±31.97	0.179
BV (ml)	3724.17±1216.56	3873.13±1282.59	3716.46±1056.12	3800.83±1174.50	0.673
PV (ml)	897.71±166.26	932.29±174.43	916.46±169.02	919.79±179.53	0.246
ACD-A	228.33±86.23	306.46±100.35	251.25±73.62	263.54±91.89	<0.0001
0.9%NaCl (ml)	903.13±168.51	912.92±184.53	902.71±183.21	869.38±199.93	0.341

SBP – systolic blood pressure, DBP – diastolic blood pressure, CL – cycle lenght, BV – blood volume, PV – plasma volume, ACD – Anticoagulant Citrate Dextrose Solution A, 0.9%NaCl – saline solution.

The LVPE cycles resulted in a significant reduction in both SBP ($F = 6.648$; $p < 0.0001$) and DBP ($F = 8.599$; $p < 0.0001$), indicating effective blood pressure regulation. However, HR, processed BV, and removed PV did not show significant changes. The consumption of ACD-A increased significantly across cycles ($F = 8.376$; $p < 0.0001$), with no significant change in the consumption of the saline solution.

Hematological and Biochemical Measurements

Hematological Measurements

The study assessed the impact of four LVPE cycles on hematological parameters, revealing significant changes in specific measurements (Table 3).

Table 3
Hematological Parameters: CBC and SE before I and after IV LVPE cycle (mean±SD)

Variables	Before I cycle	After IV cycle	p Values
SE	7.81±5.87	4.69±3.28	<0.0001
Leucocytes	7.23±1.64	7.45±1.89	0.256
Erythrocytes	4.75±0.44	4.76±0.51	0.863
Hemoglobin	142.77±16.29	142.75±17.52	0.985
Hematocrit	42.56±4.56	42.57±5.12	0.326
MCV	89.52±4.52	89.48±4.64	0.622
MCH	30.02±1.79	30.01±1.83	0.877
MCHC	335.19±6.29	334.52±6.90	0.501
Platelates	232.02±53.08	217.92±53.50	<0.002
Lymphocytes	36.47±8.77	38.87±9.45	0.077
Monocytes	3.59±1.16	3.29±1.52	0.223
Granulocytes	59.90±9.29	57.83±10.30	0.145
RDW	14.66±0.81	14.55±0.87	0.215
PCT	0.17±0.04	0.17±0.04	0.375
MPV	7.55±0.70	7.80±0.75	<0.001
PDW	17.11±0.71	17.02±0.84	0.498

SE – sedimentation rate, MCV – Mean corpuscular volume, MCH – Mean corpuscular hemoglobin, MCHC – Mean corpuscular hemoglobin concentration, RDW – Red cell distribution width, PCT – plateletcrit, MPV – Mean platelate volume, PDW – Platelate cell distribution width

Following the four LVPE cycles, significant decreases were observed in SE ($t = 5.678$; $p < 0.0001$) and platelet count ($t = 3.312$; $p < 0.002$), along with a significant increase in MPV ($t = 3.700$; $p < 0.001$). Other complete blood count parameters remained unchanged.

Cardiometabolic Biomarkers in Serum Samples

The study explored the impact of LVPE cycles on cardiometabolic biomarkers in serum samples (Table 4).

Table 4
Cardiometabolic Markers in Serum Samples before I and after IV cycle (mean±SD)

Variables	Before I cycle	After IV cycle	p Values
Glucose (mg/L)	5.58±1.64	4.79±1.08	<0.0001
Cholesterol (mmol/L)	5.53±1.36	4.84±0.99	<0.0001
Triglycerides (mmol/L)	1.94±1.48	1.34±1.35	<0.011
HDL-C (mmol/L)	1.40±0.38	1.28±0.35	<0.006
LDL-C (mmol/L)	3.09±0.95	2.96±0.89	0.260
CHD index	3.98±1.13	3.92±1.28	0.265
AI index	2.28±0.80	2.42±0.98	0.342
HbA1c (%)	5.67±0.81	5.70±0.78	0.729

HDL-C – high-density lipoprotein cholesterol, LDL-C – low density lipoprotein cholesterol, CHD – index for coronary heart diseases, AI – atherosclerosis index, HbA1c – glycolisate hemoglobin.

Significant decreases were recorded in glucose ($t = 3.899$; $p < 0.0001$), total cholesterol ($t = 4.746$; $p < 0.0001$), triglycerides ($t = 2.660$; $p < 0.011$), and HDL-C ($t = 2.899$; $p < 0.006$). However, there were no significant changes in LDL-C or HbA1c. Calculated indices for CHD and AI did not exhibit significant alteration.

Cardiometabolic biomarkers in removed plasma

The study also investigated cardiometabolic biomarkers in removed plasma after each cycle of LVPE (Table 5).

Table 5

Cardiometabolic biomarkers in removed plasma after each cycle (mean±SD)

Variables	I cycle	II cycle	III cycle	IV cycle	p Values
Glucose (mg/L)	27.89±4.99	28.21±5.57	27.43±5.18	27.95±5.56	0.802
Cholesterol (mmol/L)	2.01±0.95	1.92±0.96	1.99±0.91	1.88±0.76	0.806
Tryglicerides (mmol/L)	0.72±0.81	0.72±0.63	0.70±0.63	0.66±0.66	0.780
HDL-C (mmol/L)	0.51±0.30	0.49±0.31	0.49±0.35	0.45±0.25	0.672
LDL-C (mmol/L)	1.15±0.69	1.07±0.73	1.10±0.68	1.11±0.60	0.904

HDL-C – high-density lipoprotein cholesterol, LDL-C – low density lipoprotein cholesterol

No significant differences were observed in glucose, cholesterol, triglycerides, HDL-C, and LDL-C in the removed plasma samples after each individual LVPE cycle.

The regression model indicated overall significance for the analyzed biomarkers in both serum and removed plasma samples, with varying degrees of correlation (R-squared values) for each biomarker: glucose ($F = 4.639$; $p < 0.002$, $R^2 = 0.361$), cholesterol ($F = 7.277$; $p < 0.001$, $R^2 = 0.464$), triglycerides ($F = 41.050$; $p < 0.001$, $R^2 = 0.830$), HDL-C ($F = 13.742$; $p < 0.001$, $R^2 = 0.644$), and LDL-C (F 6.794; $p < 0.001$, $R^2 = 0.485$).

Parameters of intestinal permeability, inflammation, and low-grade inflammation

Table 6

Serum concentrations of Zonulin, IL-6, Vitamin D3, CRP, and hsCRP before I and after IV LVPE cycle (mean±SD)

Variables	Before I cycle	After IV cycle	p Values
Zonulin (ng/ml)	16.37±10.94	16.62±8.41	0.800
IL-6 (pg/ml)	3.16±3.03	3.06±3.90	0.801
VitD3 (nmol/L)	89.59±49.85	75.98±52.46	<0.001
CRP (mg/L)	5.04±3.04	3.54±3.44	<0.02
hsCRP (mg/L)	2.31±2.33	1.78±1.70	0.060

IL-6 – interleukin 6, VitD3 – vitamin D3, CRP – C-reactive protein, hsCRP – high sensitive CRP

Significant decreases were observed in the serum concentrations of Vitamin D3 ($t = 5.633$; $p < 0.001$) and CRP ($t = 2.409$; $p < 0.02$) after the fourth LVPE cycle. Other parameters did not exhibit significant alterations (Table 7).

Table 7

Concentrations of Zonulin, IL-6, Vitamin D3, CRP, and hsCRP in removed plasma samples after each cycle of LVPE (mean±SD)

Variables	I cycle	II cycle	III cycle	IV cycle	p Values
Zonulin (ng/ml)	9.67±5.65	9.37±5.46	10.43±6.32	9.86±5.78	0.656
IL-6 (pg/ml)	1.80±0.94	1.98±1.15	2.09±1.46	2.04±1.22	0.119
VitD3 (nmol/L)	30.56±17.62	28.16±14.20	29.76±13.45	29.21±16.46	0.685
CRP (mg/L)	3.78±6.01	2.66±2.32	2.76±2.73	3.29±4.04	0.321
hsCRP (mg/L)	0.86±0.78	0.84±0.89	0.76±0.67	0.97±0.88	0.423

IL-6 – interleukin 6, VitD3 – vitamin D3, CRP – C-reactive protein, hsCRP – high sensitive CRP.

Overall linear regression models highlighted the significance of these parameters, indicating varying degrees of correlation for each biomarker: Zonulin ($F = 23.421$; $p < 0.001$, $R^2 = 0.741$), Vitamin D3 ($F = 90.227$; $p < 0.001$, $R^2 = 0.917$), IL-6 ($F = 11.598$; $p < 0.001$, $R^2 = 0.580$), CRP ($F = 9.639$; $p < 0.001$, $R^2 = 0.534$), and hsCRP ($F = 23.937$; $p < 0.001$, $R^2 = 0.740$).

Summary of the interaction models with β-coefficient and 95% confidence interval

Association Between Zonulin Concentration and Anthropometric Measurements

Before the initial LVPE cycle, a significant association was observed between Zonulin concentration and sex ($\beta = 0.790$; $p = 0.023$). No significant associations were found with other anthropometric parameters.

Association between Zonulin concentration and cardiometabolic biomarkers

Before the first LVPE cycle, significant associations were found between Zonulin concentration and HDL-C ($\beta = 1.406$; $p = 0.002$), LDL-C ($\beta = -1.263$; $p = 0.012$), and IA ($\beta = 1.648$; $p = 0.047$). After the fourth LVPE cycle, significant associations were identified between Zonulin concentration and HbA1c ($\beta = 0.342$; $p = 0.025$), total cholesterol ($\beta = 0.570$; $p = 0.001$), and CHD ($\beta = 0.803$; $p = 0.039$).

Association between Zonulin concentration and markers of inflammation and low-grade inflammation

Before the first LVPE cycle, Zonulin concentration showed a significant association with hsCRP ($\beta = 0.302$; $p = 0.046$). However, after completing the LVPE protocol, no significant associations were observed with markers of inflammation and low-grade inflammation.

Discussion

The current study investigates the potential of nanomembrane-based LVPE as an innovative method to improve gut barrier permeability in individuals affected by MetSy, a global public health concern. The prevalence of MetSy ranges from 13 to 36% in the European population [31] and one-fourth to one-fifth in the Mediterranean region [32].

Significant differences in anthropometric measures were noted, highlighting distinct physical variations between male and female participants diagnosed with MetSy. These observed differences align with established literature on sexual dimorphism and physical disparities [33, 34].

Nanomembrane-based LVPE introduces an innovative method for plasma filtration and purification, leveraging nanotechnology and specially engineered microscopic Lavsan film membranes. These membranes, created through argon particle irradiation in a collider [35, 36, 37], feature pores ranging from 30 to 50 nanometers in diameter. They demonstrate the capability to filter molecules weighing less than 40 kilodaltons and can accommodate a filling volume of up to 70 milliliters [38, 39].

The LVPE process involves the exchange of components within the plasma, utilizing a minimal volume of replacement fluid. In our study, we embraced a low-volume approach, extracting up to 30% of the plasma and substituting it exclusively with a saline solution. This method ensures the preservation of plasma quality while effectively achieving our purification objectives. We conducted four cycles of LVPE every other day, removing up to 1–1.5 times the volume of circulating plasma [40].

According to our findings, four cycles of LVPE successfully regulated BP, leading to a significant reduction in both SBP and DBP. Parameters such as HR, CL, processed BV, and removed PV did not show significant changes. The increased consumption of ACD-A highlights its importance in stabilizing blood during the procedure, while saline solution consumption remained consistent. These results provide valuable insights into the physiological effects of LVPE cycles.

These filters, owing to nanotechnology, effectively preserve blood cells through the size of the pores and their rounded edges [35, 27, 41]. Nevertheless, observed changes in hematological parameters in our study, including SE, platelet count, and MPV, suggest that LVPE may influence inflammatory and coagulation pathways.

Recent studies propose that LVPE can positively influence carbohydrate and lipid metabolism in patients with diabetes mellitus (DM) by reducing levels of cholesterol, triglycerides, fibrinogen, as well as LDL-C [42]. In our study, LVPE demonstrated a favorable impact on several key cardiometabolic markers, specifically leading to reduced levels of glucose, total cholesterol, triglycerides, and HDL-C. The stability observed in LDL-C and HbA1c suggests that these parameters may not be significantly affected by LVPE treatment. Furthermore, there seem to be no significant differences in the levels of cardiometabolic biomarkers (glucose, cholesterol, triglycerides, HDL-C, and LDL-C) in the removed plasma samples after each individual LVPE cycle. The absence of significant differences in individual cycles implies a consistent response of cardiometabolic biomarkers to LVPE. The overall significance in the regression model indicates that the LVPE procedure has a measurable impact on these biomarkers collectively. The varying degrees of correlation among biomarkers suggest that each biomarker responds differently to LVPE, with triglycerides showing the highest correlation. Additionally, the stability of glucose, cholesterol, triglycerides, HDL-C, and LDL-C levels in removed plasma after LVPE cycles may indicate the procedure's safety in terms of maintaining these cardiometabolic parameters.

The study aimed to evaluate parameters related to intestinal permeability, inflammation, and low-grade inflammation before the first and after the fourth cycle of LVPE. Serum concentrations of Zonulin, IL-6, Vitamin D3, CRP, and hsCRP were examined to understand the impact of LVPE on these biomarkers. According to the literature, circulating IL-6 has been suggested to act as a promoter of the Zonulin gene, increasing its circulating levels [43]. Although no significant alterations were observed in Zonulin and IL-6 serum concentrations before and after LVPE cycles, these results suggest the stability of these markers in response to the cycles. MetSy has been reported to be associated with inflammatory status, with subjects showing high concentrations of hsCRP [44]. Additionally, CRP, produced in response to IL-6, can induce chronic inflammation at higher levels [45]. Onthe other hand, Vitamin D3 has a wide range of impacts, including influencing gene expression, modulating immune response, inflammation, oxidative stress, and the gut microbiota signature [46]. A significant decrease was noted in serum Vitamin D3 levels, accompanied by a significant reduction in CRP after the fourth LVPE cycle, as well as a decreasing trend in hsCRP. The decline in Vitamin D3 may implicate altered immune responses, while the reduction in CRP and hsCRP indicates an anti-inflammatory effect post-LVPE. Furthermore, the decrease in Vitamin D3, CRP, and hsCRP levels post-LVPE suggests potential immunomodulatory effects. Overall linear regression models emphasized the significance of the parameters, revealing varying degrees of correlation. Strong correlations were found for Zonulin, Vitamin D3, IL-6, CRP, and hsCRP, indicating interrelated dynamics among these biomarkers.

In our study, we aim to explore the relationship between Zonulin concentration and anthropometric measurements, cardiometabolic biomarkers, and markers of inflammation. Existing literature suggests that higher Zonulin levels are linked to increased waist circumference (Wc), diastolic blood pressure (DBP), fasting glucose levels, and an elevated risk of overweight, obesity, and hyperlipidemia [47]. This implies that serum Zonulin levels may be more dependent on metabolic conditions. Our results also highlight the role of Zonulin in metabolic and cardiovascular health, as evidenced by its significant association with cardiometabolic biomarkers both before the first and after the fourth cycle of LVPE. Moreover, the noteworthy association with hsCRP before the first cycle of LVPE suggests a potential involvement of Zonulin in inflammation. Additionally, a significant association with gender indicates that Zonulin concentration may be influenced by sex differences. Further research is warranted to comprehensively understand the underlying mechanisms and causality behind the observed associations.

Conclusion

In conclusion, our study advocates for the use of nanomembrane-based LVPE as a targeted method to enhance gut barrier permeability in individuals with MetSy. By integrating nanotechnology into LVPE, we achieve a breakthrough in precision plasma filtration, maintaining blood cell integrity. Through four LVPE cycles, our research validates the efficacy of this approach in correcting carbohydrate and lipid metabolism. Notably, our investigation reveals LVPE's potential immunomodulatory effect on inflammatory pathways.

The association between Zonulin concentration – a marker of impaired gut barrier function – and anthropometric measurements, cardiometabolic biomarkers, and markers of inflammation provides a nuanced understanding of its role in metabolic and cardiovascular health. Gender and biomarker associations underscore the complexity, prompting further research to unveil underlying mechanisms.

In essence, our study contributes to refining therapeutic interventions for MetSy. The innovative application of nanomembrane-based LVPE, coupled with observed physiological impacts, positions it as a promising avenue for future research and clinical applications, offering new possibilities for enhancing treatment strategies and improving health outcomes.

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PREVALENCE OF INTRAOPERATIVE COMPLICATIONS WITH OPEN SINUS LIFT AND UNDERWOOD SEPTA

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SUMMARY

The loss of maxillary masticatory teeth is associated with a decrease in both the height and width of the alveolar bone mass. In addition to the bone limits, implant placement to replace the missing tooth is complicated by the close proximity of the maxillary sinus floor. The above can negatively affect the success of the patient's surgical rehabilitation. The maxillary sinus lift (MS), or sinus lift, can optimize the procedure and the results of dental implantation. Maxillary sinus floor lift surgery is a procedure with predictable results and a low complication rate, with an expected success rate of over 90% in the long term. However, like any surgical procedure, a sinus lift comes with some complications. One of the most common complications is Schneider's membrane perforation, which occurs either for iatrogenic reasons related to improper surgical actions or due to anatomical features of a particular patient that may complicate the procedure. A particularly interesting fact is the association of the incidence of MS membrane perforation with individual patient anatomy, particularly the presence of frontal or sagittal bony septa. ***The purpose*** *of this study is to determine the relationship of the incidence of Schneider's membrane perforation during sinus lift surgery in patients with and without bony septa in the MS.* ***Materials and Methods.*** *The present study included 100 patients who underwent open sinus lift surgery with subsequent implant placement. The participants were divided into 2 groups after studying the data of preoperative CBCT: group 1 – patients without septum in the MS (control group – 30 patients), group 2 – patients with septum in the MS (experimental group – 70 patients). Postoperative follow-up of the patients of both groups to monitor the presence of complications from Schneider's membrane was performed on the 3rd,5th,7th day according to clinical symptoms.* ***Results.*** *For group 1 patients (MS without septum), the rate of Schneider's membrane perforation during sinus lift was 20%, whereas for group 2 patients (MS with septum), the rate of perforation was 77.2%.* ***Conclusions.*** *The obtained data indicate a higher incidence of Schneider membrane damage during open sinus lift surgery in patients with individual anatomical features of the MS compared to patients with classic MS anatomy. The above-mentioned necessitates a more thorough preoperative planning of the invasive intervention, as well as a detailed analysis of 3D radiographs (CBCT) of the maxillary sinus.*

KEYWORDS: *sinus lift, perforation, CBCT, complications, implantation.*

CONFLICT OF INTEREST. The authors declare no conflict of interest.

РАСПРОСТРАНЕННОСТЬ ВНУТРИОПЕРАЦИОННЫХ ОСЛОЖНЕНИЙ ПРИ ОТКРЫТОМ СИНУС–ЛИФТИНГЕ И НАЛИЧИЕМ ПЕРЕГОРОДОК АНДЕРВУДА

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РЕЗЮМЕ

Потеря жевательных зубов верхней челюсти сопряжена со снижением как высоты, так и ширины костного массива альвеолярного отростка. Помимо костных лимитов, постановка имплантата для замещения отсутствующего зуба осложняется близким расположением дна гайморовой пазухи. Вышесказанное способно негативно повлиять на успех хирургической реабилитации пациента. Операция по подъему дна верхнечелюстной пазухи (ВЧП), другими словами, синус-лифтинг, способна оптимизировать процедуру и результаты дентальной имплантации. Операция по подъёму дна верхнечелюстной пазухи — процедура с предсказуе-

мыми результатами и низкой частотой осложнений, ожидаемый процент успеха которой составляет более 90% в долгосрочной перспективе. Однако, как и любое хирургическое вмешательство, синус-лифтинг сопряжен с некоторыми осложнениями. Одним из наиболее часто встречающихся осложнений является перфорация мембраны Шнайдера, возникающая либо по ятрогенным причинам, связанным с неправильными хирургическими действиями, либо из-за анатомических особенностей конкретного пациента, которые могут затруднить процедуру. Особенно интересным фактом является связь частоты перфорации мембраны ВЧП с индивидуальной анатомией пациента, в частности, наличием фронтальных или сагиттальных костных перегородок. ***Целью*** *данного исследования является определение взаимосвязи частоты перфорации мембраны Шнайдера в ходе операции синус-лифтинг у пациентов с костными перегородками в ВЧП и без них.* ***Материалы и методы.*** *В настоящее исследование были включены 100 пациентов, которым проводилась операция открытый синус-лифтинг с последующей установкой имплантата. Участники были разделены на 2 группы после исследования данных предоперационной КЛКТ: 1 группа – пациенты без перегородки в ВЧП (контрольная группа – 30 пациентов), 2 группа – пациенты с перегородкой в ВЧП (экспериментальная группа – 70 пациентов). Послеоперационное наблюдение за пациентами обеих групп для контроля наличия осложнений со стороны мембраны Шнайдера проводилось на 3, 5, 7 сутки по клинической симптоматике.* ***Результаты.*** *Для пациентов 1 группы (ВЧП без перегородки) частота перфорации мембраны Шнайдера в ходе синус-лифтинга составила 20%, в то время как для пациентов 2 группы (ВЧП с перегородкой) частота перфораций составила 77,2%.* ***Выводы.*** *Полученные данные свидетельствуют о более частом повреждении шнайдеровой мембраны в ходе операции открытый синус-лифтинг у пациентов с индивидуальными анатомическими особенностями ВЧП, по сравнению с пациентами классической анатомией ВЧП. Вышеобозначенное диктует необходимость более тщательного предоперационного планирования хода инвазивного вмешательства, а также детального анализа 3Д-рентгенограмм (КЛКТ) верхнечелюстной пазухи.*

КЛЮЧЕВЫЕ СЛОВА: синус-лифтинг, перфорация, КЛКТ, осложнения, имплантация.

КОНФЛИКТ ИНТЕРЕСОВ. *Авторы заявляют об отсутствии конфликта интересов.*

Introduction

Currently, implantation is considered a routine dental surgical procedure with few complications and predictable prospective results [1,2]. However, in some cases, it is possible to compromise the procedure of implant placement by anatomical limitations of bone tissue, especially with the close location of the floor of the maxillary sinus (MS). In cases of prolonged absence of teeth due to their removal, a decrease in the residual alveolar process and progressive pneumatization of MS is one of the most important factors affecting the support, fixation, stability and chewing function of the implant [3, 4, 5].

Accordingly, with prolonged absence of teeth in the lateral part of the upper jaw, both vertical and horizontal volumes of the alveolar process decrease, and the bottom of the MS becomes easily accessible for injury with surgical instruments, which makes implantation an impossible task under specified conditions.

In order to increase the volume of bone tissue in the masticatory sections of the upper jaw for optimal positioning of the implant and minimize intraoperative risks, an operation is performed to raise the floor of the maxillary sinus (sinus lifting). Maxillary sinus floor lift surgery is a procedure with predictable results and a low complication rate, with an expected success rate of over 90% in the long term. However, like any surgical procedure, sinus lifting is associated with some complications [6–8].

The literature describes both general complications associated with surgery, such as swelling, hematoma formation, and specific ones – chronic rhinosinusitis, blockage of the mouth of the MS and others [1]. One of the most common intraoperative complications of sinus lifting, both open and buried, is perforation of the Schneider membrane, which occurs either for iatrogenic reasons related to improper surgical procedures, or due to anatomical features of a particular patient that may make it difficult to perform the procedure [9–12].

A particularly interesting fact is the relationship between the frequency of perforation of the MS membrane and the individual anatomy of the patient, in particular, the presence of transversal or sagittal bone septa. The septa, or septa of the maxillary sinus, are barriers of cortical bone that divide the floor of the maxillary sinus into several compartments called recesses/pockets. They are one of the most common anatomical variations found in the maxillary sinuses (28–58% according to various authors) [13, 14]. Dr. Underwood first described this anatomical formation in 1910, which is why it is sometimes called the Underwood septum. According to literature data, septa are often found in the projection area of the 1st and 2nd molars or between these teeth, which is one of the deep places of the maxillary sinus [9, 12–14].

When chewing teeth are removed, bone tissue is remodeled and the height of the bone of the alveolar process recedes, which determines the patient's need for an implant with a preliminary increase in bone volume. The septa may partially protrude from the walls of the maxillary sinus or lead to a complete separation of the sinus into smaller paranasal sinuses [15, 16]. Being part of the internal configuration of the sinus, the septa can interfere with the preparation of the surgical site, making it difficult to lift the Schneider membrane without perforating it.

The above dictates the need for a preoperative diagnosis of the presence of additional bone structures of the HPV for optimal planning of the position and formation of the lateral window during the sinus lifting procedure, as well as to minimize intraoperative complications of the operation, for example, perforation of the maxillary sinus membrane.

The purpose of this study was to determine the effect of anatomical features of the maxillary sinus, namely the bone septa, on the risks of perforation of the Schneider membrane during open sinus lifting surgery.

Materials and Methods

This study was conducted in a private clinic of surgical dentistry. All patients selected for the experiment were warned about the course of the work and informed about possible risks and adverse effects associated with this surgical intervention. Informed voluntary consent was obtained and signed by each participant in the study.

A single operator performed all open sinus lift operations. The operator unified his manipulations, using instruments and techniques that minimize possible intraoperative complications and increase the probability of successful completion of the operation.

In this work, 100 patients who required open sinus lift surgery for subsequent prosthodontic rehabilitation of partial secondary adentia in the area of tooth 1.6 were included. The following inclusion criteria were developed to select the participants:

1. Age 25–35;
2. Partial secondary adentia of tooth 1.6;
3. The bone height of the alveolar process in the area of the proposed surgical intervention is 3–4 mm;
4. Absence of organic and inflammatory pathologies of the maxillary sinus.

The criteria for non-inclusion were:

1. Age under 25 and over 35;
2. Presence of tooth 1.6 in the dental arch or previously performed implant-supported prosthesis of tooth 1.6;
3. Somatic diseases in the stage of decompensation;
4. Uncontrolled diabetes mellitus of any type;
5. Bone height of the alveolar process in the area of intended surgical intervention is more or less than 3 4 mm;
6. Presence of organic and inflammatory pathologies on the side of the maxillary sinus;
7. Pregnancy.

The main exclusion criterion was the patient's willingness to end participation in the experiment.

The participants selected for the study were divided into 2 groups after preoperative CBCT and its analysis:

Group 1: 70 patients with septum in the MS (experimental group);

Group 2: 30 patients without septum in the MS (control group).

Each of the patients underwent open sinus lift surgery according to the following protocol:

Application anaesthesia (DiSiLan, Russia), after double negative aspiration test – infiltration anaesthesia Sol. Ultracaini D-S 4.0% 1:200.000 – 5.1 ml (3 carpules), an incision of the gingival mucosa to the bone is made in the centre of the alveolar process of the maxilla in the projection of the missing tooth 1.6 and a vertical loosening incision distally. The mucosa-adcostal flap is peeled off. In the anterolateral wall of the maxillary sinus at the level of the missing tooth 1.6, an oval-shaped osteotomy is performed in the anterolateral wall of the maxillary sinus with a ball-shaped bur using a physiodispenser. The Schneider's membrane is peeled off, placed horizontally, thereby raising the level of the floor of the maxillary sinus. The formed space is filled with BioplastDent 1g biomaterial and overlapped with BioplastDent 25×25 membrane. The flap is placed in place. The wound is sutured without tension with Vicryl 5-0 knotted sutures. Achieving haemostasis. Long-term planning of implantation 6–8 months after the intervention.

An ANOVA test was performed using StatPlus 6 software (AnalystSoft, CA, USA) for the mean data obtained in each study group. Data were also analysed using Fisher's exact test to assess the correlation of MS perforations with the presence of bony septa within the sinus ($p < 0.05$).

Results and Discussion.

Two groups of patients were compared for analysis: with and without bony septum in the maxillary sinus. The main variables are summarized in Table 1.

Table 1

Analyses comparing patients with and without bony septum in the maxillary sinus

Parameter	Group with septum (n=70)	Group without septum (n=30)	P-value
Average age (years)	39,9 ± 4,9	38,6 ± 4,8	>0,05[1]
Time of missing teeth in the target area (months)	30,7 ± 10,1	32,3 ± 8,1	>0,05[1]
Residual bone height (mm)	3 (2,75;4)	3 (3;4)	>0,05[2]
Gender (male/female)	42/28	16/14	>0,05[3]
Smoking/non-smoking	34/36	13/17	>0,05[3]

[1] – T-student's test, [2] – Mann – Whitney test, [3] – Fisher's exact test

In the group with septum, the mean age was 39.9±4.9 years, which was almost the same as in the group without septum (38.6±4.8 years). The differences did not reach statistical significance ($p > 0.05$).

The mean time of missing teeth was similar between the groups: 30.7±10.1 months in the group with septum and 32.3±8.1 months in the group without septum. These differences were also not significant ($p > 0.05$).

The median height of the residual bone was 3 mm in both groups. Interquartile ranges of 2.75 and 4 for the group with septum and 3 and 4 for the group without septum indicated no significant differences ($p > 0.05$).

More males were observed in the group with septum (42 males and 28 females), while the sex ratio was almost equal in the group without septum (16 males and 14 females). However, the differences were not significant ($p > 0.05$).

The proportion of smoking and nonsmoking patients was comparable between the groups. There were 34 smokers and 36 nonsmokers in the group with partition, whereas in the group without partition these figures were 13 and 17, respectively. The differences did not reach statistical significance ($p > 0.05$).

Comparison of baseline characteristics of patients in both groups revealed no statistically significant differences in any of the analysed parameters. This indicates the similarity of the groups, which allows us to consider them as homogeneous for further analysis of complications and treatment results.

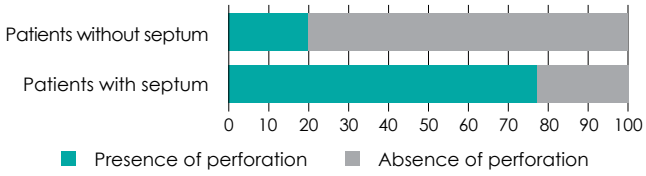

Fig. 1. Comparison of the presence of septal perforation in the two groups, %

The study analyzed the results of sinus lift in patients with and without septum in the maxillary sinus in terms of the frequency of Schneider's membrane perforation. 100 patients were included in the study and divided into two groups: with septum (70 patients) and without septum (30 patients).

A group with a partition, 54 patients (77.2%) showed perforation of Schneider's membrane, whereas 16 patients (22.8%) had no perforation.

A group without a partition, of the 30 patients in this group, 6 patients (20%) showed perforation of Schneider's membrane, while 24 patients (80%) had no perforation (Figure 1).

Data analysis using Fisher's exact test revealed statistically significant differences between groups in the incidence of Schneider's membrane perforation ($p < 0.05$. The odds ratio for the occurrence of perforation was OR = 13.5 (95% CI: 4.7–38.7), indicating a 13.5-fold increased risk of perforation in the group with septum (Table 2). Perforations were significantly more frequent in the group with septum than in the group without septum. This result suggests that the presence of a septum in the maxillary sinus is a risk factor for membrane perforation during sinus lift surgery.

Table 2

Odds ratio for the occurrence of perforation in patients with the presence and absence of a bone septum in the maxillary sinus

	Membrane perforation (n)	No perforation (n)	p	OR
Patients with bone septum (n=70)	54	16	<0,05[1]	13,5
Patients with no bone septum (n=30)	6	24		

[1] – point Fisher's criterion.

In studying the factors that influence the risk of Schneider's membrane perforation during a sinus lift procedure, the relationship between the height of the residual bone and the perforation rate was assessed, and the combined effect of the height of the residual bone and the presence of a septum on the complication rate was analysed.

To study the direct relationship between the height of the residual bone and the presence of membrane perforation, the correlation coefficient φ and Cramer's V were calculated. The coefficient values were $\varphi = -0.208$ and $V = 0.208$ ($p = 0.037$), indicating a weak feedback relationship (Figure 2). These results suggest that as the height of the residual bone increases, the probability of membrane perforation decreases slightly. However, the strength of the association remains low, limiting the possibility of using bone height as the sole predictor.

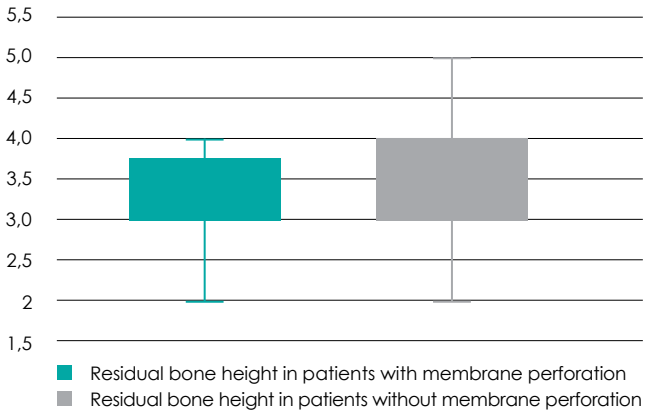

Fig. 2. Relationship between the height of the residual bone and the presence of membrane perforation, mm

A binary logistic regression model was constructed to assess the combined effect of residual bone height and septal presence. The results showed that residual bone height was not a significant predictor of perforation rate ($B = -0.204$), ($p = 0.393$) despite an 18.4% decrease in the odds of perforation ($Exp(B) = 0.816$) with each additional millimetre of height. This may indicate the influence of other factors that offset the role of bone height when an additional variable, the presence of a septum, is included in the model.

The presence of septum was the key factor that significantly increased the risk of membrane perforation ($B = 2.600$), ($p < 0.001$); $Exp(B) = 13.469$. This means that in the presence of a septum, the likelihood of complication increases more than 13-fold. This result emphasizes the need to consider the anatomical features of the maxillary sinus when planning a sinus lift procedure.

The difference between correlation analysis and regression model results can be explained by the interaction effect between variables as well as the influence of group factor. In direct correlation analysis, bone height shows a weak inverse relationship with perforation. However, in pooled estimation, the interaction with the presence of septum leads to a decrease in the statistical significance of bone height. This indicates a dominant role of septum in determining the risk of complications.

One of the possible postoperative complications of sinus lift is migration of bone material into the maxillary sinus, which is sometimes accompanied by the development of sinusitis. Analysing the frequency of these complications depending on the presence of a septum in the maxillary sinus, the following results can be noted:

1. Group with presence of septum (n=70):
   - Five patients (7.1%) had cases of material migration into the sinus with or without sinusitis.
   - There were no complications in 65 patients (92.9%).
2. Group without septum (n=30):
   - No cases of material migration or sinusitis have been reported.

Fisher's exact test was used to statistically evaluate the differences between the groups. The results of the analysis showed that there were no statistically significant differences in the frequency of these complications between the groups ($p > 0.05$) (Table 3).

Table 3

Migration of bone material into the sinus and development of sinusitis

	Was (n)	None (n)	p-value
Patients with bone septum (n=70)	5	65	>0,05[1]
Patients with no bone septum (n=30)	0	30	

[1] – point Fisher's criterion.

The findings suggest that the presence of a septum in the maxillary sinus is not a statistically significant factor that increases the risk of bone migration and sinusitis.

The results of this study emphasise the complexity of the relationships between anatomical factors that influence the risk of complications in sinus lift surgery. More detailed analyses with other factors, such as surgeon experience, surgical technique and soft tissue status, are required to further clarify the mechanism of bone height and septal height interaction.

Conclusion

Residual bone height has a weak inverse association with the risk of membrane perforation, but its value as a predictor decreases when the septum variable is included. The presence of maxillary sinus septum remains a key factor that significantly increases the risk of complications. This emphasises the need for careful preoperative diagnosis and individualisation of treatment.

The findings support the need for more thorough preoperative assessment of the anatomical features of the maxillary sinus and caution when performing the sinus lift procedure in patients with septum, which may reduce the risk of complications.

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THE USAGE OF PHARMACOPUNCTURE IN MEDICAL COMPLEXES FOR LUMBOSACRAL DORSOPATHIES

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SUMMARY
The material is devoted to the results of a number of own studies in the field of local drug stimulation (pharmacopuncture) – a technique for irritating reflexology points with small doses of drugs. In this respect, the topic being developed fits well into the general course of the problem of low-energy therapeutic effects, interest in which has only increased recently. In the mechanisms of technology, the role of prolongation of the reflex response and the formation of the depot of the drug used is distinguished. However, the issues of summation and, moreover, potentiation of these influences remain unclear, which determined the implementation of a series of works. The object of observation was lumbosacral dorsopathy, since the bulk of research on local stimulation is devoted to the correction of these conditions. Naturally, the enduring medical, social and economic significance of the problem of dorsopathies was taken into account. In the work performed, the mechanisms and effectiveness of pharmacopuncture with Alflutop, shown in the pathology under study, were analyzed. The evaluation of the effectiveness of the method included in the complex therapy programs was based on taking into account the dynamics of clinical and additional (psychological, electrophysiological) characteristics of the patient's condition. At the same time, the addition of the reflex and drug links of the method was confirmed, which determines its significant superiority over the compared methods. In this regard, the structural-modifying effect in the form of shifts in the state of the intervertebral discs, observed in the course of the combined application of the selected technology and electromagnetic stimulation, was of fundamental importance. In addition, within the framework of the affected direction, an effective scheme of exposure was proposed, combining the techniques of drug blockade according to the method of A.V. Vishnevsky and pharmacopuncture with Alflutop.

KEYWORDS: *lumbosacral dorsopathies, reflexology, reflexology points, pharmacopuncture, local stimulation, blockade according to the Vishnevsky method of the drug, Aflutop.*

CONFLICT OF INTEREST. The authors declare no conflict of interest.

ПРИМЕНЕНИЕ ФАРМАКОПУНКТУРЫ В КОМПЛЕКСНОМ ЛЕЧЕНИИ ПРИ ПОЯСНИЧНО–КРЕСТЦОВЫХ ДОРСОПАТИЯХ

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РЕЗЮМЕ
Статья обобщает результаты собственных исследований в области одного из направлений рефлексотерапии – фармакопунктуры или, иначе, локальной стимуляции. Под этим термином в нашем случае подразумевается способ раздражения точек рефлексотерапии малыми дозами лекарственных средств, рассматриваемых в качестве факторов низкоэнергетического воздействия. Синонимами метода, отражающими мало существенные различия, являются «биопунктура», «мезотерапия» и некоторые другие. В механизмах технологии выделяют значимость пролонгации рефлекторного ответа вследствие изменения объема тканей в области активируемых точек и формирования множественных депо используемого препарата. Однако вопросы более тонких звеньев остаются до конца не ясными, что и определило цель работы – выявление как такового целенаправленного действия медикаментов, используемых путем локальной стимуляции. В качестве исследовательской «модели» были выбраны пояснично-крестцовые дорсопатии, что в известной степени связано со становлением рефлексотерапии в стране, способы которой оттачивались на «модели» неврологических болевых синдромов. Естественно, учитывали медико-социальную и экономическую значимость проблемы. В серии выполненных диссертационных работ наших сотрудников проанализированы терапевтические возможности локального применения препарата Алфлутоп, прямо показанного при изучаемой патологии. Оценка эффективности данного подхода базировалась на учете динамики клинических и дополнительных характеристик и, в частности, результатах психологического и электрофизиологического обследования, включая зональную термографию, «сосудистые» пробы и др.

При этом отмечено сложение и даже потенцирование рефлекторного и медикаментозного звеньев способа, определяющее достоверное превосходство над стандартным лечебным воздействием или плацебо-контролем. Принципиально значимым в этом плане явился структурно-модифицирующий эффект применительно к состоянию межпозвонковых дисков, подтвержденный данными ультразвуковой видео денситометрии. Внимания заслуживает и факт усиления результативности фармакопунктуры за счет параллельного использования современной аппаратной техники – низкочастотной электромагнитной стимуляции. Представленные материалы также отражены в монографиях, ряде методических пособий и защищенных патентах на изобретение.

КЛЮЧЕВЫЕ СЛОВА: пояснично-крестцовые дорсопатии, рефлексотерапия, точки рефлексотерапии, фармакопунктура, локальная стимуляция, препарат Афлутоп.

КОНФЛИКТ ИНТЕРЕСОВ. *Авторы заявляют об отсутствии конфликта интересов.*

Introduction

The article is devoted to the generalization of the results of our own research in the field of pharmacopuncture – a method of local stimulation of reflexology points with small doses of drugs [1, 3, 10]. Synonyms of the method, reflecting little significant, mainly external differences, are “aquapuncture”, “biopuncture”, “mesotherapy” and some others. In Russia, the method, officially included in the arsenal of a reflexologist, is consistently spelled out in a number of documents reflecting the stages of the formation of the discipline: the Unified Curriculum (1999), the State Educational Standard (2000) and, accordingly, the List of Knowledge and Skills of a Specialist. In the following decades, there were no special additions to these documents, with the exception of the order of the Ministry of Health and Social Development No. 266 of 13.04.07 “On approval of recommended lists of medical indications and contraindications for the use of reflexology in clinical practice” and several later by-laws that confirmed the existing realities.

In order to ascertain the priority in the issue under discussion: in 2002, for the first time in the country, we presented a textbook for the system of higher and additional medical education “Pharmacopuncture” [1], and also developed and implemented a program of the same name for postgraduate training of specialists lasting 144 hours.

A series of own studies is devoted to this topic, revealing the mechanisms and effectiveness of point stimulation with dorsopathies at the lumbosacral level. The choice of this pathology is to a certain extent associated with the formation ofreflexology in the country, the methods of which were largely honed on the “model” of neurological pain syndromes. Naturally, the medical, social and economic significance of the problem was taken into account: the widest coverage of the working-age population, almost at the level of a pandemic, the protracted course of the process and the severity of the consequences of dorsopathies, including the frequency of disability of patients [2, 8]. These characteristics determine the search and implementation of effective treatment complexes, part of which may be such a method of reflexology as local stimulation.

At the same time, they technically adhere to uniformity in the selection of points. So, in the case of lumbosacral dorsopathies of interest to us, two or three segmental points are chosen along the median and lateral lines of the back and five to six distant points in the region of the lower extremities, located mainly in the projection of pain. The manipulations themselves consist in subcutaneous and/or intradermal administration of the drug substance in a volume of 0.2–0.3 ml per locus.

There are several key points in the mechanisms of action of the method. First, they indicate a prolongation of the reflex response due to changes in the volumetric characteristics of tissues in the area of activated points. Secondly, they take into account the formation of multiple depots of drugs, which contributes to the strengthening of their influence. However, the issues of finer links, including the specificity of the action of medicines as such, remain unclear, giving the problem the character of a “black box”. For example, the comparability of therapeutic results in response to the introduction of the antioxidant Actovegin or an isotonic solution of sodium chloride into acupuncture points in tunnel neuropathy of the hands indicates, in fact, the prevalence of the reflex over the drug effect [9]. According to others, including our data [2], the use of pharmacopuncture in dorsopathies is accompanied by the summation of the therapeutic links of the method. This moment determined the purpose of research on the identification of the purposeful action of drugs during local stimulation as such. Work on the stated subject was carried out by using the drug Alflutop (Biotechnos, Romania), the choice of which was explained by such proven effects as analgesic, anti-inflammatory and chondroprotective.

In the dissertation research of O.A. Tikhaya (2007), patients with lumbosacral dorsopathy, with the dominance of the vascular component, were divided into three treatment groups. In addition to standard therapy, in the first two groups, the drug was administered intramuscularly: in the 1st independently, in the 2nd – in combination with classical acupuncture, i.e., in the form of a rather laborious and not fully justified complex. In the 3rd group, the basic treatment was supplemented with pharmacopuncture with this remedy. As a result, a significant advantage of both the proposed complex and the pharmacopuncture itself over the standard intramuscular use of the drug was established. Important here was the implementation in the case of pharmacopuncture of a qualitatively new, vascular effect, in principle uncharacteristic for the drug Alflutop itself. This effect, verified by the results of objective analysis, can be explained, first of all, by the significance of the reflex link of the techno-logy [7].

In terms of further development of the information obtained, and, in general, increasing the effectiveness of the impact, our dissertator from Kazakhstan S.K. Makina (2014) proposed a combination of Alflutop pharmacopuncture and zonal low-frequency electromagnetic stimulation.

According to the design of the study, patients with exacerbation of lumbosacral dorsopathy were divided into four groups in which standard treatment was performed, and in the control group it was the main one. Along with it, electromagnetic therapy was used in the 1st group, pharmacopuncture with Alflutop in the 2nd group, and a combination of these two methods in the 3rd. The treatment course in all groups included 10 procedures carried out three times a week.

In the course of the study, it was demonstrated that the proposed injection-hardware complex provided a distinct improvement in a number of clinical and instrumental characteristics that significantly exceeded the indicators of the compared groups. Fundamentally significant in this regard was the structural-modifying effect in relation to the "weak link" – intervertebral discs, confirmed by the data of ultrasound video densitometry of these structures. In particular, the indicators reflecting the state of the nucleus pulposus and, accordingly, the integrative echographic coefficient of the disc underwent maximum positive changes only in the 3rd, main group. Attention should also be paid to the fact of enhancing the effectiveness of pharmacopuncture due to the parallel use of modern hardware technology [6].

The obtained data because of these two works form the basis of the patent for the invention "Method for treating patients with lumbosacral dorsopathy", registered in 2021 and revealing the algorithm, safety and efficacy of injecting Alflutop into the area of reflexology points for this pathology.

In 2021, we proposed an original scheme of therapeutic effects for vertebrogenic syndromes, combining the techniques of blockade according to the Vishnevsky method and pharmacopuncture with Alflutop (L.G. Agasarov, E.S. Sahakyan, publications of 2020–2021). A total of 90 patients with exacerbation of dorsopathy at the lumbosacral level were divided into three groups, with conventional treatment as a baseline. The effect in the 1st group was limited to it, and in the other two, drug stimulation of a number of loci was additionally carried out. In particular, points were selected along the middle and lateral lines of the back (visually forming a semblance of an "anatomical lattice" from 12–14 injections performed) and the actual acupuncture points of the lower extremities. At the same time, Lidocaine was injected intradermal into the areola of the "lattice" at a dosage of 0.1 ml per locus, while various agents were injected subcutaneously into the projection of the points of the legs and feet: in the 2nd group – the drug Alflutop, the 3rd – saline, as a placebo. The volume of both substances was 0.2 ml per acupuncture point, and the treatment cycle itself consisted of 10 procedures performed every other day.

The reverse dynamics of the evaluated indicators testified to the advantage of both variants of local stimulation, confirmed by the improvement of the patient's condition within 60% of cases – against 46.6% of cases in response to only the generally accepted effect. In parallel with the reduction of neurological manifestations in the groups of pharmacopuncture (both true and false), there was a regression of pathological vascular reactions, confirmed by the data of thermo- and rheovasography and explained primarily by the positive role of the reflex link of the method. However, there were differences within these effective groups: with the overall comparability of the rate of pain reduction, their level at the end of therapy was significantly lower in the case of pharmacopuncture with Alflutop. These data were consistent with the tendency to normalize the mental background in patients of this particular group, indicating the reverse development of asthenic reactions, which, in turn, affect the level of pain perception.

The high efficacy noted in the 2nd group can be explained by the points of application of the drugs used in the study. In particular, segmental blockade with an anesthetic determines the achievement of a rapid analgesic effect, while pharmacopuncture with Alflutop (due to multi-purpose effect) provides the maximum final effectiveness [4, 5].

This information is reflected in the registered patent for the invention "Method for treating patients with lumbosacral dorsopathy using the method of local stimulation "Anatomical path" (2021).

Conclusion. Based on the results of the performed work, the clinical efficacy, therapeutic reliability and safety of pharmacopuncture performed by the selected drug were generally predictably confirmed. At the same time, the addition and even potentiation of the reflex and drug links of this method was noted, which determines a significant superiority over the standard exposure or placebo control. This fact to a certain extent testifies in favor of the purposeful influence of the medication used. Attention should also be paid to improving the effectiveness of pharmacopuncture through the additional use of modern hardware technology.

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