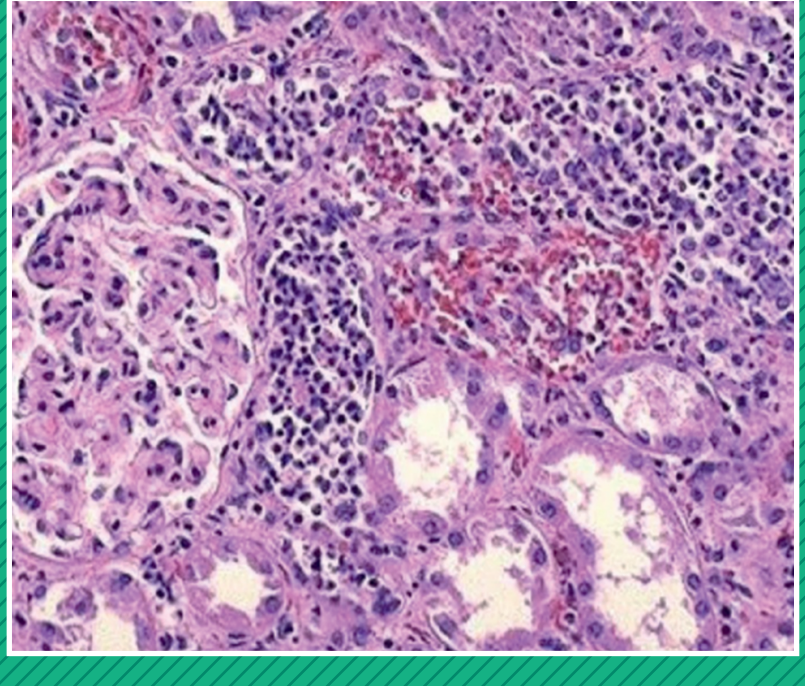
ISSN 2658-6584
eISSN 2658-6576

РОССИЙСКИЕ БИОМЕДИЦИНСКИЕ ИССЛЕДОВАНИЯ

RUSSIAN BIOMEDICAL RESEARCH



2024
Volume 9
3

RUSSIAN BIOMEDICAL RESEARCH

2024, VOLUME 9, N 3 **SCIENTIFIC AND PRACTICAL JOURNAL**

Рецензируемый научно-практический журнал
РОССИЙСКИЕ БИОМЕДИЦИНСКИЕ ИССЛЕДОВАНИЯ
RUSSIAN BIOMEDICAL RESEARCH

Основан в 2016 году в Санкт-Петербурге

ISSN 2658-6584

eISSN 2658-6576

Выпускается 4 раза в год

Журнал реферируется РЖ ВИНИТИ

Издатели, учредители:
Федеральное государственное бюджетное образовательное учреждение высшего образования «Санкт-Петербургский государственный педиатрический медицинский университет» Минздрава России (адрес: 194100, Санкт-Петербург, Литовская ул., д. 2),
Фонд НОИ «Здоровые дети — будущее страны» (адрес: 197371, Санкт-Петербург, ул. Парашютная, д. 31, к. 2, кв. 53).

Журнал зарегистрирован Федеральной службой по надзору в сфере связи, информационных технологий и массовых коммуникаций (РОСКОМНАДЗОР)
ПИ № ФС77-74228 от 02 ноября 2018 г.

*Журнал входит в **Перечень ведущих научных журналов и изданий ВАК**, в которых должны быть опубликованы основные результаты диссертаций на соискание ученых степеней кандидата и доктора наук (Распоряжение № 435-р от 15.11.2021).*

Журнал индексируется в РИНЦ. Договор на включение журнала в базу РИНЦ: № 538-10/2016 от 06.10.2016, страница журнала в Российской научной электронной библиотеке http://elibrary.ru/title_about.asp?id=62014

Проект-макет: Титова Л.А.
Layout project: Titova L.A.

Электронная версия / Electronic version
http://www.gpmu.org/science/pediatrics-magazine/Russian_Biomedical_Research, http://elibrary.ru

Титова Л.А. (выпускающий редактор)
Варламова И.Н. (верстка)
Titova L.A. (Commissioning Editor)
Varlamova I.N. (layout)

Адрес редакции: Литовская ул., 2,
Санкт-Петербург, 194100;
тел./факс: (812) 295-31-55; e-mail: lt2007@inbox.ru

Address for correspondence:
2 Lithuania, Saint Petersburg 194100, Russian Federation
Tel/Fax: +7 (812) 295-31-55, e-mail: lt2007@inbox.ru

Статьи просьба направлять по адресу: avas7@mail.ru, https://ojs3.gpmu.org/index.php/biomedical-research
Please send articles to: avas7@mail.ru, https://ojs3.gpmu.org/index.php/biomedical-research

Формат 60 × 90/8. Усл.-печ. л. 14,5. Тираж 100 экз. Распространяется бесплатно. Оригинал-макет изготовлен ФГБОУ ВО СПбГПМУ Минздрава России.

Format 60 × 90/8. Cond.-printed sheets 14,5. Circulation 100. Distributed for free. The original layout is made Saint Petersburg State Pediatric Medical University.

Отпечатано ФГБОУ ВО СПбГПМУ Минздрава России
Литовская ул., 2, Санкт-Петербург, 194100.
Заказ 72. Дата выхода 22.10.2024.

Printed by Saint Petersburg State Pediatric Medical University.
2 Lithuania, Saint Petersburg 194100, Russian Federation.
Order 72. Release date 22.10.2024.

2024, ТОМ 9, № 3 **НАУЧНО-ПРАКТИЧЕСКИЙ ЖУРНАЛ**

РОССИЙСКИЕ БИОМЕДИЦИНСКИЕ ИССЛЕДОВАНИЯ

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DOI: 10.56871/RBR.2024.58.48.001
UDC 616.36-003.826+577.175.324+612.35+611.36+599.323.4

MORPHOFUNCTIONAL STATE OF THE LIVER IN RATS WITH FATTY HEPATOSIS MODELING AND ALTERED THYROID STATUS

© Albina A. Kondratenko[1], Natalia D. Prokhorova[1], Aleksandr A. Minchenko[1], Anton I. Poloskov[1], Nikolay S. Dedanishvili[2], Sarng S. Pyurveev[2], Ruslan I. Glushakov[1]

[1] Military Medical Academy named after S.M. Kirov. 6 Akademician Lebedev str., Saint Petersburg 194044 Russian Federation
[2] Saint Petersburg State Pediatric Medical University. 2 Lithuania, Saint Petersburg 194100 Russian Federation

Contact information: Ruslan I. Glushakov — Doctor of Medical Sciences, Assistant Professor of the Department of Pharmacology with the course of Clinical Pharmacology and Pharmacoeconomics SPbSPMU; Head of the Department Medical and Biological research of the Research Center of Military Medical Academy named after S.M. Kirov. E-mail: glushakoffruslan@yandex.ru
ORCID: https://orcid.org/0000-0002-0161-5977 SPIN: 6860-8990

For citation: Kondratenko AA, Prokhorova ND, Minchenko AA, Poloskov AI, Dedanishvili NS, Pyurveev SS, Glushakov RI. Morphofunctional state of the liver in rats with fatty hepatosis modeling and altered thyroid status. Russian Biomedical Research. 2024;9(3):5–14.
DOI: https://doi.org/10.56871/RBR.2024.58.48.001

Received: 20.06.2024 **Revised: 29.07.2024** **Accepted: 16.09.2024**

Abstract. ***Introduction.*** The prevalence of thyroid pathology, along with the increasing incidence of hepatobiliary diseases, necessitates studying the influence of thyroid status on the "natural history" of liver disease development. ***Objective.*** To evaluate the morphofunctional state of the liver in rats with drug-induced hypo- and hyperthyroidism using a model of chronic fatty hepatosis. ***Materials and methods.*** Models of hyperthyroidism (I) and hypothyroidism (II) were reproduced. Animals in the experimental groups received 15 and 30% fructose solutions instead of drinking water. Decapitation was performed after 45 days. Liver fragments were fixed in 10% neutral formalin for 24 hours. Sections with a thickness of 3–4 μm were prepared and subjected to histological examination. ***Results.*** The vascularization index was highest in group I with a 15% fructose load. Liver sinusoids occupied the maximum area relative to the area of the liver tissue image. With a 30% fructose load against a background of hypo- and hyperthyroidism, the lumen of the sinusoids appeared narrowed. The relative content of connective tissue in the liver parenchyma of the experimental groups did not statistically significantly depend on the thyroid status and the level of fructose load. The inflammatory activity index averaged 5–6 points in all experimental groups. Condition I influenced the volume of infiltration by neutrophils, while dystrophic changes in hepatocytes were more dependent on the level of fructose load. Pronounced granular dystrophy of hepatocytes was revealed in all experimental groups, as well as a decrease in glycogen stores. In group II, already at a 15% fructose load, individual cells were in a state of ballooning degeneration. With a twofold increase in fructose consumption, discomplexation of hepatic plates, granular protein structures, and significant lipid accumulation in the cytoplasm of hepatocytes were observed in groups I and II. ***Conclusions.*** A high level of thyroid hormones significantly affects the indicators of inflammatory and proliferative activity of liver tissue. A low level of thyroid hormones affects the severity of dystrophic changes in hepatocytes. With an increase in fructose load, both with hypo- and hyperthyroidism, hepatocytes undergo intense dystrophic changes.

Keywords: non-alcoholic fatty liver disease, thyroid status, rats

МОРФОФУНКЦИОНАЛЬНОЕ СОСТОЯНИЕ ПЕЧЕНИ КРЫС ПРИ МОДЕЛИРОВАНИИ ЖИРОВОГО ГЕПАТОЗА И ИЗМЕНЕННОМ ТИРЕОИДНОМ СТАТУСЕ

© Альбина Александровна Кондратенко[1], Наталья Дмитриевна Прохорова[1], Александр Александрович Минченко[1], Антон Иванович Полосков[1], Николай Сергоевич Деданишвили[2], Сарнг Саналович Пюрвеев[2], Руслан Иванович Глушаков[1]

[1] Военно-медицинская академия им. С.М. Кирова. 194044, г. Санкт-Петербург, ул. Академика Лебедева, 6
[2] Санкт-Петербургский государственный педиатрический медицинский университет. 194100, г. Санкт-Петербург, ул. Литовская, 2

Контактная информация: Руслан Иванович Глушаков — д.м.н., доцент кафедры фармакологии с курсом клинической фармакологии ифармакоэкономики СПбГПМУ, начальник отдела медико-биологических исследований научно-исследовательского центра ВМедА им. С.М. Кирова. E-mail: glushakoffruslan@yandex.ru ORCID: https://orcid.org/0000-0002-0161-5977 SPIN: 6860-8990

Для цитирования: Кондратенко А.А., Прохорова Н.Д., Минченко А.А., Полосков А.И., Деданишвили Н.С., Пюрвеев С.С., Глушаков Р.И. Морфофункциональное состояние печени крыс при моделировании жирового гепатоза и измененном тиреоидном статусе // Российские биомедицинские исследования. 2024. Т. 9. № 3. С. 5–14. DOI: https://doi.org/10.56871/RBR.2024.58.48.001

Поступила: 20.06.2024 **Одобрена: 29.07.2024** **Принята к печати: 16.09.2024**

Резюме. ***Введение***. Распространенность тиреоидной патологии наряду с повышением инцидентности болезней гепатобилиарной системы определяет необходимость изучения влияния тиреоидного статуса на «естественную историю» развития заболеваний печени. ***Цель*** — оценить морфофункциональное состояние печени крыс при медикаментозно индуцированном гипо- и гипертиреозе на модели хронического жирового гепатоза. ***Материалы и методы.*** Воспроизведены модели гипертиреоза (I) и гипотиреоза (II). Животные экспериментальных групп (крысы) вместо питьевой воды получали 15 и 30% раствор фруктозы. Через 45 суток осуществляли декапитацию. Фрагменты печени фиксировали в 10% нейтральном формалине в течение 24 ч. Изготавливали срезы толщиной 3–4 мкм и проводили гистологическую оценку. ***Результаты.*** Индекс васкуляризации имел наибольшие значения при состоянии I с 15% фруктозной нагрузкой. Синусоиды печени занимали максимальную площадь относительно площади снимка ткани печени. При 30% фруктозной нагрузке на фоне гипо- и гипертиреоза просвет синусоидов выглядел суженным. Относительное содержание соединительной ткани в паренхиме печени опытных групп статистически значимо не зависело от тиреоидного статуса и уровня фруктозной нагрузки. Индекс воспалительной активности в среднем составил 5–6 баллов во всех опытных группах. Состояние I влияло на объем инфильтрации нейтрофильными лейкоцитами, в то время как дистрофические изменения в гепатоцитах сильнее зависели от уровня нагрузки фруктозой. Выявлены выраженная зернистая дистрофия гепатоцитов во всех опытных группах и снижение запасов гликогена. При II — уже при 15% фруктозной нагрузки отдельные клетки находились в состоянии гиалиново-капельной дистрофии. При увеличении потребления фруктозы в два раза наблюдали дискомплексацию печеночных пластинок, зернистые белковые структуры и значительное накопление липидов в цитоплазме гепатоцитов в I и II группах. ***Выводы.*** Высокий уровень тиреоидных гормонов значимо влияет на показатели воспалительной и пролиферативной активности ткани печени. Низкий уровень тиреоидных гормонов влияет на выраженность дистрофических изменений в гепатоцитах. При увеличении фруктозной нагрузки как при гипо-, так и при гипертиреозе гепатоциты подвергаются интенсивным дистрофическим изменениям.

Ключевые слова: неалкогольная жировая болезнь печени, тиреоидный статус, крысы

INTRODUCTION

Thyroid gland (thyroid) diseases are the most common among all endocrine diseases. Hypo- and hyperthyroid conditions are in the first and the third place in the structure of endocrinologic pathology [7, 8], while epidemiologic studies demonstrate that the proportion of subclinical thyroid pathology is several times higher than the official statistics [1, 9].

Thyroid hormones regulate the expression of more than 100 genes, with tissue-specific changes in the gene expression [3, 10]. In turn, the products of thyroid-dependent transcription interact at the level of the whole organism, and the resulting effects determine comorbidity in thyroid pathology [5, 11].

In addition, liver disease is currently a serious threat to public health due to the high prevalence of viral hepatitis, increased alcohol consumption, obesity epidemic and somatic pathology [4, 12, 13].

Thus, the high prevalence of thyroid pathology along with the increased incidence and prevalence of hepatobiliary system disease determines the need to study the influence

of thyroid status on the "natural history" of liver disease development.

AIM

To evaluate the morphofunctional state of rats liver in the drug-induced hypo- and hyperthyroidism on the model of fatty change of liver.

MATERIALS AND METHODS

Discription of the general design of the experimental study. Two series of experimental observations were performed with the inclusion of 90 Wistar rats (Federal State Unitary Enterprise "Rappolovo Laboratory Animal Nursery", Leningrad Region, Russia) aged 30±10 days of both sexes of 3–4 months old, weighing 250±35 g at the beginning of the experiment. The number of laboratory animals was determined by the calculated number of rats necessary to test the statistical hypothesis (Table 1). In each series of experiments, each group of laboratory animals was composed of same-sex individuals. Thus, the experiment was performed on an equal number of males and females. The duration of quarantine (an acclimatization period) for all animals was at least 14 days. During the quarantine, each animal was examined (their behavior and general condition) twice a day (in the morning and evening hours). Laboratory animals suspected of any disease and/or having behavioral changes were excluded from the study during quarantine. Rats within each gender were randomized into three equal groups after the end of quarantine. Randomization of laboratory animals was performed using the closed envelope method. The total duration of the experiment excluding quarantine was 45 days.

Animal housing conditions. The food and the maintenance of laboratory animals were in accordance with the norms of the order of the USSR Ministry of Health 1179 of October 10th, 1983 "Sanitary rules for the arrangement, equipment and maintenance of experimental-biological clinics". Each group of animals was kept with no more than 4–6 same-sex individuals per group and had access to water and food ad libidum.

Drug induction of hypo- and hyperthyroidism. Laboratory animals of the first (I, hyperthyroid, n=32) and the second (II, hypothyroid, n=32) groups were reproduced the model of drug-induced hyperthyroidism and hypothyroidism, respectively, by administration of the investigated substances. The following drugs were administrared: L-thyroxine (dry substance, RUP "Belmedpreparaty", Republic of Belarus) at a dose of 100±10 μg per 100 g of animal body weight once a day, propylthiouracil (dry substance, Merck Selbstmedikation GmbH, Germany) 2.0±0.15 mg per 100 g of animal body weight once a day, intragastrically through atraumatic polyurethane probe daily, starting from the first day of the experiment. After weighing the laboratory animals (at least once every 3 days), the required amount of the tested substance was dissolved in 1.0 ml of indifferent food gelatin gel (Henan Boom Gelatin Co., Ltd., PRC) and administered to individuals of the corresponding group. In order to create the same stress factor, laboratory animals of comparison group III (conditional normothyroidism) also received 1.0 ml of gel intragastrically through a probe.

A model of fatty change of the liver. Animals were divided into equal subgroups within groups I, II and III (hypo-, hyperthyroidism, conditional normothyroidism) in which instead of drinking water rats received 15 and 30% fructose solution throughout the research. In the comparison group animals against the background of induction of drug-induced hypo- and hyperthyroidism received drinking water. 8 laboratory animals were absolute control group.

Blood sampling and withdrawal from the experiment. After 45 days the animals were removed from the experiment

Table 1

Distribution of animals by groups. Number of series of experiments (total number of animals in the group)

Таблица 1

Распределение животных по группам. Количество серий экспериментов (суммарное количество животных в группе)

Экспериментальные группы / Experimental groups	Номер группы / Group number		
	I	II	III
Тиреоидный статус / Thyroid status	Гипертиреоз / Hyperthyroidism	Гипотиреоз / Hypothyroidism	Условный нормотиреоз / Conditional normothyroidism
15% фруктоза в поилке, n / 15% fructose in the drinker, n	12	12	10
30% фруктоза в поилке, n / 30% fructose in the drinker, n	12	12	10
Интактные, n / Intact, n	8	8	6

by ether vapor overdose. Mixed arteriovenous blood was collected by puncture from the heart, transferred into a clean plastic tube and left at room temperature for an hour. Blood was centrifuged for 15 min at 3000 rpm to obtain serum. Serum from each animal was examined individually. The content of transaminases (alanine aminotransferase and aspartate aminotransferase) of serum was analyzed by UV kinetic method without pyridoxal phosphate. Total protein was analyzed by biuret method, total bilirubin was analyzed by diazosulfanil method ("Vector-Best", Russia). The analysis was performed according to the instructions. The levels of the studied hormones were determined by solid-phase enzyme immunoassay using standard kits produced by "NVO Immunotech" for free T_4 (ImmunoFA-T4), free T_3 (ImmunoFA-T3) and TSH (ImmunoFA-TSH).

Morphological study description. Liver fragments were fixed in 10% neutral formalin for 24 h, after which they were embedded in paraffin according to the standard technique. Slices 3–4 microns thick were made and stained with hematoxylin and eosin, Van Gieson's picrofuchsin, Gaidengain's azocarmine, and Periodic Acid — Schiff (PAS) reaction. Histological preparations were analyzed using a light-optical microscope Carl Zeiss Axio Scope A1 at different magnifications. Morphometric evaluation was performed in ImageJ program, plugins segmentation. Five blocks of liver tissue were made from each animal, 5 sections were made from each block, 20 fields of view were examined in each tissue section. A total of 500 measurements of each studied parameter were made. Total relative areas of sinusoidal capillaries (C) and parenchyma (P) were determined. Hepatocyte necrosis was measured in points (0 to 10), the severity of dystrophic changes and inflammatory infiltration in points (0 to 4). Images with an area of 64 000 μm2 (S set) were divided into 80 squares (N node=63). The following parameters were determined: the number of mitoses (NM), the number of bi-nucleated cells (BNC), the number of hepatocytes with one nucleolus in the nucleus (NON), the number of whole nucleated cells (NC), and the number of grid crossing points (GCP) not falling on the slices of hepatocytes and their nuclei.

According to the results of these measurements, the following was calculated: Parenchymatous density index (PD = 1 – GCP/N node). Functional cell mass index (FCM = = (NC/Sset) × PD × 100 000), characterizing parenchymatous-stromal relations in a unit volume of tissue. Nuclear mass index (NM = (NC+BNC)/Sset) × PD × 100,000), which characterizes parenchymatous-stromal relations per unit volume of tissue. Binuclear cell mass index (BCMI = = ((BNK/NC)/Sset) × PD × 100 000), indicating the degree of implementation of the restorative reserves of a unit of liver tissue volume. Mass-mitotic index (MMI = ((NM/NC)/Set) × × PD × 100 000), showing the proliferative activity of the liver tissue volume unit. Functional karyocellular index (FKCI = NM/FCM), which characterizes the amount of nuclear material in a cell per unit volume of liver tissue. The average hepatocyte slice area index (AHSA = (Sset/NC) × PD), which is proportional to its functional activity. Mass index of cells with one nucleolus in the nucleus (MION = ((NON/NC)/SSet) × PP × 100 000), indicating the degree of realization of protein-synthetic function of a unit volume of hepatic tissue. Vascularization index — VI = C/P. Inflammatory activity index (IAI) as the sum of scores of necrosis, dystrophy and inflammatory infiltration severity measurements.

Statistical analysis of the study results. The quantitative characteristics studied in the study were presented as an average value (M±m) or median (Me) with 95% confidence interval boundaries (or 25 and 75% quartiles). The hypothesis of distribution type was tested using the Shapiro–Wilk test. Comparison of data in subgroups was carried out depending on the variant of the distribution of the trait in the groups. The results of morphometry were recorded in tables with subsequent statistical processing of the results in STATISTICA 7.0, modules Nonparametric, ANOVA and Discriminant analysis.

Ethical rules and regulations. The work was conducted in accordance with the ethical principles established by theEuropean Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (adopted in Strasbourg on 18.03.1986 and confirmed in Strasbourg on 15.06.2006) and approved by the Local Ethical Committee.

RESULTS

Thyroid stimulating hormone (TSH) levels in intact animals were: 1.43±0.06 (1.28–1.57) ulU/mL. In model animals with hyperthyroidism the level of TSH in blood was not determined, which is probably due to the peculiarity of sensitivity. In the hypothyroidism model it amounted to 6.24±0.84 (4.67–6.88) ulU/mL. The levels of T4 and T3 free fractions and transaminases in the serum of experimental and intact animals are presented in Table 2.

The vascularization index had the highest values in hyperthyroidism with 15% fructose load (0.24±0.0036). The liver sinusoids occupied the maximum area relative to the liver tissue imaging area (9.1±0.25%). When animals were fed 30% fructose on the background of hypo- and hyperthyroidism, the lumen of sinusoids looked narrowed (Fig. 1).

The relative content of connective tissue in the liver parenchyma of the experimental groups was statistically significantly independent of thyroid status and the level of fructose load ($p < 0.05$) (Fig. 2).

Table 2

Free thyroid hormone and transaminase fractions content M±m (95%CI), p <0.05

Таблица 2

Содержание фракций свободных тиреоидных гормонов и трансаминаз M±m (95%CI), p <0,05

Экспериментальные группы/ Experimental groups	fT4, pmol /L	fT3, pmol/L	ALT, U/L	AST, U/L
Гипертиреоз, 15% фруктоза / Hyperthyroidism, 15% fructose	24,20±1,66 (20,44–27,95)	3,76±0,08 (3,57–3,94)	35,90±0,80 (34,07–37,73)	234,10±29,34 (167,74–300,46)
Гипертиреоз, 30% фруктоза / Hyperthyroidism, 30% fructose.	52,45±3,26 (45,08–59,12)	4,07±0,16 (3,70–4,44)	49,10±1,05 (46,70–51,49)	374,30±3,49 (366,40–382,20)
Гипотиреоз, 15% фруктоза / Hypothyroidism, 15% fructose	8,28±0,16 (7,90–8,65)	5,40±0,13 (5,09–5,70)	32,70±2,05 (28,05–37,35)	150,10±2,32 (143,49–156,71)
Гипотиреоз, 30% фруктоза / Hypothyroidism, 30% fructose	5,26±0,11 (5,02–5,49)	<1,64	54,50±1,49 (51,12–57,87)	320,90±7,34 (304,29–337,51)
Условный нормотиреоз, 15% глюкоза / Conditional normothyroidism, 15% glucose	23,40±1,75 (19,82–23,67)	5,56±0,16 (4,57–5,98)	35,70±2,15 (28,05–37,35)	140,10±2,46 (143,49–156,71)
Условный нормотиреоз, 30% глюкоза / Conditional normothyroidism, 30% glucose	24,79±2,09 (18,29–24,38)	5,47±0,28 (3,98–5,84)	44,60±1,49 (41,16–52,63)	265,70±5,34 (227,43–287,11)
Интактный контроль / Intact control	20,74±0,77 (18,99–22,49)	5,78±0,08 (5,59–5,96)	27,60±1,15 (24,98–30,22)	120,50±1,91 (116,18–124,82)

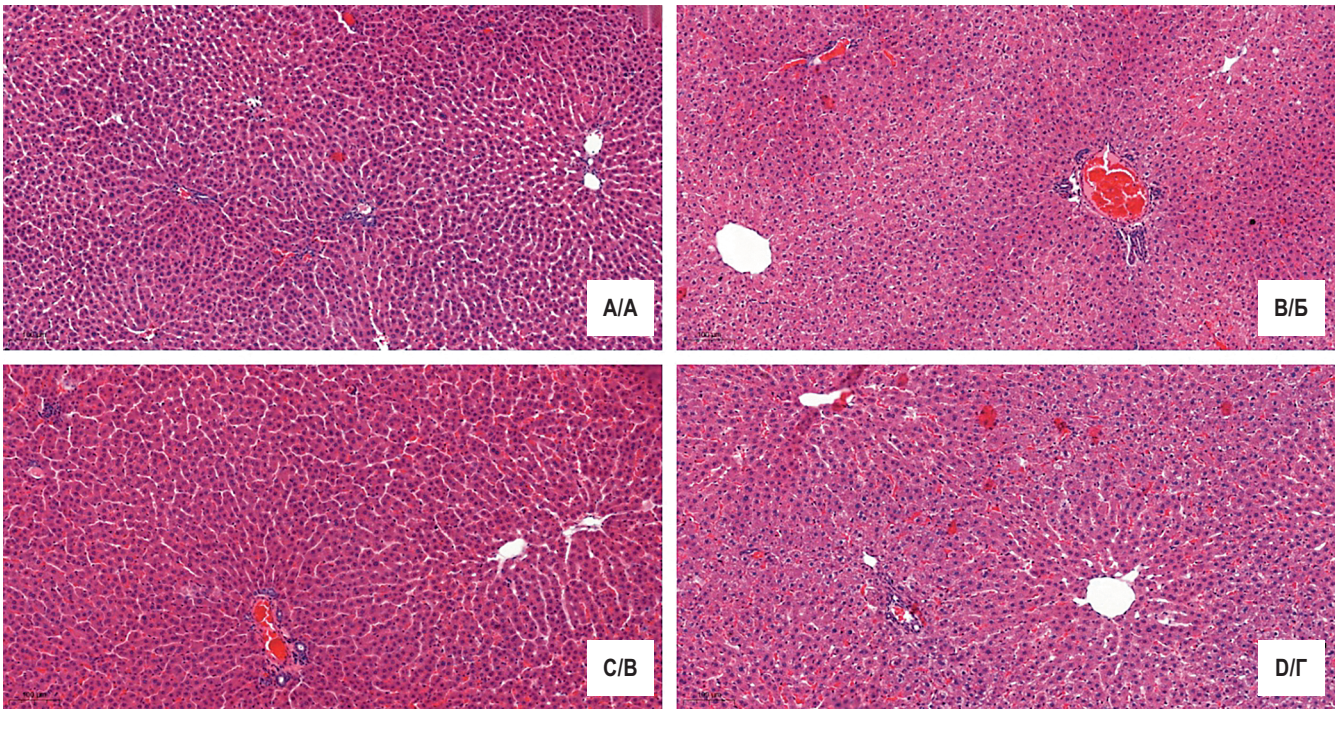

Fig. 1. **Liver tissue of rats of experimental groups: A — received 15% fructose in the drink on hypothyroidism background; B — received 30% fructose in the drink on hypothyroidism background; C — received 15% fructose in the drink on the background of hyperthyroidism; D — received 30% fructose in the drinker on the background of hyperthyroidism. Hematoxylin and eosin staining, ×100**

Рис. 1. **Ткань печени крыс экспериментальных групп: А — получали 15% фруктозу в поилке на фоне гипотиреоза; Б — получали 30% фруктозу в поилке на фоне гипотиреоза; В — получали 15% фруктозу в поилке на фоне гипертиреоза; Г — получали 30% фруктозу в поилке на фоне гипертиреоза. Окраска гематоксилин и эозин, ×100**

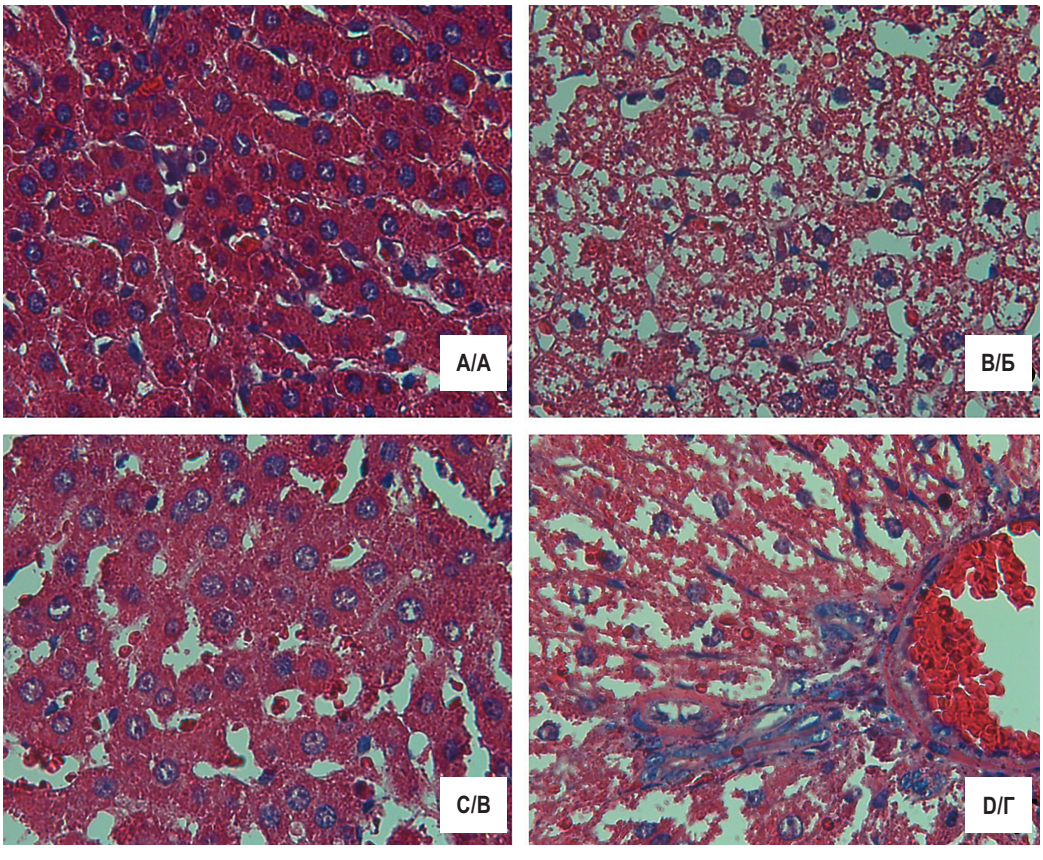

Fig. 2. **Liver tissue of rats of experimental groups: A — received 15% fructose in the drink on hypothyroidism background; B — received 30% fructose in the drink on hypothyroidism background; C — received 15% fructose in the drink on the background of hyperthyroidism; D — received 30% fructose in the drinker on the background of hyperthyroidism. Azocarmine staining by Gaidengain, ×400**

Рис. 2. **Ткань печени крыс экспериментальных групп: А — получали 15% фруктозу в поилке на фоне гипотиреоза; Б — получали 30% фруктозу в поилке на фоне гипотиреоза; В — получали 15% фруктозу в поилке на фоне гипертиреоза; Г — получали 30% фруктозу в поилке на фоне гипертиреоза. Окраска азокармином по Гайденгайну, ×400**

The index of inflammatory activity averaged 5–6 points in all experimental groups and statistically significantly differed from this index in intact animals. The state of hyperthyroidism most significantly affected the volume of infiltration by neutrophilic leukocytes, while dystrophic changes in hepatocytes were more strongly dependent on the level of fructose loading ($p < 0.005$). Azocarmine staining of slices according to Gaidengain (Fig. 2) and Periodic Acid — Schiff (PAS) reaction reaction (Fig. 3) revealed pronounced granular dystrophy of hepatocytes in all experimental groups and decreased glycogen stores. In the hypothyroid state, already at 15% fructose load individual cells were in a state of hyaline granular dystrophy. Liver plate dyscomplexation, granular protein structures and significant lipid accumulation in the cytoplasm of hepatocytes in hypo- and hyperthyroidism were observed with doubled fructose intake.

The indices of nuclear mass, BCMI, MMI and FKCI in the state of hyperthyroidism were statistically significantly higher than the values in hypothyroidism regardless of the level of fructose load.

AHSA when drinking 30% fructose instead of drinking water in hypothyroidism state was the highest (345.04±1.40). The total relative number of cells containing single nucleoli was maximum in hyperthyroidism irrespective of the level of fructose load (0.113±0.00046).

As a result of stepwise selection, all studied morphometric parameters were statistically significantly informative by Fisher's F-criterion. The BCMI, FKCI and MION signs changed most significantly. The changes in IAI and AHSA parameters were less pronounced (Table 3).

DISCUSSION

Our reproduced model of chronic liver damage associated with excessive fructose consumption leads to pathologic

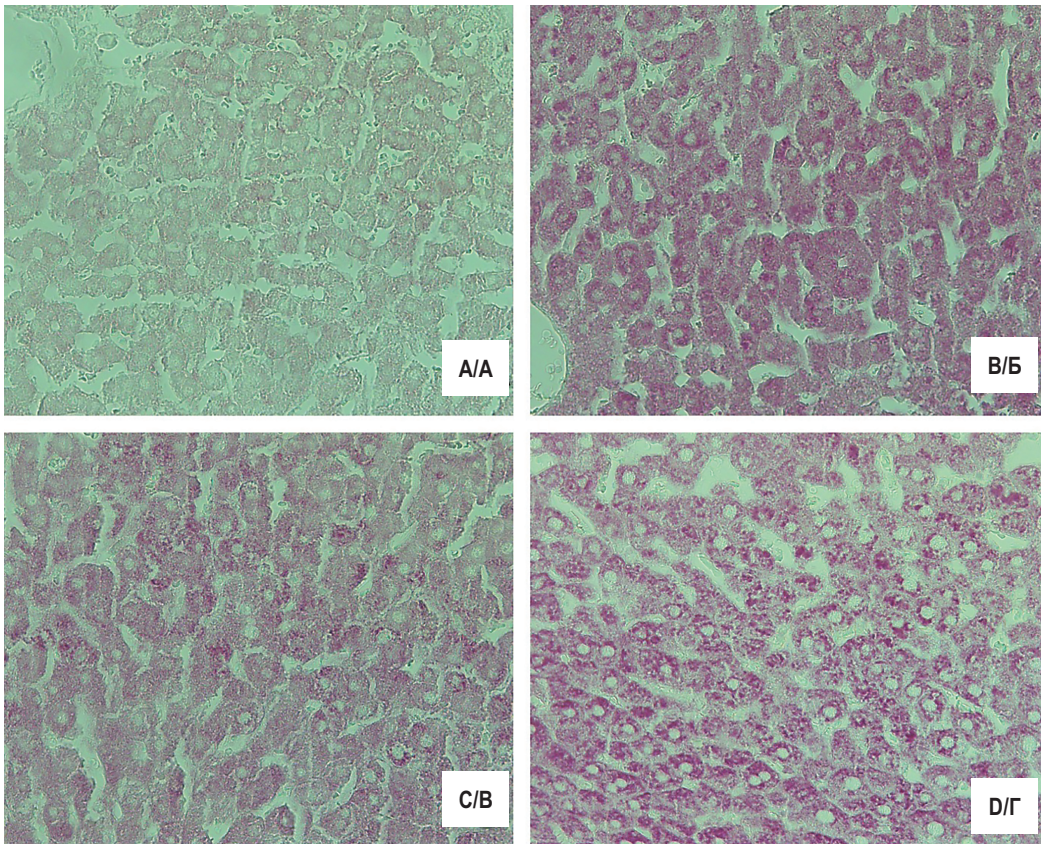

Fig. 3. **Liver tissue of rats of experimental groups: A — received 15% fructose in the drink on hypothyroidism background; B — received 30% fructose in the drink on the background of hypothyroidism; C — received 15% fructose in the drink on the background of hyperthyroidism; D — received 30% fructose in the drink on the background of hyperthyroidism. SHIC reaction, ×400**

Рис. 3. **Ткань печени крыс экспериментальных групп: А — получали 15% фруктозу в поилке на фоне гипотиреоза; Б — получали 30% фруктозу в поилке на фоне гипотиреоза; В — получали 15% фруктозу в поилке на фоне гипертиреоза; Г — получали 30% фруктозу в поилке на фоне гипертиреоза. ШИК-реакция, ×400**

Table 3

Morphometry of liver tissue of intact animals and rats of experimental groups, M±m (95% CI), p<0.005, M±m (95% CI), p <0,005

Таблица 3

Морфометрия ткани печени интактных животных и крыс опытных групп M±m (95% CI), p <0,005, M±m (95% CI), p <0,005

Морфометрические показатели / Morphometric indices	Гипертиреоз / Hyperthyroidism		Гипотиреоз / Hypothyroidism		Условный нормотиреоз / Conditional normothyroidism		Интактные / Intact
	15% фруктоза / 15% fructose	30% фруктоза / 30% fructose	15% фруктоза / 15% fructose	30% фруктоза / 30% fructose	15% фруктоза / 15% fructose	30% фруктоза / 30% fructose	
ИВА / IVA	5,96±0,045 (4,61-–6,65)	6,18±0,04 (5,60–6,63)	5,42±0,04 (4,61–6,64)	6,10±0,03 (5,57–6,83)	2,46±0,16 (2,21–3,09)	4,35±0,05 (3,96–4,75)	0,60±0,035 (0,30–0,65)
ИМДК / IMDC	0,22±0,005 (0,21–0,23)	0,23±0,011 (0,20–0,25)	0,16±0,008 (0,17–0,21)	0,15±0,011 (0,16–0,21)	0,15±0,008 (0,17–0,21)	0,17±0,009 (0,17–0,22)	0,03±0,002 (0,02–0,03)
ФККИ / FCCI	1,19±0,004 (1,18–1,20)	1,21±0,009 (1,18–1,23)	1,17±0,008 (1,15–1,19)	1,17±0,009 (1,15–1,19)	1,16±0,008 (1,15–1,19)	1,17±0,017 (1,15–1,18)	1,16±0,008 (1,15–1,17)
СПСГ / SPSG	308,22±5,58 (296,07–320,37)	296,10±8,20 (278,23–313,97)	287,90±5,38 (276,18–299,62)	288,72±4,87 (278,00–299,44)	280,90±4,48 (274,28–289,12)	282,60±6,12 (277,58–294,37)	279,11±4,20 (274,23–309,07)
ИМОЯ / IMOJA	0,11±0,003 (0,09–0,15)	0,09±0,005 (0,06–0,13)	0,06±0,005 (0,05–0,09)	0,08±0,003 (0,06–0,010)	0,06±0,005 (0,05–0,09)	0,06±0,005 (0,05–0,09)	0,05±0,003 (0,04–0,09)

transformation and dystrophy of hepatocytes. Insufficiency of adenosine triphosphate (ATP) synthesis and decreased redox potential leads to mitochondrial dysfunction and altered fat and carbohydrate metabolism [14]. Presumably, the activity of hydrolytic enzymes of lysosomes leads to coagulation of cytoplasm proteins with the appearance of cellular inclusions in the form of "grains". When fructose load is doubled, the excessive amount of carbohydrates is transformed into triacylglycerides, damaging hepatocytes [15], which is laboratory expressed in a significant increase in the level of serum transaminases.

Modern knowledge about the mechanisms of action of iodothyronines has been extended to the understanding of proangiogenic activation by iodothyronines due to non-genomic effects arising from interaction with $\alpha_V\beta3$ integrin, and the quantitative effect of angiogenesis activation at supraphysiological concentrations of iodothyronines is comparable to the effect of vascular endothelial growth factor and fibroblast growth factor [6, 16]. The immunomodulatory effects of T_4 have also been studied, which consist in an increase in the expression of tissue-specific proinflammatory genes, while a reduced cytotoxic activity of NK-cells and a decrease in chemotaxis and macrophage phagocytosis are noted, which at the systemic level leads to the restoration of the balance between pro- and anti-inflammatory factors [17]. In our study, the index of inflammatory activity had maximum values in the hyperthyroid state, which agrees with the data of other authors on the proinflammatory properties of iodothyronines.

Our study also demonstrates that the degree of realization of regenerative reserves and proliferative activity were higher in the state of hyperthyroidism, as evidenced by the indices of the amount of nuclear material per unit volume of liver tissue and the index of the proportion of hepatocytes with a single nucleus in their nucleus. A significant part of tumor cells in the liver of transgenic mice contain a single nucleus in the nucleus. According to various studies, thyroid hormones are potent mitogens of hepatocytes, activating the E2F family of transcription factors. It leads to overexpression of cell cycle inducers — cyclins and cyclin-dependent kinases (CDK) and promotes the transition of hepatocytes from G1 to S-phase. Thyroid hormones increase the levels of cyclins A, D1 and E and the activity of complexes of cyclin A with cyclin-dependent kinase 2 (CDK2) and cyclin D1-CDK4 and decrease the levels of CDK inhibitors p16 and p27. Expression of vascular endothelial growth factor (VEGF) and nuclear antigen Ki-67 in the liver against the background of thyroid hormone preparations increases [16]. However, this increase in proliferative activity is transient and in long-term hyperthyroidism leads to a decrease in the proliferative potential of functional tissue and the development of fibrosis [19]. We have previously demonstrated that long-term hyperthyroidism in reproductive organs leads to pronounced fibrotic changes, while hypothyroidism leads to fatty dystrophy [20].

Discussing the relationship between the functional activity of the liver and the thyroid gland, it should be noted that osteopontin secretion is induced by polarization of M1-fraction of macrophages, which due to paracrine mechanisms can inhibit the expression of TRb-receptor in hepatocytes, on the one hand, suppressing the action of thyroid hormones and, accordingly, aggravating lipid deposition in the liver, on the other hand, compensatory increasing the level of TSH in serum. Elevated TSH levels promote osteopontin secretion by the M1 fraction of macrophages. This study demonstrates a positive feedback between the thyroid gland and the liver, possibly playing an important role in maintaining and enhancing the pathologic process of nonalcoholic fatty liver disease [2, 18].

Given the different effector actions of thyroid hormones after interaction with different isoforms of TRa and TRb nuclear receptors, including with respect to carbohydrate and lipid metabolism in the liver, future treatment strategies are aimed at weakening the effects of TRa stimulation and enhancing the effects of TRb targeting. Currently, about 10 drugs have been patented whose affinity to TRb is 10–40 times higher than to TRa. At the same time, experimental data confirm the efficacy of selective TRb-thyromimetic action in the treatment of experimental non-alcoholic fatty liver disease [19]. The altered thyroid status modulates the transformation of functional liver tissue in two directions: toward the enhancement of dystrophic changes and fatty transformation in hypothyroidism and toward the activation of inflammation and fibrotic changes in hyperthyroidism.

CONCLUSION

1. High level of thyroid hormones most significantly affects the indices of inflammatory and proliferative activity of liver tissue.

2. Low level of thyroid hormones affects the severity of dystrophic changes in hepatocytes.

3. In the process of fructose load increase both in hypo- and hyperthyroidism hepatocytes undergo intensive dystrophic changes.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

Experiments with animals. The work was carried out in accordance with the ethical principles established by the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (adopted in Strasbourg on March 18, 1986 and confirmed in Strasbourg on June 15, 2006), and approved by the Local Ethics Committee.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Эксперименты с животными. Работа проведена в соответствии с этическими принципами, установленными Европейской конвенцией по защите позвоночных животных, используемых для экспериментальных и других научных целей (принятой в Страсбурге 18.03.1986 г. и подтвержденной в Страсбурге 15.06.2006 г.), и одобрена Локальным этическим комитетом.

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DOI: 10.56871/RBR.2024.67.22.002
UDC 616.13-004.6-005.4+617.58-005+616-089.811

EXTRAANATOMIC CROSSOVER AUTOVENOUS BYPASS — RECONSTRUCTION OF THE RESERVE IN PATIENTS WITH A HIGH RISK OF AMPUTATION AND LOW LIFE EXPECTANCY OR AN ALTERNATIVE TO TRADITIONAL TREATMENT?

© Alexey G. Borisov[1], Alisa V. Atmadzas[1], Kirill A. Atmadzas[1], Nikita N. Gruzdev[1], Vitalyi B. Kozhevnikov[1, 3], Arshed A. Kuchay[1], Aleksandr N. Lipin[1, 2], Anton G. Orlov[1], Sofya E. Pak[3], Roman S. Sobolev[1], Yanis P. Eminov[1], Irina M. Khokhlova[1]

[1] Limb Salvage Center, City Hospital No. 14. 19/9 Kosinov str., Saint Petersburg 198099 Russian Federation
[2] Military Medical Academy named after S.M. Kirov. 6 Akademician Lebedev str., Saint Petersburg 194044 Russian Federation
[3] North-Western State Medical University named after I.I. Mechnikov. 41 Kirochnaya str., Saint Petersburg 191015 Russian Federation

Contact information: Alexey G. Borisov — Cardiovascular Surgeon. E-mail: borisov_spb@yahoo.com ORCID: https://orcid.org/0009-0003-3900-2652 SPIN: 8049-4107

For citation: Borisov AG, Atmadzas AV, Atmadzas KA, Gruzdev NN, Kozhevnikov VB, Kuchay AA, Lipin AN, Orlov AG, Pak SE, Sobolev RS, Eminov YaP, Khokhlova IM. Extraanatomic crossover autovenous bypass — reconstruction of the reserve in patients with a high risk of amputation and low life expectancy or an alternative to traditional treatment? Russian Biomedical Research. 2024;9(3):15–20.
DOI: https://doi.org/10.56871/RBR.2024.67.22.002

Received: 24.06.2024 **Revised: 02.08.2024** **Accepted: 16.09.2024**

Abstract. Introducion. Critical limb threatening ischemia is worst peripheral artery disease with high percent of morbidity and disability. ***Purpose of the study*** — to evaluate early (complications and major adverse events) and long-term (patency, limb salvage, survival) outcomes in patients with chronical limb threatening ischemia who underwent crossover autovenous bypass surgery. ***Material and method.*** A retrospective analysis of the early and long-term results of observation of 28 patients who underwent cross-bypass surgery performed in 2017–2023 was carried out. 100% of bypass operations were performed with autovenous material. High comorbidity (coronary artery disease, arterial hypertension, dyslipidemia, history of myocardial infarction, history of acute stroke, cardiac arrhythmias, diabetes mellitus, obstructive bronchitis, anemia, obesity). Follow-up is 12 months. ***Results.*** Early postoperative complications were: 14.3% — wound complications, 3.6% — bleeding, 7.2% — bypass thrombosis, 3.6% — acute cerebrovascular disturbance, 17.9% — high limb amputation (in 4 of 5 observations, revascularization was performed to reduce the level of amputation), 3.6% — death. Results after 12 months were: bypass patency — 82.1%, limb salvage — 71.4%, survival — 89.3%. There were no cases in which critical ischemia of the healthy lower limb developed. ***Conclusion.*** Crossover autovenous bypass can be considered by a vascular surgeon both as a reserve option for redo-surgery on the arteries of the lower extremities and as an alternative to traditional anatomical reconstructions. This study demonstrates the low complication rate and good long-term patency of this reconstructions.

Keywords: atherosclerosis, chronic limb threatening ischemia, extraanatomic bypass, autogenous vein bypass

ПЕРЕКРЕСТНЫЙ АУТОВЕНОЗНЫЙ ШУНТ — РЕКОНСТРУКЦИЯ РЕЗЕРВА У ПАЦИЕНТОВ С ВЫСОКИМ РИСКОМ АМПУТАЦИИ И НЕВЫСОКОЙ ОЖИДАЕМОЙ ПРОДОЛЖИТЕЛЬНОСТЬЮ ЖИЗНИ ИЛИ АЛЬТЕРНАТИВА ТРАДИЦИОННЫМ ОПЕРАЦИЯМ?

© Алексей Геннадьевич Борисов[1], Алиса Владимировна Атмадзас[1], Кирилл Александрович Атмадзас[1], Никита Николаевич Груздев[1], Виталий Борисович Кожевников[1, 3], Аршед Ахмад Кучай[1], Александр Николаевич Липин[1, 2], Антон Георгиевич Орлов[1], Софья Эдуардовна Пак[3], Роман Сергеевич Соболев[1], Янис Павлович Эминов[1], Ирина Михайловна Хохлова[1]

[1] Городская больница № 14. 198099, г. Санкт-Петербург, ул. Косинова, 19/9
[2] Военно-медицинская академия им. С.М. Кирова. 194044, г. Санкт-Петербург, ул. Академика Лебедева, 6
[3] Северо-Западный государственный медицинский университет имени И.И. Мечникова. 191015, г. Санкт-Петербург, ул. Кирочная, 41

Контактная информация: Алексей Геннадьевич Борисов — врач сердечно-сосудистый хирург. E-mail: borisov_spb@yahoo.com
ORCID: https://orcid.org/0009-0003-3900-2652 SPIN: 8049-4107

Для цитирования: Борисов А.Г., Атмадзас А.В., Атмадзас К.А., Груздев Н.Н., Кожевников В.Б., Кучай А.А., Липин А.Н., Орлов А.Г., Пак С.Э., Соболев Р.С., Эминов Я.П., Хохлова И.М. Перекрестный аутовенозный шунт — реконструкция резерва у пациентов с высоким риском ампутации и невысокой ожидаемой продолжительностью жизни или альтернатива традиционным операциям? // Российские биомедицинские исследования. 2024. Т. 9. № 3. С. 15–20. DOI: https://doi.org/10.56871/RBR.2024.67.22.002

Поступила: 24.06.2024 **Одобрена: 02.08.2024** **Принята к печати: 16.09.2024**

Резюме. ***Введение.*** Критическая ишемия нижних конечностей — крайне тяжелое проявление заболеваний периферических артерий, сопровождающееся высоким уровнем инвалидизации и летальности ***Цель исследования*** — оценить ранние (осложнения и неблагоприятные события) и отдаленные (проходимость, сохранение конечности, выживаемость) результаты у пациентов с критической ишемией нижней конечности, которым были выполнены перекрестные аутовенозные шунтирующие операции. ***Материалы и методы исследования.*** Проведен ретроспективный анализ ранних и отдаленных результатов наблюдения 28 пациентов, перенесших перекрестные шунтирования, проведенных в 2017–2023 гг. 100% шунтирующих операций выполнены аутовенозным материалом. Пациенты коморбидны (ишемическая болезнь сердца, артериальная гипертензия, дислипидемия, инфаркт миокарда в анамнезе, острое нарушение мозгового кровообращения в анамнезе, нарушения ритма сердца, сахарный диабет, хроническая обструктивная болезнь легких, анемия, ожирение). Период наблюдения — 12 месяцев. ***Результаты.*** Ранние послеоперационные осложнения: 14,3% — раневые осложнения, 3,6% — кровотечения, 7,2% — тромбоз шунта, 3,6% — острое нарушение мозгового кровообращения, 17,9% — высокая ампутация конечности (в 4 из 5 наблюдений реваскуляризация была выполнена с целью снижения уровня ампутации), 3,6% — летальный исход. Результаты через 12 месяцев: проходимость шунта — 82,1%, сохранение конечности — 71,4%, выживаемость — 89,3%. Наблюдений, при которых развилась критическая ишемия здоровой нижней конечности, не выявлено. ***Заключение.*** Перекрестное аутовенозное шунтирование может рассматриваться сосудистым хирургом и как операция резерва при повторных реконструктивных вмешательствах на артериях нижних конечностей, и как альтернатива традиционным анатомическим реконструкциям. Данное исследование демонстрирует низкую частоту осложнений и хорошую отдаленную проходимость таких реконструкций.

Ключевые слова: атеросклероз, критическая ишемия нижней конечности, экстраанатомическое шунтирование, аутовенозное шунтирование

INTRODUCTION

Chronic limb threatening ischemia (CLTI) is an extremely severe manifestation of peripheral arterial disease. Due to unfavorable prognosis (according to literature data, mortality and high amputation within a year from the disease manifestation amounted to 22%, and in the distant period — quite disappointing results: high limb amputation within 4 years is up to 67.3%, the risk of patients' death within 4 years is up to 63.5%), this condition is singled out by researchers and clinicians as a separate nosology [1]. CLTI patients often have multilevel lesions of lower limb arteries, including prolonged occlusion of iliac arteries [1, 2]. The absolute majority of patients with CLTI are polymorbid and, in addition to multifocal atherosclerosis, have concomitant diseases of cardiovascular, respiratory, endocrine systems, and cancer is common [1, 2, 10]. Most studies recommend anatomical reconstructions - balloon angioplasty with/without stenting of iliac arteries, aorto/iliac-femoral bypass [1–5, 11, 12] in case of occlusion of iliac arteries. Endovascular option in the treatment of patients with multilevel lesions is not always available due to pronounced calcinosis and prolonged occlusion of the arteria. The open anatomic revascularization is often associated with high risks of adverse effects and long duration of intervention, especially in patients with previous reconstructions in this area. The

presence of extensive scarring in the area of surgery, the presence of a possible infectious focus and synthetic prosthesis in the area of future reconstruction, and possible previous ligation of native arteries may also be factors that require caution when performing anatomic reconstructions. Due to comorbidity and high perioperative risk, even in studies recommending anatomic reconstruction in the aorto-iliac segment, the possibility of extraanatomic bypass for patients in this group is preserved and recommended [1–5, 13, 14]. There are also studies that suggest crossover bypass surgery as primary surgery for unilateral occlusion of the iliac arteries [6-8, 15], including intermittent claudication [9, 16].

AIM

To evaluate early (complications and adverse events) and long-term (patency, limb preservation, survival) outcomes in patients with critical lower extremity ischemia who underwent crossover bypass surgery.

MATERIALS AND METHODS

A retrospective analysis of early and long-term follow-up results of 28 patients who underwent crossover bypasses in 2017–2023 in the "St. Petersburg State Budgetary Healthcare Institution "City Hospital No. 14" was performed.

The study was performed in accordance with the standards of good clinical practice and the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients before inclusion in the study.

Inclusion criteria: patients who underwent extraanatomic (crossover) bypass by autologous vein to bypass iliac artery occlusion for the treatment of CLTI (100% of patients with trophic defects of ischemic genesis).

Exclusion criteria: patients whose contact was lost immediately after discharge from the hospital.

Characteristics of the group: an average age was 63.9 years. There was 3 women (10.7%) and 25 men (89.3%).

The average period of hospitalization was 41 days, which was due to the need to treat trophic changes in the lower limb suffering from CLTI.

Concomitant pathology: coronary heart disease (CHD) (100%), arterial hypertension (95.7%), dyslipidemia (80.4%), history of myocardial infarction (28.6%), history of acute cerebral circulatory failure (25%), cardiac rhythm disorders (50%), diabetes mellitus (25%), chronic obstructive pulmonary disease (COPD) (78.2%), anemia (42.9%), obesity (42.9%).

Full perfusion of the two lower limbs in these patients was ensured in most cases due to passable (without hemodynamically significant stenoses) iliac arteries on the limb-donor of the inflow artery, which at the time of the study had no symptoms of peripheral arterial disease, or anamnestically there were indications of a mild degree of intermittent claudication (painless walking for a distance of 100 meters or more). In one case (3.6%) a passable aorto-bifemoral shunt was used, in one case (3.6%) balloon angioplasty of the iliac arteries was preventively performed on the healthy limb in order to perfuse two limbs from one lumen of the iliac arteries if there was an indication of ligation of the iliac arteries of the limb suffering from CLTI.

The level of proximal anastomosis (inflow artery for the shunt), N (%) — common femoral artery — 23 (82.1%), deep femoral artery — 2 (7.1%), superficial femoral artery — 2 (7.1%), functioning branche of the aorto-bifemoral shunt — 1 (3.6%). Level of distal anastomosis (outflow artery for the shunt), N (%) — contralateral common femoral artery — 6 (21.4%), contralateral deep femoral artery — 12 (42.8%), contralateral superficial femoral artery — 4 (14, 3%), contralateral poplitea artery — 3 (10.7%), contralateral posterior tibial artery — 1 (3.6%), contralateral anterior tibial artery — 1 (3.6%), contralateral femoral-popliteal bypass — 2 (7.1%).

15 patients (53.6%) had a history of lower limb arterial interventions for CLTI, of which 10 (35.7% of the total group) underwent aorto-femoral bifurcation or linear bypass with a synthetic prosthesis.

100% of the bypass surgeries were performed with autovenous. In 8 cases (28.6%) the in situ vein technique was used, in the remaining 20 cases (71.4%) a reversed vein was used. Autovenous material used: 21 (75%) — trunk of the great saphenous vein of the limb suffering from CLTI used, 4 (14.3%) — small saphenous vein used, 2 (7.1%) — trunk of the great saphenous vein of the contralateral lower limb used.

13 patients (46.4%) required necrectomy or small amputations during hospitalization. The peculiarity of this group of patients was the high frequency of "non-preserved" feet — in 4 cases (14.3%) due to the lack of possibility of preserving a supportable foot or high risk of sepsis development (the decision was made by a consilium consisting of a multidisciplinary group of specialists) a cross bypass operation was performed to reduce the amputation level. Thus, performing amputation at the level of the tibia in such observations was a success of surgical intervention (in 100% of cases, technical success was achieved — it was possible to heal the wounds of the stump of the tibia with primary

tension). A clinical example of such a foot is presented in Figure 1.

Preoperative examination: a search for autovenous material was performed sonographically. An assessment of steno-occlusive arterial lesions and choice of the method of surgical intervention was performed according to the data of direct subtractive angiography and/or computed tomography with angiocontrast.

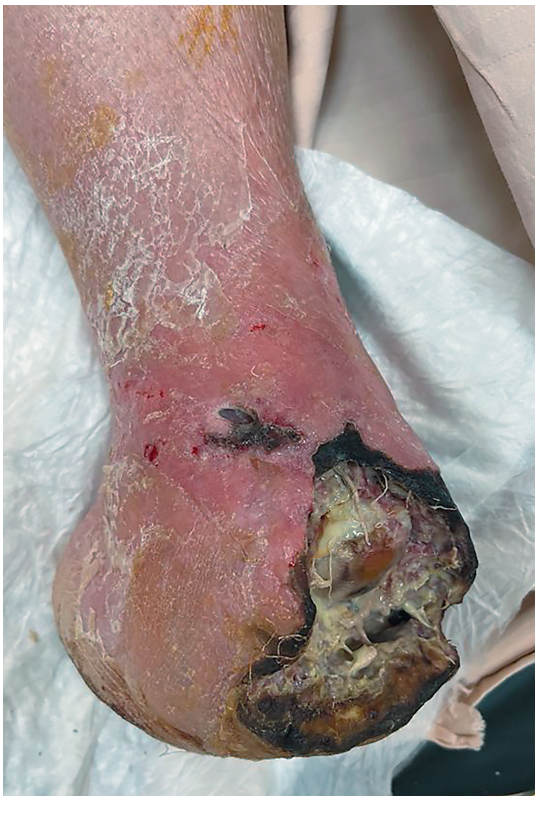

Fig. 1. An example of a foot requiring amputation. Patient K., 53 years old, admitted with wet gangrene of the distal parts of the left foot; at the time of admission, sanitation of the necrotic lesion was performed, the possibility of preserving a weight-bearing foot was lost (deep and extensive tissue necrosis, exposure of the articular surfaces of the talus and calcaneus). 6 days after foot resection, revascularization surgery was performed. The photo shows a foot wound on the first day after revascularization. In the presented clinical case, the patient managed to save his knee joint

Рис. 1. Пример стопы, требующей ампутации. Пациент К., 53 года, поступил с влажной гангреной дистальных отделов левой стопы, при поступлении выполнена санация некротического очага, возможность сохранения опороспособной стопы потеряна (глубокий и обширный некроз тканей, оголение суставных поверхностей таранной и пяточной костей). Спустя 6 суток после резекции стопы выполнена реваскуляризирующая операция. На фото представлена рана стопы в первые сутки после реваскуляризации. В представленном клиническом случае пациенту удалось сохранить коленный сустав

Postoperative therapy: within three days — low molecular weight heparins (enoxaparin) administered subcutaneously in a prophylactic dose, further — acetylsalicylic acid 100 mg + rivaroxaban 5 mg daily get per os during the life.

RESULTS AND DISCUSSION

Complications and undesirable effects detected in the early postoperative period (within 30 days) are presented in Table 1.

The long-term results (evaluated after 12 months) demonstrate that crossed shunts have good patency rates in the long-term period. After discharge from the hospital, only one shunt occlusion was detected during one year of follow-up (Table 2).

Satisfactory indices of distant patency, limb preservation, and survival rates after extraanatomic bypasses have been shown, indicating their effectiveness. It should be noted that during the study there were no cases of critical ischemia or amputation of the lower limb, on the side of which the driving anastomosis of the shunt was performed (healthy limb, donor limb) — a factor that most often causes fear of cross-reconstructions in vascular surgeons.

CONCLUSION

1. Cross-over autovenous bypass may be considered by the vascular surgeon as a backup operation for repeated reconstructive interventions on lower limb arteries or as an alternative to traditional anatomic reconstructions.

2. This study demonstrates a low complication rate and good long-term patency of such reconstructions.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

Consent for publication. Written consent was obtained from the patient for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования

Table 1

Early postoperative complications

Таблица 1

Ранние послеоперационные осложнения

Осложнение/неблагоприятное событие / Complication/adverse event	Число наблюдений / Number of observations	%
Раневые осложнения (лимфорея, нагноение раны, гематома) / Wound complications (lymphorrhea, wound suppuration, hematoma)	4	14,3
Большие кровотечения / Major bleeding	1	3,6
Тромбоз шунта / Shunt thrombosis	2	7,2
Острое нарушение мозгового кровообращения / Acute cerebrovascular accident	1	3,6
Инфаркт миокарда / Myocardial infarction	0	0
Тромбоэмболия легочной артерии / Pulmonary embolism	0	0
Высокая ампутация нижней конечности, страдающей критической ишемией, из них — случаи, при которых показанием к шунтирующей операции служило снижение уровня высокой ампутации / High amputation of the lower limb suffering from critical ischemia, including cases in which the indication for bypass surgery was to reduce the level of high amputation	5 4	17,9 14,3
Высокая ампутация нижней конечности, со стороны которой формировался приводящий анастомоз, не страдающей критической ишемией / High amputation of the lower limb, from which the adducting anastomosis was formed, not suffering from critical ischemia	0	0
Летальный исход / Death	1	3,6

Table 2

Long term results after 12 months

Таблица 2

Отдаленные результаты через 12 месяцев

Фактор / Factor	Число наблюдений / Number of observations	%
Проходимость шунта / Shunt patency	22	82,1
Сохранение конечности, к которой была выполнена шунтирующая операция от контралатеральной нижней конечности / Preservation of the limb to which bypass surgery was performed from the contralateral lower limb	20	71,4
Сохранение контралатеральной нижней конечности (из числа пациентов, достигнувших периода наблюдения) / Preservation of the contralateral lower limb (among patients who reached the follow-up period)	25	100
Выживаемость / Survival	25	89,3

и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Информированное согласие на публикацию. Авторы получили письменное согласие пациентов на публикацию медицинских данных.

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DOI: 10.56871/RBR.2024.91.11.003
UDC 613.84+577.112.386.2+575.174+577.164.1(470.11)

THE EFFECT OF TOBACCO SMOKING ON HOMOCYSTEINE METABOLISM IN HEALTHY NICOTINE-DEPENDENT PEOPLE LIVING IN THE ARKHANGELSK REGION

© Alexandra S. Vorontsova, Nadezda A. Vorobyeva, Alyona I. Vorobyeva, Elizaveta Yu. Melnichuk

Northern State Medical University. 51 Troitsky Ave., Arkhangelsk 163000 Russian Federation

Contact information: Alexandra S. Vorontsova — Assistant at the Department of Clinical Pharmacology and Pharmacotherapy.
E-mail: baklab1gkb@yandex.ru ORCID: https://orcid.org/0000-0003-3643-0515 SPIN: 1495-7061

For citation: Vorontsova AS, Vorobyeva NA, Vorobyeva AI, Melnichuk EYu. The effect of tobacco smoking on homocysteine metabolism in healthy nicotine-dependent people living in the Arkhangelsk Region. Russian Biomedical Research. 2024;9(3):21–27.
DOI: https://doi.org/10.56871/RBR.2024.91.11.003

Received: 30.05.2024 **Revised: 01.08.2024** **Accepted: 16.09.2024**

Abstract. ***Introduction.*** Tobacco smoking remains a global medical, social and economic problem worldwide. One of the pathological effects of nicotine and tobacco smoke components is the suppression of folate metabolism and a decrease in B vitamins in the human body, which, together, entails a violation of homocysteine metabolism and leads to endothelial dysfunction and the development of adverse vascular events. ***The purpose of the study*** — to identify the effect of tobacco smoking and the concentration of vitamins (B_6, B_9, B_{12}) on homocysteine metabolism in healthy young volunteers. ***Materials and methods.*** The study was carried out on a sample of ethnic Russians living in the city of Arkhangelsk. 259 healthy volunteers of both sexes of young age from 18 to 32 years old were included, a survey of participants was conducted, the levels of folic acid, vitamin B_6 and B_{12}, homocysteine were analyzed by immunological method. Statistical processing of the data obtained during the study was carried out by methods of descriptive and analytical statistics using the R 4.2.3 programming language in the Rstudio 1.2.5019 program. ***Results.*** There were no statistically significant differences in all defined indicators between the group of smokers and non-smokers. But the average homocysteine level in the smoker group is higher (Iu=8.00) than in the non-smoker group (Iu=7.00). At the same time, the participants who smoked cigarettes had higher homocysteine levels (Iu=8.6) than those who smoked electronic cigarettes (Iu=7.2). The average serum folic acid concentration in smokers is lower (Iu=4.00) than in non-smokers (Iu=6.5). In the group of smokers, folate deficiency was registered in 13 participants. Folic acid deficiency was not detected in the non-smoking group. An inverse relationship of average strength between the level of homocysteine and the concentration of folic acid in the blood serum ($p < 0.01$) was revealed. ***Conclusion.*** In this study, the relationship between smoking and homocysteine levels was not revealed, however, the average homocysteine level in the smoker group is higher than in the non-smoker group. The lack of correlation may be due to the short smoking experience, the small number of cigarettes smoked per day, the low smoker index and the young age of the study participants. It was revealed that the average homocysteine level in smokers of traditional cigarettes was higher than in participants using electronic tobacco heating systems.

Keywords: tobacco smoking, homocysteine, folate metabolism, B vitamins, Arkhangelsk Region

ВЛИЯНИЕ ТАБАКОКУРЕНИЯ НА ОБМЕН ГОМОЦИСТЕИНА У ЗДОРОВЫХ НИКОТИНЗАВИСИМЫХ ЛИЦ, ПРОЖИВАЮЩИХ НА ТЕРРИТОРИИ АРХАНГЕЛЬСКОЙ ОБЛАСТИ

© Александра Сергеевна Воронцова, Надежда Александрова Воробьева, Алёна Ивановна Воробьева, Елизавета Юрьевна Мельничук

Северный государственный медицинский университет. 163000, г. Архангельск, пр. Троицкий, 51

Контактная информация: Александра Сергеевна Воронцова — ассистент кафедры клинической фармакологии и фармакотерапии.
E-mail: baklab1gkb@yandex.ru ORCID: https://orcid.org/0000-0003-3643-0515 SPIN: 1495-7061

Для цитирования: Воронцова А.С., Воробьева Н.А., Воробьева А.И., Мельничук Е.Ю. Влияние табакокурения на обмен гомоцистеина у здоровых никотинзависимых лиц, проживающих на территории Архангельской области // Российские биомедицинские исследования. 2024. Т. 9. № 3. С. 21–27. DOI: https://doi.org/10.56871/RBR.2024.91.11.003

Поступила: 30.05.2024 **Одобрена: 01.08.2024** **Принята к печати: 16.09.2024**

Резюме. ***Введение.*** Табакокурение во всем мире остается глобальной медико-социальной и экономической проблемой. Никотин и компоненты табачного дыма влияют на фолатный обмен, снижают уровень витаминов группы В, что в совокупности влечет за собой нарушение обмена гомоцистеина, приводя к развитию эндотелиальной дисфункции и неблагоприятных сосудистых событий. ***Цель исследования*** — выявить влияние табакокурения и концентрации витаминов группы В (B_6, B_9, B_{12}) на обмен гомоцистеина у здоровых добровольцев молодого возраста. ***Материалы и методы.*** Исследование выполнено на выборке этнических русских, проживающих на территории Архангельской области. Включено 259 здоровых добровольцев обоих полов молодого возраста от 18 до 32 лет, проведено анкетирование, анализ уровня фолиевой кислоты, витаминов B_6 и B_{12}, гомоцистеина методом иммуноферментного анализа. Статистическая обработка данных, полученных в ходе исследования, проводилась методами описательной и аналитической статистики с использованием языка программирования R 4.2.3 в программе Rstudio 1.2.5019. ***Результаты.*** Статистически значимых различий по всем анализируемым показателям между группами курящих и некурящих участников не выявлено. Среднее значение уровня гомоцистеина в группе курильщиков было выше (Me=8,00), чем в группе некурящих (Me=7,00), при этом у участников, курящих сигареты, уровень гомоцистеина был выше (Me=8,6), чем у курящих электронные сигареты (Me=7,2). Среднее значение концентрации фолиевой кислоты в сыворотке у курящих было ниже (Me=4,00), чем у некурящих (Me=6,5). В группе курильщиков дефицит фолатов отмечен у 13 участников, в группе некурящих дефицита фолиевой кислоты не выявлено. Выявлена обратная связь средней силы между уровнем гомоцистеина и концентрацией фолиевой кислоты в сыворотке крови ($p < 0,01$). ***Заключение.*** В данном исследовании взаимосвязь между курением и уровнем гомоцистеина не выявлена, вместе с тем среднее значение уровня гомоцистеина в группе курильщиков было выше, чем в группе некурящих. Отсутствие взаимосвязи, возможно, связано с малым стажем курения, небольшим числом выкуренных сигарет в день, низким индексом курильщика и молодым возрастом участников исследования. Выявлено, что у курящих традиционные сигареты средний уровень гомоцистеина оказался выше, чем у участников, использующих электронные системы нагревания табака.

Ключевые слова: табакокурение, гомоцистеин, фолатный обмен, витамины группы В, Архангельская область

INTRODUCTION

According to the World Health Organization (WHO), tobacco smoking kills almost half of people who use it [16]. Globally, more than 8 million people a year die from tobacco exposure, including 1.3 million non-smokers from the effects of secondhand smoke [16]. The results of numerous studies around the world confirm that tobacco smoking is a significant risk factor for the development of various pathological processes and conditions, primarily diseases of the cardiovascular, respiratory, genitourinary systems, as well as cancer and complications of pregnancy [4, 15].

It is shown that in nicotine-dependent persons the risk of atherosclerosis and myocardial infarction increases from 1.5 to 6 times compared to non-smokers. The proven adverse effects of nicotine on the cardiovascular system include its effect on the chemoreceptors of the sinocarotid zone, leading to reflex excitation of respiration and increased blood pressure, increased production of catecholamines, contributing to myocardial damage, cytotoxic effect on endothelial cells, realized through fixation of tobacco smoke components on the cell surface and formation of antibodies to them [9, 10].

It is proved that nicotine reduces the level of vitamin B_6 in the blood, which acts as a cofactor in the reactions of homocysteine transsulfuration. Pyridoxine deficiency leads to impaired neutralization of homocysteine in the body and, as a consequence, to an increase in the level of homocysteine in blood plasma [9]. It is important that nicotine has the ability to slow down the folate cycle, the main function of which is the remethylation of homocysteine into methionine, resulting in the accumulation of excess homocysteine in plasma [7].

Homocysteine, being an extremely cytotoxic substance, has various mechanisms of damaging effect on the cardiovascular system, leading to the development of

endothelial dysfunction. Thus, homocysteine damages endothelial cells, which leads to its destabilization and loosening of vessel walls, participates in the formation of atherosclerotic plaque, being a component of "foam cells", has mitogenic properties that contribute to the development of vascular wall stiffness. Excess homocysteine stimulates increased platelet aggregation, triggers the processes of hypercoagulation, is involved in the development of oxidative stress through the formation of active oxygen radicals that trigger the process of lipid peroxidation. Hyperhomocysteinemia leads to the accumulation of asymmetric dimethylarginine (ADMA), which is an inhibitor of endothelial NO synthetase, resulting in blocked production of nitric oxide (NO), a strong antiaggregant and vasodilator [1].

Numerous studies demonstrate the relationship between tobacco smoking and elevated homocysteine levels in the blood of patients with various cardiovascular diseases [5, 7]. From the position of preventive medicine, it is of particular interest to study the effect of tobacco smoking on homocysteine levels in healthy young people even before the realization of adverse vascular events.

AIM

To determine the effect of tobacco smoking and concentration of B vitamins (B_6, B_9, B_{12}) on homocysteine metabolism in healthy young volunteers.

MATERIALS AND METHODS

The prospective one-stage cross-sectional study was performed on a sample of ethnic russians living in the territory of the Arkhangelsk. The bases of the study were the Department of Clinical Pharmacology and Pharmacotherapy of the Federal State Budgetary Educational Institution of Higher Professional Education "Northern State Medical University", the Regional Center of Antithrombotic Therapy of the State Budgetary Institution of Health Care "The First City Clinical Hospital named after E.E. Volosevich".

Inclusion criteria: healthy volunteers of Russian nationality of both sexes of young age (18 to 32 years); the absence of chronic diseases associated with endothelial dysfunction; the absence of pregnancy; the absence of taking medications, dietary supplements, vitamin complexes; written voluntary informed consent for participation in the study. *Exclusion criteria:* refusal to participate at any stage of the study.

The complex clinical and laboratory study included 259 volunteers, the participants were questioned. The level of folic acid, vitamins B_6 and B_{12}, homocysteine was analyzed by immunoenzymatic analysis. The study was approved by the local ethical committee of the Northern State Medical University (protocol No. 01/02-23 of 15.02.2023).

The level of homocysteine in serum was determined by solid-phase enzyme-linked immunosorbent assay using ELISA Kit For Homocysteine (HCy) reagents (Claud-Clone Corp., USA). Folate AccuBind ELISA reagents (Monobind, USA) were used to determine folic acid concentration. The reference interval, located in the range from 3.2 to 13.7 ng/mL, was considered as sufficient level of folic acid in serum. Concentration less than 3.2 ng/mL was defined as low level of folic acid. In order to determine the level of pyridoxine and cobalamin in blood, ELISA Kit For Vitamin B (VB_6) and ELISA Kit For Cyanocobalamin (CNCbl) (Claud-Clone Corp., USA) were used. Laboratory studies were performed at the laboratory of the First City Clinical Hospital named after E.E. Volosevich.

Statistical processing of the data obtained during the study was performed by methods of descriptive and analytical statistics using the programming language R 4.2.3 in the program Rstudio 1.2.5019. The nature of data distribution was assessed using the Shapiro-Wilk criterion. The data distribution was considered to be different from the normal distribution (Gaussian distribution) when the statistical significance level (p) was less than 0.05. The arithmetic mean (M) and standard deviation (σ) in the format of M±σ were used to describe the obtained data whose distribution did not differ from the Gaussian distribution. Data whose distribution differed from the Gaussian distribution are presented as median (Me), the first (Q1) and the third (Q3) quartiles. The Mann–Whitney criterion was used to compare independent samples with a distribution type that differed from the normal distribution. Differences between groups were considered statistically significant when the p-value (p) was less than 0.05. The Spearmans rank correlation coefficient was used to assess the relationship between two variables.

RESULTS

The study included 259 participants. The gender distribution of the participants was as follows: the proportion of women was 68.0% (n=176), men proportion was 32.0% (n=83). The age of the participants ranged from 21 to 30 years (Me=23 [22;28]). During the study, the sample was divided into two groups. The first group included non-tobacco smoking participants (n=137) and the second group included tobacco smoking participants (n=122). Serum levels of homocysteine, folic acid, vitamins B_6 and B_{12} were assessed in all participants. The results of the study and characterization of the study groups are presented in Table 1.

Table 1

Results of the study and characteristics of the groups (n=259)

Таблица 1

Результаты исследования и характеристика групп (n=259)

Показатель / Indicator	Некурящие участники (n=137) / Non-smoking participants (n=137)	Курящие участники (n=122) / Smoking participants (n=122)	p-значение / p-value
Возраст, годы / Age, years	Me=22 [22;28]	Me=23 [22; 26]	0,68
Индекс массы тела / Body mass index	Me=22,9 [20,0; 25,8]	Me=23,5 [20,6; 26,2]	0,72
Уровень фолиевой кислоты в сыворотке (нг/мл) / Serum folic acid level (ng/ml)	Me=6,5 [4,5; 8,0]	Me=4,00 [3,05; 6,00]	0,48
Уровень гомоцистеина в сыворотке крови (мкмоль/л) / Serum homocysteine level (mmol/l)	Me=7,0 [5,7; 10,0]	Me=8,00 [6,5; 9,0]	0,13
Уровень витамина B_6 в сыворотке крови (нг/мл) / Serum vitamin B_6 level (ng/ml)	Me=18,7 [15,8; 21,0]	Me= 8,2 [13,8; 22,3]	0,92
Уровень витамина B_{12} в сыворотке крови (пг/л) / Serum vitamin B_{12} level (pg/l)	Me=558 [384; 635]	Me=529 [329; 752]	0,74

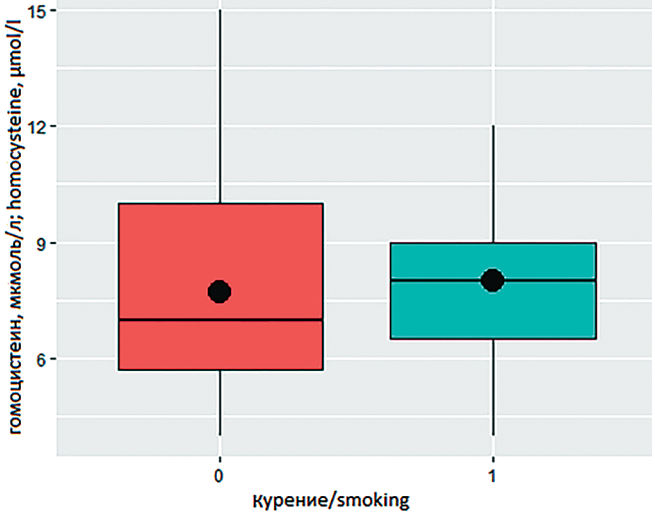

Fig. 1. The relationship between serum homocysteine levels and smoking

Рис. 1. Взаимосвязь уровня гомоцистеина в сыворотке крови и курения

Nicotine delivery to the body in the group of smokers in 68% of cases was due to electronic systems of heating tobacco, in 32% by the traditional way, with the cigarettes. Smoking experience in the smoking group averaged 3.5 years but did not exceed 5 years, and the number of cigarettes smoked per day ranged from 3 to 10. The smoking index of the cigarette-smoking participants ranged from 0.75 to 2.5 packs/year.

Comparative analysis of the groups showed that the body mass index (BMI) of the participants in the first and second groups did not differ. 85% of the participants of the first and the second groups had normal BMI (18.5–25.0), 15% of the participants of both groups were overweight (26.0–29.5), and BMI over 30, indicating the obesity, did not occur in the study sample.

The level of folic acid, homocysteine, vitamins B_6 and B_{12} in blood serum was determined in all study participants. No statistically significant differences in all determined parameters between the analyzed groups were found. It is important to note that the mean value of homocysteine level in the group of smokers was higher (Me=8.00) than in the group of non-smokers (Me=7.00). Participants smoking cigarettes having higher homocysteine levels (Me=8.6) than those smoking electronic cigarettes (Me=7.2). All participants in the first and the second groups had homocysteine levels within the reference values of 5.0 to 10.0 µmol/L. The data is presented in Figure 1.

A similar trend was observed in folate levels. Thus, the mean value of serum folate concentration in smokers was lower (Me=4.00) than in nonsmokers (Me=6.5). In addition, folate deficiency, where serum folic acid concentration was less than 3.2 ng/mL, was recorded in 13 participants in the smokers group. No folic acid deficiency was found in the non-smoker group.

The relationship between homocysteine levels and smoking and between homocysteine levels and folic acid concentration was analyzed. The data is presented in Figure 2.

The study revealed an inverse relationship of medium strength between homocysteine level and serum folic acid concentration ($p < 0.01$): the lower the folic acid level

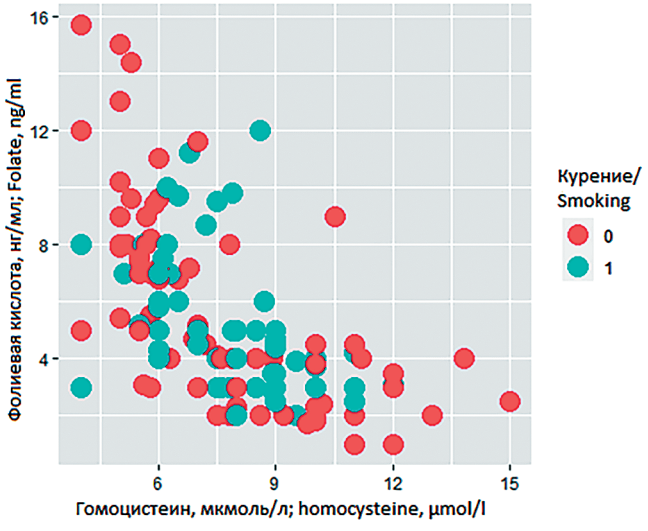

Fig. 2. The relationship between homocysteine levels, smoking and serum folate concentrations

Рис. 2. Взаимосвязь уровня гомоцистеина, курения и концентрации фолиевой кислоты в сыворотке крови

was, the higher the serum homocysteine level was. No relationship was found between serum homocysteine levels and smoking in this study (p=0.13).

DISCUSSION

Research data from recent years show that among young people under 30 years of age who smoke, the leading method of nicotine-containing product delivery is via various electronic systems such as vape, vaporizer, electronic cigarette and others [6, 8]. Our study also confirms this trend. Among the smoking participants, 68% used electronic nicotine delivery systems to deliver nicotine to the body. It is known that electronic nicotine delivery systems do not contain many toxic components of tobacco smoke, which are usually formed in cigarette smoke during combustion, but at the same time have in their composition such carcinogenic substances as formaldehyde, acetaldehyde, acetone, nitrosamines, propylene glycol, glycerol, phenols, and others. The nicotine in tobacco is addictive and dependent, which is especially dangerous for young people. Electronic devices, like normal cigarettes, contain high concentrations of nicotine, which has an extremely negative impact on the health of smokers [3, 11, 13].

At present, there is accumulated evidence of the effect of tobacco smoking on the level of homocysteine in the blood. It has been shown that homocysteine levels are significantly higher in healthy smokers than in nonsmokers [5, 14]. Evidence is presented that homocysteine levels depend on the number of cigarettes smoked per day, smoking history, and smoker's index. Each cigarette smoked increases homocysteine levels by 0.5% in men and 1% in women [2, 9]. In our study, there was a tendency to increase homocysteine levels in the smoking group, where the mean value of homocysteine levels in the smoking group was higher (Me=8.00) than in the non-smoking group (Me=7.00), however, no statistically significant difference could be obtained. No hyperhomocysteinemia condition was registered in any participant of the group. The absence of statistically significant differences in homocysteine levels in the first and second groups may be due to the short smoking experience (up to 5 years), as well as low smoking index (from 0.75 to 2.5 packs/year) in the participants of the second group, as well as the young age of the study subjects. No relationship between smoking and homocysteine levels was found in this study, but an average value of homocysteine levels in the group of smokers was higher than in the group of nonsmokers.

Folic acid is the most important determinant of the folate cycle, which results in the remethylation of homocysteine into methionine. There are many domestic and foreign studies on the role of folic acid in homocysteine metabolism. Folate deficiency leads to accumulation of the sulfur-containing amino acid homocysteine in the body, which in turn leads to endothelial dysfunction and development of adverse vascular events [12]. In our study, a statistically significant inverse relationship of medium strength between homocysteine level and serum folic acid concentration was confirmed.

CONCLUSION

1. The study revealed the effect of serum folic acid concentration on homocysteine level, while the effect of vitamin B_6 and B_{12} concentration was not found.

2. The mean value of homocysteine level in the group of smokers was higher than in the group of non-smokers, but tobacco smoking had no statistically significant effect on the serum homocysteine level.

ADDITIONAL INFORMATION

Author contribution. All authors confirm the conformity of their authorship, according to the international criteria of the ICMJE (all authors made a significant contribution to the development of the concept, conduct of the study and preparation of the article, read and approved the final version before publication). The largest contribution is distributed as follows: concept and design of the study — N.A. Vorobyeva, A.S. Vorontsova; collection and mathematical analysis of data — A.S. Vorontsova, E.Yu. Melnichuk; literature review,

manuscript preparation — A.S. Vorontsova, N.A. Vorobyeva, A.I. Vorobyeva.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

Consent for publication. Written consent was obtained from the patient for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы подтверждают соответствие своего авторства, согласно международным критериям ICMJE (все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией). Наибольший вклад распределен следующим образом: концепция и план исследования — Н.А. Воробьева, А.С. Воронцова; сбор и математический анализ данных — А.С. Воронцова, Е.Ю. Мельничук; литературный обзор, подготовка рукописи — А.С. Воронцова, Н.А. Воробьева, А.И. Воробьева.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Информированное согласие на публикацию. Авторы получили письменное согласие пациентов на публикацию медицинских данных.

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ЛИТЕРАТУРА

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DOI: 10.56871/RBR.2024.90.67.004
UDC 616.613-003.7-005.1-08-055.1+615.254+578.834.1+616-036.21

STATUS OF HEMOSTATIC SYSTEM IN MEN WITH UROLITHIASIS TREATED UNDER DURING COVID-19 PANDEMIC

© Zaur K. Emirgaev, Nair S. Tagirov, Andrey G. Vasiliev, Omar K. Emirgaev

Saint Petersburg State Pediatric Medical University. 2 Lithuania, Saint Petersburg 194100 Russian Federation

Contact information: Zaur K. Emirgaev — Postgraduate Student, Pathophysiology Department. E-mail: zaur.emirgaev@mail.ru SPIN: 6771-7532

For citation: Emirgaev Z.K., Tagirov N.S., Vasiliev A.G., Emirgaev O.K. Status of hemostatic system in men with urolithiasis treated under during COVID-19 pandemic. Russian Biomedical Research. 2024;9(3):28–34. DOI: https://doi.org/10.56871/RBR.2024.90.67.004

Received: 03.07.2024 **Revised: 12.08.2024** **Accepted: 16.09.2024**

Abstract. ***Introduction.*** Androgen replacement therapy has been shown to be effective in the treatment of patients with urolithiasis and androgen deficiency. ***The aim of the work*** was to find out whether androgen replacement therapy is applicable in the treatment of patients with androgen deficiency in the specific conditions of the COVID-19 pandemic with regard to its possible influence on the most important link in the pathogenesis of COVID-19 — blood coagulation. ***According to the results*** of hospital treatment of 199 men suffering from urolithiasis, it was found that androgen replacement therapy is not an obstacle for therapeutic measures aimed at persistent restriction of coagulation processes. ***Conclusion.*** In case of pandemic recurrence, androgen replacement therapy can be used in the treatment of urolithiasis.

Keywords: urolithiasis, hemostasis, androgen therapy, COVID-19

СОСТОЯНИЕ СИСТЕМЫ ГЕМОСТАЗА У МУЖЧИН, БОЛЬНЫХ УРОЛИТИАЗОМ, ПРОХОДИВШИХ ЛЕЧЕНИЕ В УСЛОВИЯХ ПАНДЕМИИ COVID-19

© Заур Келбялиевич Эмиргаев, Наир Сабирович Тагиров,
Андрей Глебович Васильев, Омар Келбялиевич Эмиргаев

Санкт-Петербургский государственный педиатрический медицинский университет. 194100, г. Санкт-Петербург, ул. Литовская, 2

Контактная информация: Заур Келбялиевич Эмиргаев — аспирант кафедры патологической физиологии с курсом иммунопатологии. E-mail: zaur.emirgaev@mail.ru SPIN: 6771-7532

Для цитирования: Эмиргаев З.К., Тагиров Н.С., Васильев А.Г., Эмиргаев О.К. Состояние системы гемостаза у мужчин, больных уролитиазом, проходивших лечение в условиях пандемии COVID-19// Российские биомедицинские исследования. 2024. Т. 9. № 3. С. 28–34. DOI: https://doi.org/10.56871/RBR.2024.90.67.004

Поступила: 03.07.2024 **Одобрена: 12.08.2024** **Принята к печати: 16.09.2024**

Резюме. ***Введение.*** Андрогенная заместительная терапия показала свою эффективность в лечении больных с мочекаменной болезнью и андрогенным дефицитом. **Целью работы** было выяснить, применима ли андрогенная заместительная терапия в лечении больных с андрогенным дефицитом в специфических условиях пандемии COVID-19 в том, что касается ее возможного влияния на важнейшее звено патогенеза COVID-19 — процессы свертывания крови. **По результатам** стационарного лечения 199 мужчин, страдающих уролитиазом, установлено, что андрогенная заместительная терапия не является препятствием для проведения лечебных мероприятий, направленных на стойкое ограничение коагуляционных процессов. **Вывод.** У больных, страдающих от инфекции COVID-19 и одновременно получающих андрогенную заместительную терапию как часть лечения уролитиаза, достижимо стойкое ограничение коагуляционных процессов, и андрогенная заместительная терапия препятствием для этого не является. В будущем, в случае повторения пандемии, андрогенная заместительная терапия может быть применена в лечении уролитиаза.

Ключевые слова: мочекаменная болезнь, гемостаз, андрогенная терапия, COVID-19

INTRODUCTION

Androgen replacement therapy has shown its effectiveness in the treatment of patients with urolithiasis and androgen deficiency [4–6]. The pandemic of a new coronavirus infection has made adjustments in the use of a significant part of treatment methods for a wide range of diseases.

Articles published by urologists in scientific journals during the coronavirus pandemic focus more or less on organizational issues: the impact of reduced physical activity during the pandemic on the course of urolithiasis [10]; impact of drug treatment of nephrolithiasis on the efficacy of COVID-19 vaccination [20]; assessment of the burden on urologic units during the pandemic [11, 12]; management of urologic units in this setting [19]; triage of patients [8, 9, 13] and, in particular, the possibility of postponing surgical treatment until after the pandemic [17]; methods of preoperative assessment of patients and the choice of anesthetic techniques to provide urological operations [15]; risk of postoperative complications [16] and the quality of life of patients undergoing surgical treatment for nephrolithiasis in pandemic conditions [23].

The pathophysiology of urolithiasis complicated by coronavirus infection remains practically unstudied in the world. The influence of androgen deficiency and, even more so, the effectiveness of androgen replacement therapy, carried out against the background of a new coronavirus infection, are not considered.

At the same time, disturbances in the blood coagulation system — an increase in coagulation, endothelial inflammation, suppression of fibrinolysis are known as one of the main manifestations of COVID-19 infection [1, 2, 7, 21]. Does androgen replacement therapy have an effect on these processes? Literature data on this issue are extremely scarce.

A study of the blood coagulation system in elderly men showed a negative correlation between plasma testosterone levels and blood platelet reactivity [18]. Androgens reduce the activity of coagulation processes [14]. Their long-term use can have antithrombotic effect [24]. One of the reasons for the decrease in the activity of fibrinolysis is the increased production of PAI-1, a plasminogen activator inhibitor. However, at the same time, exogenous androgens inhibit PAI-1 and thus increase fibrinolysis [22].

AIM

To clarify whether androgen replacement therapy is applicable in the treatment of androgen-deficient patients under the specific conditions of the COVID-19 pandemic with regard to its possible effects on the coagulation processes.

MATRIALS AND METHODS

The organization of clinical studies. Laboratory tests were performed in accordance with standard methods in the laboratory department of the State Budgetary Institution “Elizavetinskaya Hospital” (St. Petersburg). The study included 199 men aged from 25 to 68 years who were patients of the urological unit (the head of the unit is Dr. N.S. Tagirov). Most of the parameters were recorded four times: at the time of the beginning of inpatient treatment, at the time of its completion, in 4 months and 1 year after its completion. Some parameters were registered three times: at the moment of the beginning of inpatient treatment, after 4 months and after 1 year. One half of the patients (100 patients) received androgen replacement therapy, the other half (99 patients) received conventional therapy (contact lithotripsy performed after the extracorporeal shock wave lithotripsy). The method of androgen replacement therapy was previously described by the head of the collective [5, 6].

Statistical analysis of the results. We used the program packages SPSS for Windows and STATISTICA v. 6.0. The significance of intergroup differences was assessed by nonparametric methods: Mann–Whitney U-test, Wilcoxon criterion and ANOVA with Bonferroni correction [3].

RESULTS

Platelets. During the whole observation period, the average number of platelets in COVID– and COVID+ groups (Fig. 1) ranged from 290±35 to 319±54 × 10^9/l and did not differ statistically significantly ($p > 0.05$). In all patients, regardless of the type of therapy, the dynamics of the index was similar: no changes were observed during the treatment ($p > 0.05$). A statistically significant decrease in platelet count ($p < 0.001$) to 270±31 to 279±36 × 10^9/l was observed by 4 months and remained at the same level up to 1 year.

Fibrinogen. The mean fibrinogen concentration in the blood of COVID– patients was near the upper limit of normal (2.0-3.9 g/L) from the beginning of hospital treatment and up to 1 year afterward (Fig. 2). Fibrinogen concentration decreased in COVID+ patients and by 4 months was 4.05±0.84 g/L ($p< 0.001$) with conventional treatment and 2.07±0.36 ($p < 0.001$) with androgen replacement therapy. COVID+ patients receiving androgen replacement therapy had 1.74 g/L ($p < 0.001$) lower plasma fibrinogen concentration by 1 year than the COVID- group. Among patients receiving conventional therapy, the fibrinogen concentration in the COVID+ group was 0.64 g/L higher ($p < 0.05$) than in the COVID– group.

D-dimer. In COVID– patients, the mean level of this parameter did not change significantly during the study; there were changes in the range of 212±44 to 250±63 ng/L (Fig. 3). D-dimer levels

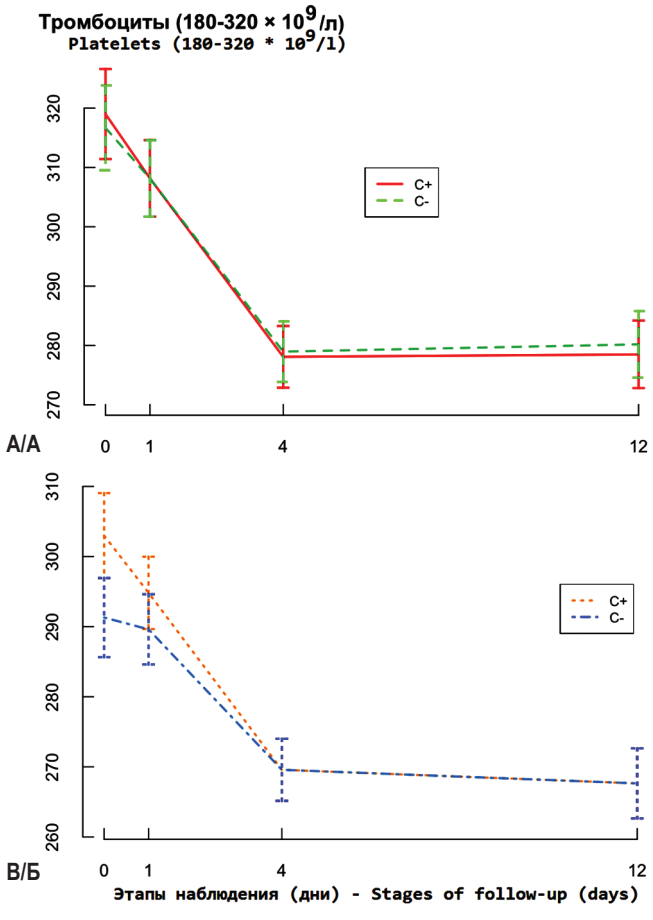

Fig. 1. Number (×10⁹/l) of platelets in the blood of patients who received traditional treatment (A) or androgen replacement therapy (B) for urolithiasis: C+ — with COVID-19; C– — without COVID-19. Stages of follow-up: 0 — at the beginning of treatment; 1 — at the time of hospital discharge; 4 — after 4 months; 12 — after 12 months. Mean ± standard deviation are presented

Рис. 1. Количество (×10⁹/л) тромбоцитов в крови больных, получавших по поводу уролитиаза традиционное лечение (А) или андрогенную заместительную терапию (Б): С+ — с COVID-19; С– — без COVID-19. Этапы наблюдения: 0 — начало стационарного лечения; 1 — окончание стационарного лечения; 4 — через 4 месяца; 12 — через 12 месяцев. Представлены средние арифметические ± среднеквадратическое отклонение

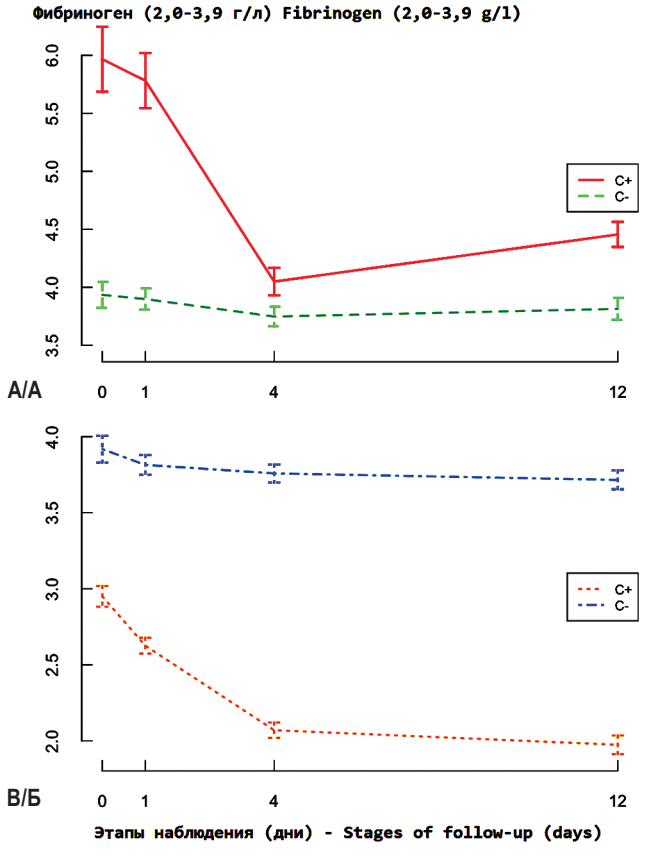

Fig. 2. Fibrinogen levels (g/L) in the blood of patients treated for urolithiasis with conventional treatment (A) or androgen replacement therapy (B): C+ — with COVID-19; C– — without COVID-19. Other designations are the same as in Fig. 1

Рис. 2. Уровень фибриногена (г/л) в крови пациентов, получавших по поводу уролитиаза традиционное лечение (А) или андрогенную заместительную терапию (Б): С+ — с COVID-19; С– — без COVID-19. Прочие обозначения те же, что и на рис. 1

were 412±163 to 398±91 ng/L in COVID+ patients at the time of treatment initiation. The level remained virtually unchanged during conventional treatment, but decreased to 282±70 ng/L after 4 months ($p < 0.001$) and to 231±26 ($p < 0.001$) after 1 year. In the case of androgen replacement therapy, the decrease in D-dimer levels to 68 ng/L ($p < 0.01$) occurred during hospitalization. By 4 months the decrease reached 124 ng/L ($p < 0.001$), after 1 year the index remained at the same level.

Activated partial thromboplastin time (aPTT). The mean value of aPTT at the beginning of hospital treatment ranged from 28.4±2.3 to 40.0±13.8 s (Fig. 4). In the COVID– group, the index decreased by 1.53-2.00 s during treatment ($p < 0.05$). APTT dynamics in COVID+ patients depended on the applied treatment. The index first increased by 2.70 s ($p < 0.05$) during androgen replacement therapy, then decreased to the baseline level. The decrease in the conventional therapy group was observed within 4 months and amounted to 8.2 s ($p < 0.05$). Later aPTT was at the same level. In general (except for the moment of hospitalization completion) aPTT in COVID+ patients was lower than in COVID- patients under androgen replacement therapy and higher under conventional therapy.

International normalized ratio (INR). At the time of inpatient treatment, the mean INR ranged from 1.19±0.23 to 1.54±0.60 (Fig. 5). INR remained at the same level or increased in the group receiving only conventional therapy and decreased in the group receiving androgen replacement

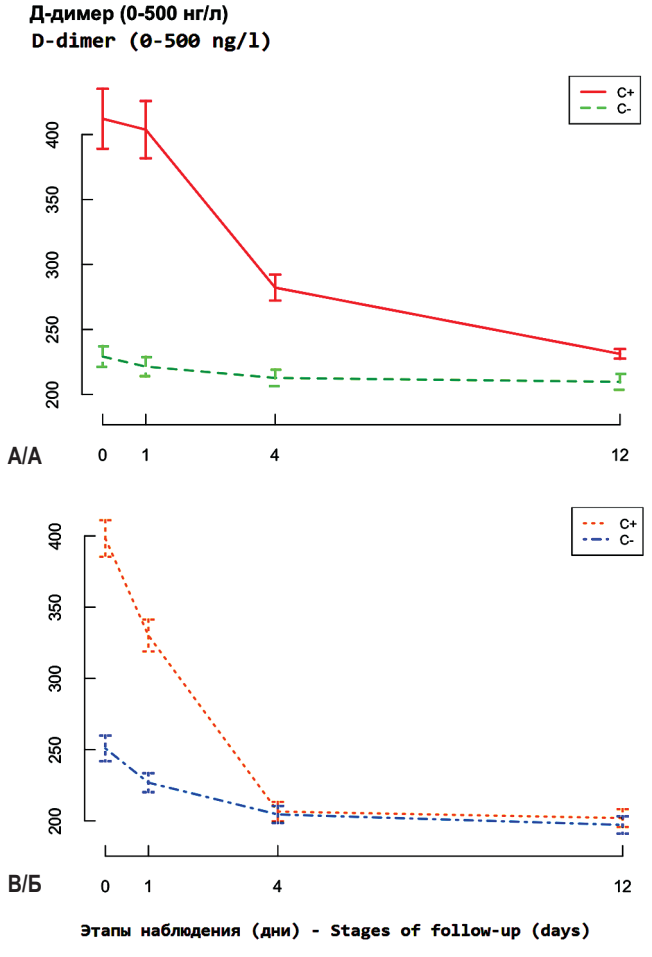

Fig. 3. D-dimer level (ng/L) in plasma of patients treated for urolithiasis with conventional treatment (A) or androgen replacement therapy (B): C+ — with COVID-19; C– — without COVID-19. Other designations are the same as in Fig. 1

Рис. 3. Уровень D-димера (нг/л) в плазме крови больных, получавших по поводу уролитиаза традиционное лечение (А) или андрогенную заместительную терапию (Б): С+ — с COVID-19; С– — без COVID-19. Прочие обозначения те же, что и на рис. 1

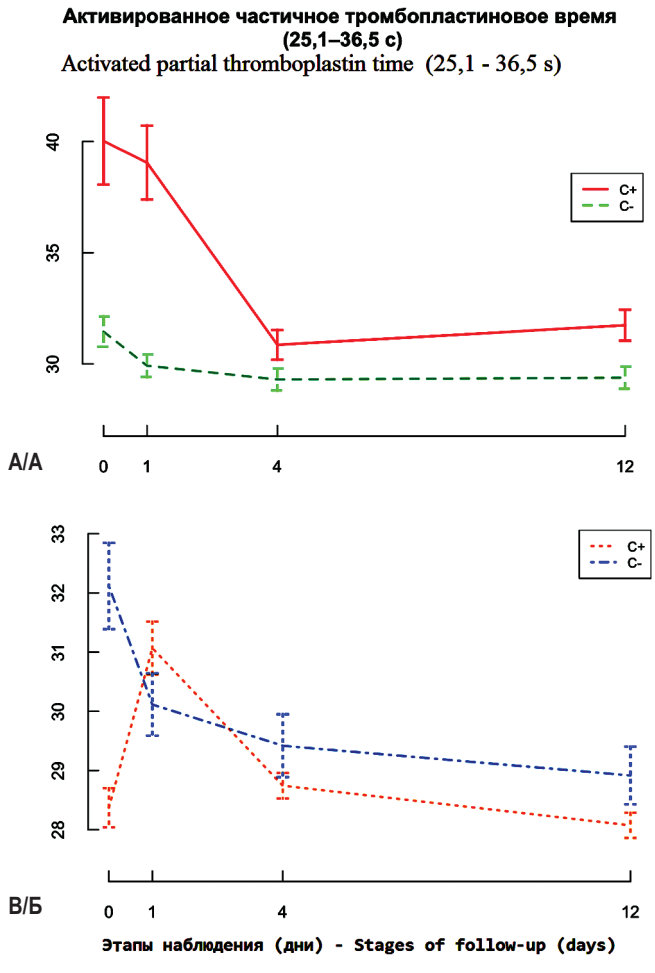

Fig. 4. Activated partial thromboplastin time (c) recorded in patients receiving conventional treatment (A) or androgen replacement therapy (B) for urolithiasis: C+ — with COVID-19; C– — without COVID-19. Other designations are the same as in Fig. 1

Рис. 4. Активированное частичное тромбопластиновое время (с), зарегистрированное у больных, получавших по поводу уролитиаза традиционное лечение (А) или андрогенную заместительную терапию (Б): С+ — с COVID-19; С– — без COVID-19. Прочие обозначения те же, что и на рис. 1

therapy during the treatment of COVID+ patients. androgen replacement therapy. By 4 months INR stabilized in the range of 1.13±0.39 to 1.21±0.17, and by 1 year there were no significant changes. The index was 1.07±0.23 to 1.19±0.47 units by the end of follow-up. Differences between COVID+ and COVID– groups were statistically significant only during the treatment period and by the time of hospital discharge, which was 0.23–0.40 units ($p < 0.01$).

DISCUSSION

Platelets. The platelet count (Fig. 1) was within the normal range (180–320×10^9/l) during the observation period and underwent similar changes: a decrease during treatment and by 4 months, later the maintenance at the same level. The dynamics of the parameter was not related to the type of urolithiasis treatment, nor to the presence or absence of COVID-19 infection. According to this indicator, new coronavirus infection is not a contraindication for treatment of urolithiasis in general and androgen replacement therapy in particular.

Fibrinogen. The amount of fibrinogen (Fig. 2) in the blood of COVID+ patients decreased sharply during treatment and in the first time after discharge from the hospital, and by 4 months it was equal to the index in the group of patients who did not suffer from a new

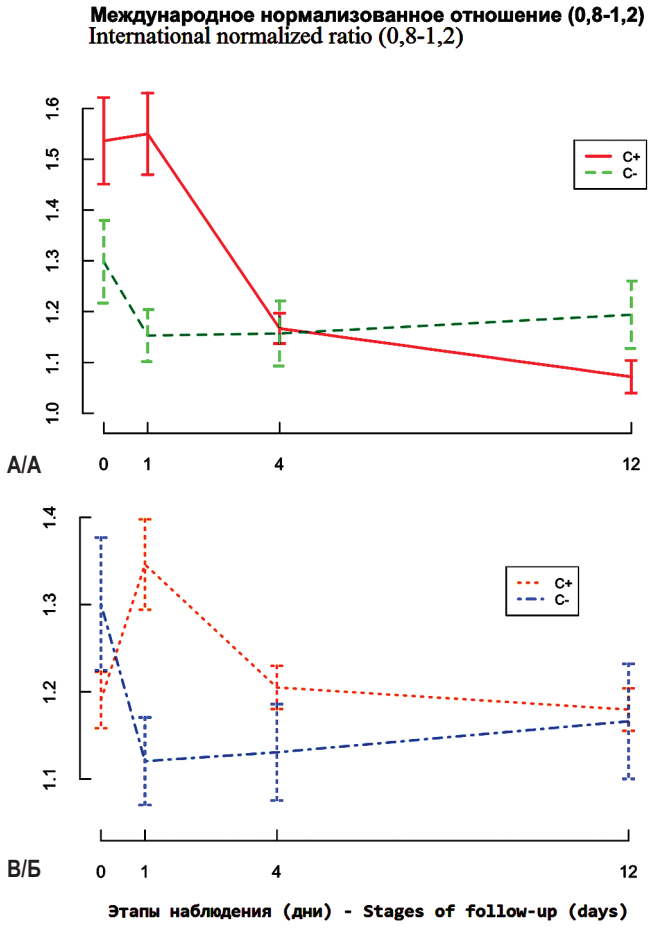

Fig. 5. **International normalized ratio recorded in patients treated for urolithiasis with conventional treatment (A) or androgen replacement therapy (B): C+ — indicates with COVID-19; C– — indicates without COVID-19. Other designations are the same as in Fig. 1**

Рис. 5. **Международное нормализованное отношение, зарегистрированное у больных, получавших по поводу уролитиаза традиционное лечение (А) или андрогенную заместительную терапию (Б): С+ — с COVID-19; С– — без COVID-19. Прочие обозначения те же, что и на рис. 1**

coronavirus infection. While baseline values differed, the dynamics of the index was not related to the type of treatment for urolithiasis. We consider these results as confirmation that androgen replacement therapy used as a component of treatment of urolithiasis is not an obstacle to attenuation of coagulation processes in patients suffering from the concurrent COVID-19 infection.

D-dimer. This indicator of fibrinolysis (Fig. 3) was within the normal range (from 0 to 500 ng/L) in all patients. The difference between COVID+ and COVID– groups leveled out by 4 months in case of androgen replacement therapy, while in case of conventional therapy it disappeared only by 1 year. We believe that the coagulation restriction used in COVID-19 is also not a contraindication for androgen replacement therapy in the treatment of urolithiasis.

Activated partial thromboplastin time. We registered multidirectional changes in aPTT (Fig. 4). Significant differences between the values of this index in COVID+ and COVID– patients were noted in the course of treatment, but only in patients receiving conventional therapy.

International normalized ratio. In COVID+ patients receiving androgen replacement therapy, INR increased by 0.16 units during treatment ($p < 0.05$), indicating coagulation limitation (Fig. 5). The index did not differ by 4 months between patients who had suffered from coronavirus infection and those who had avoided coronavirus infection. We consider these data as another indication that it is possible to treat COVID-19 infection and urolithiasis simultaneously, including with the use of androgen replacement therapy.

CONCLUSION

In patients suffering from COVID-19 infection and concomitantly receiving androgen replacement therapy as part of the treatment of urolithiasis, sustained coagulation limitation is achievable, and androgen replacement therapy is not a barrier to this. In the future, if the pandemic recurs, androgen replacement therapy may be used in the treatment of urolithiasis.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

Consent for publication. Written consent was obtained from the patient for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Информированное согласие на публикацию. Авторы получили письменное согласие пациентов на публикацию медицинских данных.

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DOI: 10.56871/RBR.2024.96.65.005
UDC 577.151+612.015.1+612.4+618.2+612.313.3-07

INDICATORS OF THE ACTIVITY OF DIGESTIVE ENZYMES AND TRANSAMINASES IN SALIVA AND COPROFILTRATE IN WOMEN DURING PREGNANCY

© Elena V. Kolodkina[1, 2], Sergey A. Lytaev[1], Michael M. Galagudza[3, 4]

[1] Saint Petersburg State Pediatric Medical University. 2 Lithuania, Saint Petersburg 194100 Russian Federation
[2] Almazov National Medical Research Centre. 2 Akkuratov str., Saint Petersburg 197341 Russian Federation
[3] Institute of Experimental Medicine. 12 Academician Pavlov str., Saint Petersburg 197022 Russian Federation
[4] Pavlov First Saint Petersburg State Medical University. 6–8 L'va Tolstogo str., Saint Petersburg 197022 Russia

Contact information: Elena V. Kolodkina — Candidate of Medical Sciences, Associate Professor of the Department of Normal Physiology SPbSPMU, Associate Professor of the Department of Pathological Physiology IMO Almazov National Medical Research Centre.
E-mail: 922-666-2045@mail.ru ORCID: https://orcid.org/0009-0001-6304-8680 SPIN: 9082-3341

For citation: Kolodkina EV, Lytaev SA, Galagudza MM. Indicators of the activity of digestive enzymes and transaminases in saliva and coprofiltrate in women during pregnancy. Russian Biomedical Research. 2024;9(3):35–41. DOI: https://doi.org/10.56871/RBR.2024.96.65.005

Received: 19.06.2024 **Revised: 02.08.2024** **Accepted: 16.09.2024**

Abstract.*Introduction.* The characteristics of enzymes and transaminases in saliva and coprofiltrate in the "Mother–placenta–fetus" system in women were studied by trimester of pregnancy and in the postpartum period. ***The purpose of the work*** — to study the enzyme profile of biological fluids during pregnancy, to establish a relationship between the content of enzymes in the blood, their excretion in the composition of excretes and recretes with the activity of transaminases in the corresponding substrates. ***Materials and methods.*** The material for the study was taken from non-pregnant and pregnant women. The dynamics of changes in the activity of hydrolases in biological fluids was studied. ***Results.*** The participation of secretory and excretory pathways of enzyme excretion from the blood and body during pregnancy has been shown, the participation of salivary glands in the recreation of hydrolases in enzyme homeostasis has been isolated. ***Conclusions.*** The participation of transaminases and alkaline phosphatase in the homeostasis of hydrolases is not excluded, which is proved by the enzyme profile of biofluids during pregnancy.

Keywords: enzymes, incretion; recreation, excretion, pregnancy, salivadiagnostics

ПОКАЗАТЕЛИ АКТИВНОСТИ ПИЩЕВАРИТЕЛЬНЫХ ФЕРМЕНТОВ И ТРАНСАМИНАЗ В СЛЮНЕ И КОПРОФИЛЬТРАТЕ У ЖЕНЩИН В ПРОЦЕССЕ БЕРЕМЕННОСТИ

© Елена Витальевна Колодкина[1, 2], Сергей Александрович Лытаев[1], Михаил Михайлович Галагудза[3, 4]

[1] Санкт-Петербургский государственный педиатрический медицинский университет. 194100, г. Санкт-Петербург, ул. Литовская, 2
[2] Национальный медицинский исследовательский центр им. В.А. Алмазова. 197341, г. Санкт-Петербург, ул. Аккуратова, 2
[3] Институт экспериментальной медицины. 197022, г. Санкт-Петербург, ул. Академика Павлова, 12
[4] Первый Санкт-Петербургский государственный медицинский университет им. академика И.П. Павлова. 197022, г. Санкт-Петербург, ул. Льва Толстого, 6–8

Контактная информация: Елена Витальевна Колодкина — к.м.н., доцент кафедры нормальной физиологии СПбГПМУ; доцент кафедры патологической физиологии Национального медицинского исследовательского центра им. В.А. Алмазова.
E-mail: 922-666-2045@mail.ru ORCID: https://orcid.org/0009-0001-6304-8680 SPIN: 9082-3341

Для цитирования: Колодкина Е.В., Лытаев С.А., Галагудза М.М. Показатели активности пищеварительных ферментов и трансаминаз в слюне и копрофильтрате у женщин в процессе беременности// Российские биомедицинские исследования. 2024. Т. 9. № 3. С. 35–41. DOI: https://doi.org/10.56871/RBR.2024.96.65.005

Поступила: 19.06.2024 **Одобрена: 02.08.2024** **Принята к печати: 16.09.2024**

Резюме. ***Введение.*** Изучались особенности ферментов и трансаминаз в слюне и копрофильтрате в системе «Мать–плацента–плод» у женщин по триместрам беременности и в послеродовый период. ***Цель исследования***—изучить ферментный профиль биологических жидкостей при беременности, установить связь между содержанием ферментов в крови, выделением их в составе экскретов и рекретов с активностью трансаминаз в соответствующих субстратах. ***Материалы и методы.*** Материал для исследования брался у небеременных и беременных женщин. Изучалась динамика изменения активности гидролаз в биологических жидкостях. ***Результаты.*** Показано участие рекреторного и экскреторного путей выделения ферментов из крови и организма при беременности, обособлено участие слюнных желез в рекреции гидролаз в ферментном гомеостазе. ***Выводы.*** В гомеостазировании гидролаз не исключено участие трансаминаз и щелочной фосфатазы, что доказывается ферментным профилем биожидкостей при беременности.

Ключевые слова: ферменты, инкреция, рекреция, экскреция, беременность, саливадиагностика

INTRODUCTION

Enzymes increted by digestive glands are irretrievably excreted from the body as part of urine, sweat, and feces, as well as excreted from the blood by recreation with their subsequent participation in the polyenzyme supply of secretions entering the gastrointestinal (GI) tract [2–4, 8, 9, 11]. A special role is assigned to the incretin enzymes, whose homeostasis is dynamically maintained under various functional states of the body, one of which is pregnancy [19]. Metabolic relations between the maternal organism and the growing fetus are established during pregnancy, which actively absorbs amino acids for protein synthesis. The fetus absorbs nutrients with amniotic fluid, which are hydrolyzed to monomers in the GI tract of the developing organism by enzymes that are recreted into the aquafetal environment (an autolytic digestion) [1, 15, 16].

The processes of excretion and recreation of such enzymes as pepsinogen, amylase, lipase, and alkaline phosphatase were previously studied by measuring their concentration/activity in urine and feces (coprofiltrate), as well as their excretion by salivary glands [5, 6, 10].

In parallel with hydrolases, transaminases were studied in the same biological fluids.

The excretion of hydrolases (pepsinogen, amylase, lipase) with excreta or as part of recretes is associated with transaminase and alkaline phosphatase activities that supply energy for translocation processes and pinocytosis (transcytosis) [14].

Cholestasis, destructive processes in hepatocytes or tension of biliary function specifically change the activity of transaminases and alkaline phosphatase [14].

De Ritis ratio (aspartate aminotransferase/alanine aminotransferase (AST/ALT)) reflects central or peripheral types of metabolic shifts, and alkaline phosphatase serves as an indicator of metabolic processes, in particular, changes in glucose levels [12].

Enzymological changes in blood reflect both diagnostic and especially metabolic sense, and in general characterize the biochemical status of the organism. Alkaline phosphatase is responsible for glucose output from cells and for the formation of phosphate pool. It is a marker of ontogenetic maturity and a regulator of transmembrane fluxes [14, 20].

AST and ALT are stable indicators. They are in a tight metabolic relationship, forming the de Ritis ratio, which integratively relates protein metabolism and characterizes total blood protein [12–14].

AIM

The aim of the study is to investigate the enzyme profile of biological fluids in pregnancy, to establish the relationship between the content of enzymes in the blood, their excreta and recreta with the activity of transaminases in the corresponding substrates.

MATERIALS AND METHODS

The material for the study was taken from non-pregnant (n=45) — control and pregnant (n=86) women — women in labor at full term.

The content and activity of pepsinogen, amylase, lipase, alkaline phosphatase and transaminases (AST, ALT) in fluids (blood, saliva, urine and coprofiltrate) in non-pregnant and pregnant women in trimesters of pregnancy and in the postpartum period were studied. The de Ritis ratio (AST/ALT) was calculated.

Total proteolytic activity was determined at low pH values of 1.5–2.0 by spectrophotometric (tyrosine) Kunitz–Northrop method in modification. Amylolytic activity was determined by amyloclastic method according to Karavey. Alkaline phosphatase activity was determined by standard constant time method using biotests by Lahema diagnosticum (Czech Republic). Lipolytic activity was

determined by unified method using olive oil as a substrate [13]. Transaminase activity (AST, ALT) was determined by colorimetric dinitrophenylhydrazine method according to Reitman and Frenkel [21].

Statistical processing of the results was performed using Microsoft Excel 2003 spreadsheets, SPSS 11.0 and Primer of biostatistics 4.03 programs.

RESULTS

Serum amylolytic activity was 13.5±0.8 units/mL in non-pregnant women. It remained almost the same in pregnant women in the I trimester, whereas in the II and especially in the III trimester it significantly increased — 2-fold (p <0.001) compared with the control group and the I trimester of pregnancy. In the postpartum period, the enzyme activity decreased, not reaching the indicators of non-pregnant women (Table 1).

Urinary amylase excretion in the control group was higher (64.1±1.6 units/mL) than in pregnant women during the I trimester of pregnancy. After the labor, there was a decrease in urinary amylase activity (1.5-fold; p <0.001).

Amylase synthesis by salivary glands tended to increase from control values and from the beginning to the end of pregnancy (Table 2).

Amylase activity decreased in the postpartum period, not reaching the values in non-pregnant women.

Table 1

Indicators of the activity of digestive enzymes and transaminases in blood and urine in the control group and pregnant women who gave birth on time, during trimesters of pregnancy and after childbirth)

Таблица 1

Показатели активности пищеварительных ферментов и трансаминаз в крови и моче у лиц контрольной группы и беременных женщин, родивших в срок, по триместрам беременности и после родов

Показатели / Indicators	Контрольная группа / Control group (n=45)	Беременные со срочными родами / Pregnant women with an urgent delivery (n=86)			
		I триместр / I trimester	II триместр / II trimester	III триместр III trimester	После родов / After giving birth
Кровь / Blood					
Амилаза (ед/мл) / Amylase) (units/ml)	13,5±0,8	11,3± 1,1	18,2±1,7**	25,0±1,3*	17,8±0,8**
Пепсиноген (тир. ед/мл) / Pepsinogen (tyr. units/ml)	58,1±1,1	44,2±3,3**	53,8±4,1**	48,2±2,6**	44,4±1,8**
Липаза (ед/мл) / Lipase (units/ml)	18,1±0,7	15,8±1,5**	21,4±1,6**	32,1±1,8*	21,3±1,7**
Щелочная фосфатаза (ед/мл) / Alkaline phosphatase (units/ml)	722,1±50,6	1015,6±102,2**	1200,1±114,2*	1287,8±102,3**	855,6±67,4
АСТ (ед/мл) / AST (units/ml)	11,1±1,2	12,1±1,2	14,3±1,2**	18,5±1,3*	14,0±1,2
АЛТ (ед/мл) / ALT) (units/ml)	8,8±0,7	13,7±1,1**	15,9±1,3**	20,5±1,7*	14,5±1,2**
АСТ/АЛТ / AST/ALT	1,26±0,04	0,88±0,01**	0,89±0,01**	0,90±0,01**	0,96±0,02**
Моча / Urine					
Амилаза (ед/мл) / Amylase (units/ml)	64,1±1,6	42,2±0,8*	50,6±1,4*	67,2±2,1	41,2±0,9*
Пепсиноген (тир. ед/мл) / Pepsinogen (tyr. units/ml)	4520,3±212,0	5200,8±186,1**	7800,1±204,1*	9650,1±211,5*	3698,5±146,7**
Липаза (ед/мл) / Lipase (units/ml)	20,6±0,8	24,4±0,4**	35,2±1,6*	41,2±1,9*	27,5±0,5
Щелочная фосфатаза (ед/мл) / Alkaline phosphatase (units/ml)	428,6±18,1	320,1±16,7**	480,7±20,6	410,9±19,1	240,4±16,2**
АСТ (ед/мл) / AST (units/ml)	5,7±0,7	4,3±0,3*	4,5±0,3*	5,1±0,4	4,7±0,3**
АЛТ (ед/мл) / (ALT) (units/ml)	5,1±0,6	4,8±0,3**	5,2±0,4	5,3±0,4	4,8±0,3**
АСТ/АЛТ / AST/ALT	1,1±0,03	0,89±0,01**	0,86±0,01**	0,96±0,02	0,98±0,02

Примечание: достоверность различий с показателями контрольной группы: * — p <0,001; ** — p <0,05.

Note: significance of differences with the indicators of the control group: * — p <0.001; ** — p <0.05.

Table 2

Indicators of the activity of digestive enzymes and transaminases in saliva and coprofiltrate in the control group and pregnant women who gave birth on time, during trimesters of pregnancy and after childbirth

Таблица 2

Показатели активности пищеварительных ферментов и трансаминаз в слюне и копрофильтрате у лиц контрольной группы и беременных женщин, родивших в срок, по триместрам беременности и после родов

Показатели / Indicators	Контрольная группа / Control group (n=45)	Беременные со срочными родами / Pregnant women with an urgent delivery (n=86)			
		I триместр / I trimester	II триместр / II trimester	III триместр / III trimester	После родов / After giving birth
Слюна / Saliva					
Амилаза (ед/мл) / Amylase (units/ml)	2385,3±264,7	2506,2±285,1	3515,1±440,8**	4781,6±423,8*	3109,0±294,2**
Пепсиноген (тир. ед/мл) / Pepsinogen (tyr. units/ml)	1520,9±247,6	1208,6±296,2**	1807,0±215,6	2612,9±218,1*	1463,3±221,6
Липаза (ед/мл) / Lipase (units/ml)	64,8±7,0	78,1±15,2**	90,3±8,4*	121,1±11,6*	70,9±5,4
Щелочная фосфатаза (ед/мл) / Alkaline phosphatase (units/ml)	215,6±22,3	722,0±38,3*	518,2±45,4*	361,8±30,2	475,3±31,6**
АСТ (ед/мл) / AST (units/ml)	8,1±1,1	7,2±0,6**	8,6±0,6	14,0±1,2*	12,5±1,0*
АЛТ (ед/мл) / (ALT) (units/ml)	6,4±0,8	6,6±0,5	10,4±0,8*	13,1±1,1*	11,2 ± 0,9*
АСТ/АЛТ / AST/ALT	1,26±0,04	1,09± 0,03	0,83±0,01**	1,07±0,03**	1,12±0,03
Копрофильтрат / Coprofiltrate					
Амилаза (ед/мл) / Amylase (units/ml)	19,5±0,8	21,6±1,5	30,2±2,2**	44,4±3,9*	18,3±0,9
Пепсиноген (тир. ед/мл) / Pepsinogen (tyr. units/ml)	442,2±20,5	410,2±16,1	270,8±20,4**	153,8±10,9*	315,3±16,8**
Липаза (ед/мл) / Lipase (units/ml)	320,8±12,6	420,3±16,0**	390,4±15,5	344,4±17,2	324,3±13,6
Щелочная фосфатаза (ед/мл) / Alkaline phosphatase (units/ml)	6220,4±248,0	5740,2±218,7	3483,1±113,2**	2236,6±158,6*	3229,2±122,1**
АСТ (ед/мл) / AST (units/ml)	4,2±0,3	9,6±0,8*	9,8±0,8*	10,7±0,8*	8,6±0,6**
АЛТ (ед/мл) / (ALT) (units/ml)	4,2±0,3	9,4±0,7*	9,4±0,6*	10,7±0,8*	8,5±0,6**
АСТ/АЛТ / AST/ALT	1,0±0,02	1,02±0,02	1,04±0,02	1,0±0,02	1,01±0,02

Примечание: достоверность различий с показателями контрольной группы: * — p <0,001; ** — p <0,05.

Note: significance of differences with the indicators of the control group: * — p <0.001; ** — p <0.05.

Coprofiltrate (fecal dilution 1:4) had a slightly higher activity than serum amylase, which acquired greater amylolytic activity during pregnancy, amounting at the end of pregnancy to values 2 times higher than the control. After delivery the values were comparable to those of non-pregnant women (Table 2).

As for the lipolytic activity of serum, except for the I trimester of pregnancy, there is an increase in its growth in the II and III trimesters, and after labor it decreases almost to the values of the control group. From trimester to trimester the excretion of lipase with urine and saliva increases, remaining above the control and after delivery. Lipolytic activity in coprofiltrate increases in the I trimester and remains elevated in the subsequent periods of pregnancy.

With regard to alkaline phosphatase, there is a high level of the enzyme in the blood in the II, III trimester of pregnancy and in the postpartum period. There is an increase in the excretion of the enzyme in the urine in the I and II trimesters, and subsequently its concentration decreases, remaining after delivery below the control values. Having increased in the I trimester, the alkaline phosphatase activity of saliva remains high compared to the data in non-pregnant women. Being high in the control group, the enzyme activity in coprofiltrate decreases during pregnancy almost 3 times (p <0.001), holding the energy reserve for the development of pregnancy.

There is an increase in both AST and ALT in serum during pregnancy compared to the control group. However, the de Ritis ratio (an indicator of adaptation of metabolic fluxes), equal to 1.26±0.04 in the control, becomes less

than 1 due to a greater increase in ALT, which is included in glucose-alanine shunt and catabolism. AST acts as an integrator of metabolism, an indicator of lipid peroxidation in the mechanism of cytolysis.

In urine, transaminase activity is not so great and decreases in pregnancy by AST in all trimesters and ALT in the I trimester. The de Ritis ratio changes accordingly to the indicator in the blood.

In the saliva of the control group, the content of AST and ALT is almost equal to that in blood, i.e. transaminase activity in these fluids is the highest. In pregnancy in the I trimester in saliva it decreases, in the II and III trimesters AST activity increases, and ALT remains decreased in the II and increases in the III trimester. Accordingly, the AST/ALT ratio, which is greater than one, changes.

While in coprofiltrate in non-pregnant women the activity of transaminases is minimal (4.2±0.3 units/mL), in pregnancy it increases more than 2-fold for AST ($p < 0.001$) and 1.8–1.9-fold for ALT ($p < 0.05$). The de Ritis ratio of coprofiltrate in pregnancy is higher than one.

DISCUSSION

The obtained results indicate an increase in amylolytic activity of blood serum, saliva and coprofiltrate during pregnancy. Moreover, the amylolytic activity of the biological fluids studied remained higher than that of the control group in the postpartum period. According to the secretion of amylase with saliva, it is possible to refer to the dynamics of pregnancy, which is currently used in salivadiagnostics [7, 9, 10, 13, 17–19, 21].

A different dynamics was observed in relation to amylase in urine: the control group had a higher index than pregnant women in the I trimester. The activity of amylase in urine decreased after the labor.

The proteolytic activity of serum and coprofiltrate decreased during pregnancy and remained at a low level in the postpartum period. Blood plasma pepsinogen reflects the metabolism of amino acids and their anabolism [5]. Its value in the control group corresponded to the average values of literature data in the control group [8].

The fate of plasma pepsinogen depends on urinary excretion of pepsinogen, which increases from trimester to trimester and sharply decreases after delivery. In addition, saliva in the II and II trimesters of pregnancy had greater proteolytic activity than the control group. Its indices decrease in the postpartum period, which corresponds to the dynamics of protein-producing function in the “mother–fetus” system [8, 10].

The data on alkaline phosphatase parameters had differently directed changes throughout pregnancy in the women studied. In serum and urine there was an increase in the level of alkaline phosphatase by the end of pregnancy compared to the values in non-pregnant women. At the same time, in saliva, the highest values of the enzyme were detected in the I trimester of pregnancy with a subsequent decrease in the postpartum period. The alkaline phosphatase activity of coprofiltrate throughout pregnancy remained lower than that of non-pregnant women.

Alkaline phosphatase occupies an intermediate position in the classification of enzymes between hydrolases and transaminases [13]. Its hydrolytic activity in blood has multiple sources (gut, pancreas, liver, bone tissue, fallopian tubes). This also dictates its polyfunctionality, namely its participation in transport, regulatory, and integrative systems [5]. Alkaline phosphatase reflects its inclusion in the process of pregnancy, especially in the I trimester, in connection with the transport of substances-metabolites during the formation of the “mother–fetus” system.

In all the biological fluids studied, we found the presence of transaminases in women in all trimesters of pregnancy with the greatest changes in serum and coprofiltrate. The data on the ratios of enzyme content in blood, saliva, urine and coprofiltrate in pregnancy are presented to illustrate this phenomenon.

CONCLUSION

1. In pregnancy, there is an increase in the activity of serum amylase, saliva and coprofiltrate with preservation of the level of indicators above the control group in the postpartum period.

2. A different dynamics is observed with respect to proteolytic activity of serum and coprofiltrate with the lowest values at the end of pregnancy.

3. Alkaline phosphatase activity has multidirectional changes from I to III trimester of pregnancy with the greatest changes in enzyme values in saliva.

4. Transaminase activity of blood serum, saliva, urine and coprofiltrate with predominant enzyme levels in serum and coprofiltrate was detected in pregnant women.

5. The obtained results indicate the presence of homeostasis pathways of hydrolases due to recretory and excretory excretion of them from blood by salivary glands, intestine and kidneys.

6. The data on the secretion of enzymes in saliva may be the basis for the use of salivadiagnostics as a noninvasive method of diagnosis.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study,

acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

Consent for publication. Written consent was obtained from the patient for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Информированное согласие на публикацию. Авторы получили письменное согласие пациентов на публикацию медицинских данных.

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DOI: 10.56871/RBR.2024.77.24.006
UDC 616.839-036.1+616.72-002.77+616.832-004.2+796.012.62

THE ROLE OF PHYSICAL ACTIVITY IN RHEUMATOLOGIC PATIENTS WITH DISTURBANCES OF VEGETATIVE REGULATION

© Asiya Akhmetova[1], Alena A. Basina[1], Shaher Salah[1], Yana A. Leineman[2], Natalia Yu. Gavrilova[1, 4], Vladimir I. Utekhin[1, 3]

[1] Saint Petersburg State University. 7–9 Universitetskaya emb., Saint Petersburg 199034 Russian Federation
[2] North-Western State Medical University named after I.I. Mechnikov. 41 Kirochnaya str., Saint Petersburg 191015 Russian Federation
[3] Saint Petersburg State Pediatric Medical University. 2 Lithuania, Saint Petersburg 194100 Russian Federation
[4] Saint Petersburg University's (SPU) N.I. Pirogov Clinic of High Medical Technologies. 154 Emb. Fontanka River, Saint Petersburg 190020 Russian Federation,

Contact information: Asiya Akhmetova —6th year student of the Faculty of Medicine. E-mail: assiya001@mail.ru
ORCID: https://orcid.org/0009-0003-6576-9072

For citation: Akhmetova A, Basina AA, Salah Sh., Leineman YaA, Gavrilova NYu, Utekhin VI. The role of physical activity in rheumatologic patients with disturbances of vegetative regulation. Russian Biomedical Research. 2024;9(3):42–52. DOI: https://doi.org/10.56871/RBR.2024.77.24.006

Received: 30.05.2024 **Revised: 26.07.2024** **Accepted: 16.09.2024**

Abstract. The autonomic nervous system regulates all internal processes of the body, thus ensuring homeostasis. A disturbance in the balance of the autonomic nervous system can lead to clinical manifestations of autonomic dysfunction, often described in rheumatologic patients. Clinical manifestations of autonomic dysfunction vary widely in patients with rheumatoid arthritis (33–86% of cases) and systemic lupus erythematosus (9–90% of cases). The phenomena of dysautonomia in rheumatologic patients may manifest before the manifestation of specific symptoms of the disease. Signs of autonomic dysfunction reduce the quality of life of patients and pose a diagnostic challenge because of the variability of the clinical picture. An important aspect in the treatment of dysautonomia is early detection and a multidisciplinary approach. This review presents evidence that there is a positive effect of regular exercise in rheumatologic patients. It is important to remember that not all patients can be physically active due to chronic pain syndrome, joint swelling and deformity, limited spinal mobility, impaired thermoregulation and other clinical manifestations. Regular exercise can help restore the balance between the sympathetic and peripheral nervous systems. An exercise program as part of rehabilitation is developed individually based on the patient's complaints and physical parameters (strength, endurance, balance and coordination).

Keywords: autonomic dysfunction, dysautonomia, rheumatologic diseases, multiple sclerosis, physical exercises

К ВОПРОСУ О РОЛИ ФИЗИЧЕСКИХ НАГРУЗОК У ПАЦИЕНТОВ РЕВМАТОЛОГИЧЕСКОГО ПРОФИЛЯ С НАРУШЕНИЯМИ ВЕГЕТАТИВНОЙ РЕГУЛЯЦИИ

© Асия Ахметова[1], Алена Алексеевна Басина[1], Шахер Салах[1], Яна Андреевна Лейнеман[2], Наталья Юрьевна Гаврилова[1, 4], Владимир Иосифович Утехин[1, 3]

[1] Санкт-Петербургский государственный университет. 199034, г. Санкт-Петербург, Университетская наб., 7–9
[2] Северо-Западный государственный медицинский университет имени И.И. Мечникова. 191015, г. Санкт-Петербург, ул. Кирочная, 41
[3] Санкт-Петербургский государственный педиатрический медицинский университет. 194100, г. Санкт-Петербург, ул. Литовская, 2
[4] Клиника высоких медицинских технологий им. Н.И. Пирогова Санкт-Петербургского государственного университета. 190020, г. Санкт-Петербург, наб. реки Фонтанки, 154

Контактная информация: Асия Ахметова — студент 6 курса медицинского факультета. E-mail: assiya001@mail.ru
ORCID: https://orcid.org/0009-0003-6576-9072

Для цитирования: Ахметова А., Басина А.А., Салах Ш., Лейнеман Я.А., Гаврилова Н.Ю., Утехин В.И. К вопросу о роли физических нагрузок у пациентов ревматологического профиля с нарушениями вегетативной регуляции// Российские биомедицинские исследования. 2024. Т. 9. № 3. С. 42–52. DOI: https://doi.org/10.56871/RBR.2024.77.24.006

Поступила: 30.05.2024 **Одобрена: 26.07.2024** **Принята к печати: 16.09.2024**

Резюме. Вегетативная нервная система регулирует все внутренние процессы организма, обеспечивая тем самым гомеостаз. Нарушение баланса в работе вегетативной нервной системы способно привести к клиническим проявлениям вегетативной дисфункции, нередко описываемой у больных ревматологического профиля. Клинические проявления вегетативной дисфункции варьируют в широких пределах у пациентов с ревматоидным артритом (33–86% случаев) и системной красной волчанкой (9–90% случаев). Явления дизавтономии у пациентов ревматологического профиля могут проявиться до манифестации специфических симптомов заболевания. Признаки вегетативной дисфункции снижают качество жизни пациентов и представляют собой проблему для диагностики из-за вариабельности клинической картины. Важным аспектом в лечении дизавтономии является раннее обнаружение и применение междисциплинарного подхода. В обзоре представлены данные, свидетельствующие о наличии положительного влияния регулярных тренировок на пациентов ревматологического профиля. Важно помнить, что не все пациенты могут быть физически активными из-за хронического болевого синдрома, отека и деформации суставов, ограниченной подвижности позвоночника, нарушений терморегуляции и других клинических проявлений. Регулярные физические упражнения могут способствовать восстановлению баланса между симпатической и периферической нервными системами. Программа тренировок как часть реабилитации разрабатывается индивидуально на основе жалоб пациента и его физических показателей (силы, выносливости, равновесия и координации).

Ключевые слова: вегетативная дисфункция, дизавтономия, ревматологические заболевания, рассеянный склероз, физические упражнения

INTRODUCTION

The group of pathologies of the rheumatological profile includes rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, gouty arthritis, multiple sclerosis and others. Pathologies of the rheumatological profile are characterized by a multitude of systemic manifestations and a high degree of disability of patients.

In recent years, the role of the autonomic nervous system in the pathogenesis of these diseases has been increasingly discussed [5, 45]. The possibility of its training to improve the quality of life of patients has been discussed too [19]. Therefore, special attention is paid to the possibility of regulating autonomic tone through physical rehabilitation.

AIM

The aim of the review is to provide an up-to-date view of the relationship between the autonomic nervous system and physical activity in rheumatologic patients.

THE AUTONOMIC NERVOUS SYSTEM AND EXERCISES

The autonomic nervous system (ANS) plays an important role in the regulation of various body functions, including the cardiovascular system (CVS). Such parameters as the heart rate (HR), conduction, myocardial contraction and relaxation force are influenced by the balance of the parasympathetic and sympathetic nervous system. When a person transitions from rest to exercise, both ANS structures must function throughout the duration of exercise, and therefore the ANS response during the transition from rest to exercise is considered to be quite complex [62].

Successful functioning of the autonomic nervous system is based on rapid analysis by brain structures of incoming information from various receptors (in blood vessels, skeletal muscles, heart, lungs) and development of an adequate response. The response is realized by the peripheral part of the nervous system, releasing the neurotransmitters acetylcholine and noradrenaline from nerve fiber endings [54]. Such signals are received by the heart, adrenal glands, and vascular smooth muscle. Changes in sympathic and vagus balance depend on the type of exercise (isometric, isotonic or isokinetic), its intensity and duration [18]. At the beginning of exercise, there is an immediate decrease in cardiac vagus nerve tone, which leads to an increase in the HR, ventricular contractility, stroke volume and, as a consequence, cardiac output [38].

The contribution of the peripheral nervous system to HR is thought to be highest during low-intensity exercise and

decreases proportionally as exercise intensity increases, especially when HR reaches 100 beats per minute or more [28]. In contrast, the contribution of the sympathetic nervous system increases linearly with increasing exercise intensity. Activation of the sympathetic nervous system and subsequent release of adrenaline from the adrenal medulla contribute to an increase in HR and ventricular contractility and cause vasoconstriction in untrained muscles and internal organs, thus redistributing cardiac output toward actively working muscles.

Physical exercise activates the release of muscle metabolites stimulating α-adrenoreceptors, which leads to a decrease in the effectiveness of sympathetic vasoconstrictor influences (functional sympatholysis) [61]. Upon cessation of exercise, there is a rapid recovery of HR, followed by a gradual decrease in HR that takes several minutes [39, 43]. Athletes with good physical training have higher activity of the peripheral nervous system. Athletes show a rapid recovery of HR after cessation of training [43] and a significant decrease in resting HR [4, 12]. Thus, the balance of the autonomic nervous system is important for proper cardiovascular response during exercise and for human well-being [28].

Changes in the balance of both the sympathetic nervous system and the peripheral nervous system can lead to clinical manifestations of autonomic dysfunction. These can be characterized by a wide range of symptoms, including neurological (headache, sleep disturbances), cardiovascular (tachy- or bradycardia, hyper- or hypotension, orthostatic disorders), pulmonary (dyspnea), gastrointestinal (nausea, abdominal bloating, diarrhea or constipation, abdominal pain), genitourinary (neurogenic bladder, erectile dysfunction), secretomotor (sweating problems, dry mouth, dry eyes), vasomotor (extremity coldness, Raynaud's phenomenon), and visual (impaired pupil response to the light, tunnel vision, double vision, blurred vision, hypersensitivity to light) [46].

AUTONOMIC DISORDERS IN PATIENTS WITH RHEUMATOLOGIC DISEASES

The great variability of autonomic nervous system lesions in rheumatologic patients is most likely related to nonspecific symptoms of dysautonomia, small statistical samples in studies, and the lack of a unified approach to the examination of patients with suspected autonomic dysfunction [71]. For example, in patients with rheumatoid arthritis, ANS lesions ranges from 33 to 86% [8], and in systemic lupus erythematosus they ranges from 9 to 90% [40, 71].

The most studied manifestation of autoimmune dysautonomia is the development of cardiovascular dysfunction [71]. The increased cardiovascular risk in patients with rheumatologic diseases, especially rheumatoid arthritis (RA) (mortality is more than 50%) [2, 38] and systemic lupus erythematosus (SLE) (mortality is from 17% to 76%) [35, 51], is not fully explained by the presence of traditional risk factors (smoking, arterial hypertension, hypercholesterolemia, diabetes mellitus). The results of most studies indicate that decreased parasympathetic activity, increased sympathetic activity, altered heart rate variability and cardiac reflex activity are predictors of a higher incidence of cardiovascular disease and mortality in these patients [8].

DYSAUTONOMIA IN PATIENTS WITH RHEUMATOID ARTHRITIS

Signs of dysautonomia in rheumatologic patients may develop first before the onset of clinical symptoms of the main disease. Patients with rheumatoid arthritis have the following symptoms of autonomic imbalance: cyanosis, peripheral vasospasm, orthostatic hypotension, or postural tachycardia syndrome [8]. It has been suggested that decreased parasympathetic activity may be a part of the pathogenesis of rheumatoid arthritis [49]. It is necessary to search for significant correlations between dysautonomia and such characteristics as the duration of the initial disease, its activity, and the index of structural damage in patients with rheumatoid arthritis [71].

AUTONOMIC DISORDERS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Autonomic nervous system dysfunction is common in patients with systemic lupus erythematosus. Various cardiovascular cardiovascular Ewing reflex tests (Valsalva test, deep breathing test, orthostatic test, isometric exercise test) are used for its evaluation. Patients with SLE had significantly more positive tests for ANS dysfunction compared to healthy individuals. In addition, there is evidence that autonomic nervous system dysfunction does not correlate with clinical neuropsychiatric manifestations or immunoserologic markers such as antiphospholipid antibodies [70]. These data suggest that ANS dysfunction may be common in patients with SLE even in the absence of specific clinical manifestations, emphasizing the importance of monitoring of autonomic function in patients with SLE [70].

AUTONOMIC REGULATION DISORDERS IN PATIENTS WITH MULTIPLE SCLEROSIS

Dysautonomia has been documented in 45–84% of patients with multiple sclerosis (MS) [7, 21]. Autonomic

dysfunction in patients with multiple sclerosis is manifested by a variety of symptoms, including cardiovascular, genitourinary, and thermoregulatory dysfunction, sweating disorders, and signs of sexual dysfunction [7]. Disturbance of autonomic regulation of cardiovascular system can occur in the absence of clinical manifestations of the main disease [1, 6]. Both parasympathetic and sympathetic components of the cardiovascular system are selectively affected at different stages of multiple sclerosis [29, 50, 53, 76]. Parasympathetic dysfunction has been shown to correlate with increasing scores on the Disability rating scale and is more common in the late stages of the disease. In contrast, sympathetic dysfunction is associated with an outcome of the disease and thus may be associated with inflammatory mechanisms in multiple sclerosis. Autonomic dysfunction contributes to the increased fatigue felt by patients with multiple sclerosis [30]. As the disease progresses, symptoms of dysautonomia may increase, leading to orthostatic intolerance, sexual dysfunction, and decreased exercise tolerance, which are significantly affect patients' quality of life. Autonomic dysfunction in multiple sclerosis has been attributed to various mechanisms: lesion of autonomic pathways, influence of inflammatory mediators, imbalance of neurotransmitters (acetylcholine and noradrenaline), axonal degeneration, including demyelination of specific structures in the central nervous system that can disrupt ANS regulation [36, 65, 77]. Imbalance between over-activated immune system and autonomic receptors (β- and α-adrenergic and D1-like and D2-like dopamine receptors) on lymphocytes causes increased production of catecholamines by lymphocytes [16, 29]. Other factors that may be involved in autonomic dysfunction in multiple sclerosis are Epstein-Barr virus infection and vitamin D deficiency [10, 52].

DYSAUTONOMIA IN PATIENTS WITH OTHER RHEUMATOLOGIC DISEASES

In systemic scleroderma (SS), increased sympathetic activity impairs microcirculation, and impaired parasympathetic regulation can lead to impaired esophageal motor function even before the manifestation of systemic scleroderma [24]. Autonomic cardiovascular dysfunction associated with right ventricular dysfunction [74], myocardial blood flow dysregulation [34], and arrhythmias preceding the development of fibrosis [17] leads to an increased morbidity and mortality in patients with systemic scleroderma [24]. The early stages of Sjögren's syndrome are also characterized by ANS dysfunction, which causes a decrease in exocrine gland function due to impaired innervation and loss of glandular tissue due to apoptosis [20]. Symptoms such as gastrointestinal dysfunction, impaired sweating and urination, in combination with other signs of peripheral nervous system damage (sensory polyneuropathy) may occur before the onset of dry eye and mouth syndrome and later in the clinical stage [44, 57].

A common group of symptoms that include chronic fatigue, widespread pain, myalgia, arthralgia, cognitive dysfunction, and cardiovascular disorders, gastrointestinal tract and urinary tract disorders, can be described not only in patients with rheumatologic diseases, but also in patients with conditions such as myalgic encephalomyelitis/chronic fatigue syndrome, fibromyalgia (FM), breast implant illness (BII), and syndrome after COVID-19 [67]. It cannot be excluded that autonomic dysfunction in these types of pathology and rheumatologic diseases may share common pathophysiologic autoimmune mechanisms [31, 67].

THE ROLE OF PHYSICAL EXERCISE IN THE RECOVERY OF AUTONOMIC REGULATION IN PATIENTS WITH RHEUMATOLOGIC PROFILE

Regular exercise can be used to rebalance the sympathetic and peripheral nervous system.

It has been demonstrated in patients and animal models with chronic heart disease that exercise can increase vagus nerve modulation and decrease sympathetic tone [32]. Achieving autonomic balance leads to improved cardiovascular and endothelial function, normalization of blood pressure, heart rate variability and cardiorespiratory function with increased oxygen uptake and more efficient redistribution of blood flow. It is generally accepted that these changes are the main result of adaptation to regular exercise [19]. Another important effect of exercise is the induction of neuronal plasticity in autonomic centers of the CNS, such as the nuclei of the vagus nerve, nuclei of the rostral ventrolateral medulla. It has also been shown that exercise during physical rehabilitation causes reorganization of neurochemical connections in the brain, provokes neurogenesis and formation of new synapses, especially in the dentate gyrus of the hippocampus, which improves cognitive abilities [55].

Physical exercise in patients with autoimmune diseases has an immunomodulatory effect due to its effect on the expression of inflammatory marker genes, changes in the levels of hormones such as cortisol and adrenaline that inhibit the secretion of proinflammatory cytokines (tumor necrosis factor (TNF)-α), and decreased expression of toll-like receptors (TLR) on monocytes [27]. Exercise also mechanistically stimulates the promotion of immune cells and immunoglobulins through lymphatic and peripheral tissues, exerting a direct anti-inflammatory effect by

enhancing the production of anti-inflammatory cytokines. The muscle myokine IL-6 produced during exercise has a direct anti-inflammatory effect by improving glucose and lipid metabolism [58, 69].

Thus, physical exercise can serve as an additional therapy to standard immunomodulatory and immunosuppressive drugs.

Exercise is especially indicated in systemic diseases with possible impairment of self-care, as in the case of multiple sclerosis. However, patients with multiple sclerosis have motor impairment as a consequence of muscle weakness, they have impaired walking mechanics, balance problems; spasticity and fatigue complete the picture, which reduces their adherence to regular exercise [36]. Additional limitations are associated with worsening symptoms of autonomic dysfunction. Patients with multiple sclerosis may have impaired thermoregulation due to impaired sweating [42], and this makes potentially dangerous the exercise in hot conditions. Symptoms such as spasticity or paresis as the disease progresses are often irreversible, preventing patients from exercising. Moreover, these symptoms worsen with decreased physical activity. At the same time, it is well known that exercise alleviates conditions associated with hypodynamia [26]. There is evidence of a positive effect of exercise training on muscle strength in people with multiple sclerosis. Results from randomized controlled trials have shown that muscle strength increases after strength training [15, 18, 22, 23, 25, 63, 75, 78], combined aerobic exercise [48], and aquatic training [33]. Robotic mechanotherapy with the use of exoskeleton in patients with gait disturbance in multiple sclerosis allows to increase the speed and distance of walking [13]. There is evidence that progressive muscle overload training, which involves gradually increasing the weight of sports equipment or increasing the number of repetitions, improves lower limb muscle strength in people with multiple sclerosis, and these improvements are limited to the muscle groups targeted by the training [47]. Physical exercise in MS helps to restore movement coordination, stabilize balance, strengthen muscle tissue, eliminate increased spasticity, and normalize muscle tone despite the damage of the nervous system [3].

An individualized exercise program, which is recommended to be included as part of rehabilitation, should be designed taking into account the patient's chief complaints, strength, endurance, balance, coordination, and fatigue [37]. It is promising to further investigate the effects of exercise in patients with multiple sclerosis, including the effects of physical rehabilitation on cellular processes such as muscle protein synthesis, mitochondrial biogenesis, and changes in muscle fiber composition, to understand how physical activity may contribute to improving the quality of life of people with this disease [14].

A number of studies have shown the effectiveness of both endurance and weight training in improving the quality of life in people with rheumatologic diseases [60, 66]. Patients with these pathological conditions are more prone to the development of cardiovascular disease as a result of the systemic action of inflammatory mediators and are predisposed to metabolic changes due to elevated glucocorticoid levels. Unfortunately, patients with rheumatologic diseases have many reasons to be physically inactive. Chronic pain syndrome, joint swelling and deformity, limited spinal mobility, muscle weakness, fatigue, and skin rashes all contribute to patients' low adherence to an active lifestyle.

Regular physical activity is safe and well tolerated by most patients with rheumatologic diseases such as systemic lupus erythematosus, rheumatoid arthritis, systemic scleroderma, and Sjögren's syndrome [59, 66, 72]. However, there are groups of patients, predominantly with cardiac and pulmonary lesions, in whom exercise may not result in clear beneficial effects [66]. Antonioli et al. [9], who studied a group of patients with systemic scleroderma, demonstrated that exercise is useful in improving exercise tolerance by reducing the HR and dyspnea scores. Endurance and weight-bearing exercises significantly improve performance (e.g., walking time in the Cooper test) and reduce fatigue in patients with rheumatic diseases [41].

It is interesting that a recent meta-analysis of home-based exercise programs as part of the treatment plan for patients with rheumatologic diseases showed that physical activity significantly improves quality of life ($p < 0.01$), increases functional capacity ($p = 0.04$), reduces disease activity ($p = 0.03$), and decreases subjective feelings of pain ($p = 0.01$) compared to patients who do not perform any physical activity. Moreover, it has been concluded that the use of home exercise programs is as effective as exercise programs in a medical institution [68]. It is known that for patients with SLE and Sjögren's syndrome, fatigue is essentially a disabling symptom. A low-intensity exercise program is able to cause a subjective reduction in the feeling of fatigue in Sjögren's syndrome [73] and in patients with SLE [11].

Evaluation of physical activity and fatigue in patients with rheumatoid arthritis has shown that patients with a high level of daily physical activity have less fatigue. The authors noted that patients complain of increased pain and fatigue at the beginning of exercise and that symptoms decreases with continued physical activity [64].

Hypodynamia in patients with rheumatic diseases is extremely harmful both physically (decreased muscle strength, increased muscle stiffness, worsening of the condition) and psychologically (a fear of movement, depres-

sion, loss of self-confidence). It is necessary to offer patients adapted aerobic exercises with moderate intensity, which can be gradually increased as the condition improves [56].

CONCLUSION

Physical exercises during rehabilitation in rheumatologic patients with autonomic dysregulation contribute to the reorganization of neurochemical connections in the brain, neurogenesis and formation of new synapses, which improves cognitive abilities.

Exercise programs in rheumatologic patients with autonomic dysregulation have an immunomodulatory effect, reducing the level of inflammatory cytokines and stimulating the immune system, contributing to an improvement in quality of life, functional capacity and reduction of disease activity. Physical rehabilitation through exercise improves cellular processes such as muscle protein synthesis and mitochondrial biogenesis, which can lead to improved quality of life.

An individual approach to the development of exercise programs, which takes into account the patient's physical parameters and complaints, is an important aspect of successful rehabilitation. Further study of the effect of regular physical training on rheumatologic patients is necessary to fully understand the mechanisms of action of exercise and to develop optimal exercise programs for these patients. Regular physical training can be used to balance the activity of the sympathetic and parasympathetic nervous systems.

ADDITIONAL INFORMATION

Authors' contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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DOI: 10.56871/RBR.2024.95.99.007
UDC 616.13.002.2-004.6+616.831-005.4+616.72-084-005.4-008+616-07-036.22

CHRONIC LIMB THREATENING ISCHEMIA — EPIDEMIOLOGY, PATHOGENESIS, DIAGNOSTICS AND TREATMENT STRATEGIES

© Arshed A. Kuchay[1, 5], Alexander N. Lipin[1, 2], Shoaib F. Padaria[3], Nikita N. Gruzdev[1], Aleksey G. Borisov[1], Hudayberdi A. Muhamedov[4, 5], Geldy B. Khojakuliev[5], Alexandr A. Revyakin[5]

[1] City Hospital No. 14, Limb Salvage Center. 19/9 Kosinov str., Saint Petersburg 198099 Russian Federation
[2] Military Medical Academy named after S.M. Kirov. 6 Akademician Lebedev str., Saint Petersburg 194044 Russian Federation
[3] Jaslok Hospital & Research Center. 15, Dr. G. Deshmukh Marg, Mumbai, India
[4] Belgorod State National Research University. 85 Pobeda str., Belgorod 308015 Russian Federation
[5] Multidisciplinary medical clinic “Diona”. 21/1 Lunacharsky Ave., Saint Petersburg 194354 Russian Federation

Contact information: Arshed A. Kuchay — Clinical researcher —Limb Salvage Center; Cardiovascular surgeon Multidisciplinary medical clinic “Diona”. E-mail: drarshedcvs@gmail.com ORCID: https://orcid.org/0000-0002-7974-9369 SPIN: 5455-9033

For citation: Kuchay AA, Lipin AN, Padaria ShF, Gruzdev NN, Borisov AG, Muhamedov HA, Khojakuliev GB, Revyakin AA. Chronic limb threatening ischemia — epidemiology, pathogenesis, diagnostics and treatment strategies. Russian Biomedical Research. 2024;9(3):53–61.
DOI: https://doi.org/10.56871/RBR.2024.95.99.007Received: 25.06.2024 Revised: 31.07.2024 Accepted: 16.09.2024

Abstract. Chronic limb threatening ischemia (CLTI) is a syndrome of chronic obliterating diseases of peripheral arteries, different in etiology and pathogenesis. Diseases caused by degenerative damage to the arterial bed can lead to CLTI, causing aneurysm and long chronic occlusions. Such diseases include: Marfan syndrome, Ehlers–Danlos, Erdheim tumor, neurofibromatosis, fibrotic dysplasia. Multiple vasculitis are found in systemic vasculitis and connective tissue diseases. The most common cause of CLTI is atherosclerosis and vascular complications associated with diabetes mellitus. In the vast majority of cases (75–80%), atherosclerosis is the pathogenetic mechanism leading to the development of chronic obliterating diseases of the lower limb arteries. All these diseases lead to a significant reduction of perfusion blood flow at the level of microcirculation, causing severe metabolic disorders. Over time, the rheological properties of the blood are impaired, contributing to the progression of tissue ischemia. With CLTI, many of the body’s compensatory capabilities have been exhausted, but conducting revascularization of the lower limb is still possible.

Keywords: atherosclerosis, chronic limb threatening ischemia, revascularization, hybrid approach, epidemiology, diagnostics

ХРОНИЧЕСКАЯ ИШЕМИЯ, УГРОЖАЮЩАЯ ПОТЕРЕЙ КОНЕЧНОСТИ, — ЭПИДЕМИОЛОГИЯ, ПАТОГЕНЕЗ, ДИАГНОСТИКА И СТРАТЕГИИ ЛЕЧЕНИЯ

© Аршед Ахмад Кучай[1, 5], Александр Николаевич Липин[1, 2], Шоаиб Ф. Падариа[3], Никита Николаевич Груздев[1], Алексей Геннадьевич Борисов[1], Худайберды Азаткулиевич Мухамедов[4, 5], Гельды Батырович Ходжакулиев[5], Александр Алексеевич Ревякин[5]

[1] Городская больница № 14, Центр спасения конечностей. 198099, г. Санкт-Петербург, ул. Косинова, 19/9
[2] Военно-медицинская академия им. С.М. Кирова. 194044, г. Санкт-Петербург, ул. Академика Лебедева, 6
[3] Больница и исследовательский центр Джаслок. 15, Др. Г. Дешмух Марг, г. Мумбаи, Индия
[4] Белгородский государственный национальный исследовательский университет. 308015, г. Белгород, ул. Победы, 85
[5] Многопрофильная медицинская клиника «Диона». 194354, г. Санкт-Петербург, пр. Луначарского, д. 21/1

Контактная информация: Аршед Ахмад Кучай — клинический исследователь Центра спасения конечностей; врач сердечно-сосудистый хирург многопрофильной медицинской клиники «Диона». E-mail: drarshedcvs@gmail.com
ORCID: https://orcid.org/0000-0002-7974-9369 SPIN: 5455-9033

Для цитирования: Кучай А.А., Липин А.Н., Падариа Ш.Ф., Груздев Н.Н., Борисов А.Г., Мухамедов Х.А., Ходжакулиев Г.Б., Ревякин А.А. Хроническая ишемия, угрожающая потерей конечности, — эпидемиология, патогенез, диагностика и стратегии лечения// Российские биомедицинские исследования. 2024. Т. 9. № 3. С. 53–61. DOI: https://doi.org/10.56871/RBR.2024.95.99.007

Поступила: 25.06.2024 **Одобрена: 31.07.2024** **Принята к печати: 16.09.2024**

Резюме. Хроническая ишемия, угрожающая потерей конечности (ХИУПК), — это синдром хронических облитерирующих заболеваний периферических артерий, различных по этиологии и патогенезу. Заболевания, вызванные дегенеративным поражением артериального русла, могут приводить к ХИУПК, вызывая аневризмы и длительные хронические окклюзии. К таким заболеваниям относятся: Синдром Марфана, Элерса–Данло, опухоль Эрдгейма, нейрофиброматоз, фиброзная дисплазия. Множественные васкулиты встречаются при системных васкулитах и заболеваниях соединительной ткани. В подавляющем большинстве случаев (75–80%) патогенетическим механизмом, приводящим к развитию хронических облитерирующих заболеваний артерий нижних конечностей и ХИУПК, являются атеросклероз и сосудистые осложнения, связанные с сахарным диабетом. Все эти заболевания приводят к значительному снижению перфузионного кровотока на уровне микроциркуляции, вызывая тяжелые метаболические нарушения. Со временем нарушаются реологические свойства крови, способствуя прогрессированию ишемии тканей. При ХИУПК многие компенсаторные возможности организма уже исчерпаны, но проведение реваскуляризации нижней конечности все еще возможно.

Ключевые слова: атеросклероз, хроническая ишемия, угрожающая потерей конечности, реваскуляризация, гибридный подход, эпидемиология, диагностика

CONCEPT OF THE TERM “CHRONIC LIMB THREATENING ISCHEMIA”

The famous scientist P.R. Bell first introduced the concept of the word combination “critical lower limb ischemia or chronic limb threatening ischemia” into medical terminology in 1982. It was intended to designate patients with occlusive lesions of lower limb arteries, which are manifested by: pain at rest, trophic defects and the threat of lower limb gangrene [8]. In 1992, at the Second European Consensus on Chronic Critical Ischemia of the Lower Extremities, the definition of critical ischemia includes such concepts as: the presence of constant or recurrent pain in the lower extremities at rest, requiring analgesia with narcotic analgesics and existing for more than two weeks [26].

The syndrome of decompensated chronic arterial insufficiency of the limb, occurs against the background of reduced hemodynamic indices:

- ankle blood pressure indices 50–70 mm Hg;
- indexes of finger arterial pressure 30–50 mm Hg;
- transcutaneous oxygen tension values 30–50 mm Hg.

In recent decades, the term “CLTI” has become more widely used, which, in addition to focusing on hemodynamic parameters of the distal part of the lower extremity, includes other factors that negatively affect the healing of the trophic defect. Such factors include indicators as: the depth of the trophic defect, the presence and degree of its infection, the general morbid background of the patient. With the increasing incidence of diabetes mellitus and the impossibility to focus solely on hemodynamic parameters of the distal limb channel, it became necessary to develop a new classification of CLTI [4]. The new WIFI classification of lower extremity critical conditions meeting these criteria has been proposed for use in patients with and without diabetes mellitus. This classification takes into account the degree of ischemia, wound depth, peripheral blood supply, presence and severity of the infectious process in the trophic defect. Using this classification, it is possible to analyze the condition of the limb, estimate the expected benefit from the proposed revascularization of the lower limb, and predict the risk of major amputation [42]. Lack of CLTI treatment leads to the disability of patients due to the high risk of lower limb amputation. To date, the treatment of CLTI still remains one of the main problems in modern vascular surgery, as there is still a high risk of lower limb amputation and high mortality of patients after it. CLTI is a terminal stage of chronic arterial insufficiency of the lower extremities, in which the combined state of microcirculation of the lower extremities, namely, reduced perfusion of the foot tissues, will not allow to achieve adequate repair of the trophic defect without limb revascularization.

EPIDEMIOLOGY OF CHRONIC LIMB THREATENING ISCHEMIA

The incidence of chronic limb threatening ischemia or critical lower limb ischemia varies from 50 to 100 cases per 100,000 population in European and US populations [69]. The prognosis in CLTI patients remains extremely unfavorable. According to the TASC document when comparing the results of treatment of patients with CLTI are comparable to the results of treatment of patients with severe oncologic diseases. Only in half of cases patients diagnosed with CLTI undergo limb revascularization, 25% undergo a course of conservative therapy, and the remaining 25% undergo primary amputation.

In the absence of adequate treatment within 5 years, only 30% of patients with CLTI manage to preserve the limb, 52% of patients undergo amputation, and the remaining 18% of patients die from complications associated with CLTI progression. Publications in domestic and foreign literature indicate that the percentage of amputations in patients with CLTI is still quite high [1, 70, 71, 79]. With the advent of high-tech methods of endovascular reconstruction, the overall amputation rate is significantly decreasing due to the possibility of successful revascularization of the tibial segment [31]. Despite the active development of reconstructive vascular surgery, up to 500 lower limb amputations per 1 million population are performed annually. The share of all performed amputations on CLTI reaches 90%. In Russia about 300 amputations per 1 million population are performed annually due to the presence of CLTI in a patient. In Finland and the USA this figure is 120 and 280 respectively [1, 2, 25]. According to different literature data, 25% of patients die within one month after high amputation of the lower limb. In 2 years after high amputation the mortality rate varies from 25 to 60%. The mortality rate within 5 years after high lower extremity amputation ranges from 50 to 70%. After 10 years, this figure reaches 90% [7, 40, 70]. Such high figures of mortality after high amputation are associated with the presence of concomitant pathology, as well as caused by: advanced age, multifocal character of atherosclerosis lesion with involvement of coronary and carotid basins and manifestation of its complications in the form of metabolic disorders and nutritional status, due to decompensated limb ischemia and endogenous intoxication, as well as the traumatic nature of the operation. Among the main causes of death after amputation: acute cardiovascular insufficiency (50–66.4%), purulent and septic complications (11–34.1%), and acute cerebral circulatory failure (3.6%) are in the first place [32, 79].

PATHOGENESIS OF CHRONIC LIMB THREATENING ISCHEMIA

CLTI is a syndrome of chronic obliterative diseases of peripheral arteries, different in etiology and pathogenesis [72]. Diseases caused by degenerative lesions of the arterial bed can lead to CLTI, being the cause of aneurysms and dissections. Such diseases include Marfan syndrome, Ehlers–Danlos syndrome, Erdheim's tumor, neurofibromatosis, fibromuscular dysplasia. Multiple vascular lesions are noted in systemic vasculitis and connective tissue diseases [73]. The most frequent cause of CLTI development is atherosclerosis and vascular complications associated with the presence of diabetes mellitus. In the vast majority of cases (75–80%), atherosclerosis is the pathogenetic mechanism leading to the development of chronic obliterative diseases of lower limb arteries [73]. All these diseases lead to a significant decrease in perfusion blood flow at the level of microcirculation, causing severe metabolic disorders. Over time, the rheological properties of blood are disturbed, contributing to the progression of tissue ischemia [73]. In CLTI, many compensatory capabilities of the organism are exhausted, but revascularization of the lower limb is still possible [74].

DIAGNOSTIC METHODS OF CHRONIC LIMB THREATENING ISCHEMIA

Ankle-brachial index

Ankle brachial index (ABI) is a non-invasive and simple method for the diagnosis of peripheral arterial disease. The sensitivity of the ABI in the presence of CLTI ranges from 80% to 95% in patients without DM. In patients with DM this indicator varies between 50–71%. The specificity of ABI in detecting CLTI in patients without diabetes ranges from 95 to 100%. In the presence of DM, the specificity of ABI is 30–96% [34]. The value of ABI up to 0.7 indicates circulatory compensation, the range of ABI from 0.7 to 0.4 indicates circulatory sub compensation. In the presence of ABI less than 0.4 blood circulation of the lower leg in the decompensation stage (CLTI). The correlation of the degree of severity of chronic limb ischemia depending on the index of ABI according to the national recommendations for the management of patients with vascular arterial pathology was used. CLTI I — ankle brachial index ≥0.9; IIa — resting ABI 0.7–0.9; II b — resting ABI less than 0.7–0.9; III — resting ankle pressure <50 mm Hg; IV — resting ankle pressure <50 mm Hg. False-positive result of ABI is observed in patients suffering from long-term diabetes mellitus, terminal stage of renal failure due to pronounced development of media calcinosis of arterial wall [13, 62]. In case of elevated ABI (more than 1.4) and ABI is considered uninformative, other non-invasive methods of measuring peripheral hemodynamics are used. Finger-brachial index (FBI) is an informative method of diagnosing CLTI in patients with the presence of DM or terminal renal failure. Normally, the FBI is greater than 0.75. FBI less than 0.25 corresponds to severe CLTI [15, 62].

Duplex or Triplex scanning of vessels

Duplex or Triplex scanning is one of the highly accurate, noninvasive methods of diagnostics of vascular pathology, both in venous and arterial basins. Triplex vascular scanning includes 3 main ultrasound modes [63]:

- Normal mode is carried out to assess the structure of vessels, vascular walls and the degree of their tortuosity, which is especially important to consider for making the correct diagnosis and in preparation for various operations.

- Dopplerography — the study of the speed and direction of blood flow in the vessels, as well as its basic digital characteristics.
- Color Doppler mapping — helps to assess the patency of vessels, to detect the presence of thrombosis and atherosclerotic plaques, narrowing the vessel lumen, due to the sensitivity to slow flows improves differentiation between severe stenosis and occlusion, and also allows visualizing small vessels not distinguishable in B-mode [75].

The limitation in the use of duplex scanning is the difficulty of visualization and assessment of the lumen of calcified arteries. Difficulty in visualization of iliac arteries, provided there is gas in the intestine. Difficulty in visualization of collateral blood flow and reduced visualization of the affected arteries of the lower leg, especially the peroneal artery [21, 76].

Laser Doppler flowmetry

The leading link in the pathogenesis of CLTI is microcirculatory disorders. Laser Doppler flowmetry (LDF) allows to evaluate the state of microcirculatory channel [9]. The LDF method is based on optical noninvasive probing of tissues with laser radiation and analysis of scattered and reflected radiation from erythrocytes moving in tissues. The use of LDF provides a deeper understanding of the pathogenesis of microcirculation disorders and allows, along with early diagnosis, to conduct objective control over therapeutic measures by analyzing the results in dynamics [24]. The absence of absolute contraindications to LDF and a wide range of indications for its use to assess both systemic and local state of microcirculation allows using this noninvasive diagnostic method in patients with severe somatic diseases [9].

Spiral computed tomography

Good visualization of the localization level and extent of the pathological process in the arteries of the lower limbs is necessary to determine the nature and scope of surgical treatment. Modern CT scanners in diagnostics of the aortoiliac segment have high sensitivity — 96% and specificity — 98%. When assessing the femoral-popliteal, femoral-tibial segments, these indicators are 97 and 94%, respectively. In assessing the state of the more distal channel, the sensitivity of the method is 95%, specificity 91% [67]. The sensitivity and specificity of this method are comparable to the invasive diagnostic method — selective angiography of lower limb arteries [3].

Application of multidetector CT angiography technique, has a number of advantages over traditional contrast angiography. One of the significant advantages of this method is the possibility to perform it at the outpatient stage. Spiral CT angiography allows visualization of arteries in several planes, creating volumetric images [49]. SCT angiography can be performed in patients who have had a pacemaker installed. CT angiography clearly visualizes calcium and implanted stents within the artery. With CT angiography, it is possible to visualize the tissues around the vessel, which allows the detection of arterial compression from the outside by a tumor, lymph nodes, cyst, or aneurysm [52]. Allergic reaction to iodine-containing contrast agents and renal insufficiency of the patient are the limitations of CT angiography.

Magnetic resonance imaging

Magnetic resonance angiography (MRA), being a noninvasive study with absence of nephrotoxic effects of magnetic resonance contrast agents and radiation exposure, provides an opportunity for objective assessment of peripheral vessels [48]. However, in case of multilevel atherosclerotic lesions of lower limb arteries, adequate visualization of the affected segment is performed using special contrast agents - paramagnetic [48, 55]. The advantage of this method is simultaneous visualization of soft tissues, which is necessary in assessing the prevalence of necrotic lesion in the presence of trophic defect [75]. Despite the fact that MRA has high specificity and sensitivity (93–100%), being a promising technique, it also has a number of disadvantages. In the presence of hemodynamic disturbances and turbulent blood flows, the degree of stenosis may be overestimated. Limitation of MRA use in the presence of stented arteries of the lower limbs, as stents may be accompanied by artifacts, simulating vessel occlusion. It is impossible to perform MRA in patients with pacemakers, as well as in patients with clipped cerebral aneurysms, presence of metal structures. In patients with elevated creatinine, magnetic resonance angiography with gadolinium contrast in rare cases may cause toxic effects on the kidneys. MRA poorly visualizes arterial calcinosis, which may significantly limit its use in planning for vascular anastomosis [48, 57, 64].

Peripheral arteriography of the lower limbs

Peripheral angiography of lower limb arteries belongs to the invasive method of investigation and is a necessary method of investigation in case a patient is planned to undergo revascularization of lower limb arteries [5, 18]. Due to the intensive development and increasing informativity of noninvasive methods of investigation, peripheral arteriography is no longer the “gold standard” in the diagnosis of lower limb peripheral arterial diseases and is performed as a diagnostic procedure less and less frequently [5, 19]. Angiography allows to determine the localization and extent of the pathological process, assess the state of the arterial or venous channel, visualize and evaluate the state of collateral circulation. Angiography of lower limb arteries is of-

ten used to visualize congenital vascular anomalies. Angiography allows visualization of stented arteries of the lower extremities without artifacts or image distortion.

There are no absolute contraindications to angiography of the lower limb arteries; relative contraindications include: acute renal or hepatic insufficiency, allergy to iodine preparations, acute stages of specific diseases (tuberculosis, viral hepatitis B and C) [20, 73].

Transcutaneous oximetry

Transcutaneous oximetry ($TcPO_2$) is a simple and non-invasive way to assess the microcirculation. Transcutaneous oximetry is monitored using a Clark electrode placed on the skin and heated. It determines the level of tissue oxygen saturation, thereby reflecting the state of microcirculation [77]. Although there are some known drawbacks, this method is the "gold standard" in assessing tissue perfusion in the presence of CLTI [70]. $TcPO_2$ is used for amputation risk stratification, and assessment of distal perfusion with $TcPO_2$ is recommended for use in patients with CLTI and DM. Some conditions limit the use of $TcPO_2$. Indications are distorted in the presence of: elevated body temperature, peripheral edema, widespread inflammation, cutaneous hyperkeratosis, and obesity [3].

TREATMENT METHODS FOR CHRONIC LOWER LIMB ISCHEMIA

Treatment of chronic critical lower limb ischemia is currently one of the unsolved problems in vascular surgery. Quite often the use of surgical method of treatment in the presence of severe concomitant pathology is not possible. Despite the achievements of modern pharmacotherapy, many existing drugs in the treatment of critical ischemia of the lower limbs are ineffective. In this regard, the search for new approaches to the solution of this problem is underway. The latest pharmacological breakthrough was the introduction of methods of angiogenesis stimulation in the affected limbs based on the possibilities of genetically engineered technology. The mechanism of action of the drug is aimed at stimulation of capillary growth and development of microcirculatory channel in ischemic tissues [29, 30, 46]. When determining the possibility of using genetically engineered method of angiogenesis stimulation in clinical practice, it turned out that the most effective use of this technology was noted in patients with CLTI of IIb–III stages according to Fonteyn-Pokrovsky classification. Taking into account the low efficacy of conservative therapy, when determining the therapeutic tactics in patients with CLTI, it is necessary, first of all, to decide on the possibility of reconstructive surgery on vessels. Surgical treatment aimed at revascularization of the lower limb is the optimal method of treatment of ischemic syndrome caused by severe morpho-functional changes in the arterial bed. Surgical treatment can be performed in all patients with CLTI in the presence of appropriate indications and absence of contraindications to intervention. Maximum restoration of blood circulation in the lower extremities is possible only by using direct revascularization: endovascular revascularization, open surgery, hybrid reconstruction [45, 47, 74].

Endovascular surgery — remains a young direction in modern vascular surgery and is increasingly used in the treatment of obliterative diseases of the arteries of the lower extremities. Balloon angioplasty and stenting of lower limb arteries are the most common endovascular interventions for pathology of lower limb arteries, allowing to restore blood flow through vessels without open surgery. Over the last decade, endovascular methods of revascularization of lower limb arteries have been rapidly improved, so in a significant number of patients they are used as a less invasive treatment for lower limb arterial disease [39, 51, 74].

For many years, open surgery was considered the "gold standard" treatment for patients with clinical presentation of CLTI. With the advent of endovascular surgery, these two methods were constantly opposed to each other [59].

Recently, however, there have been more and more reports about the desire to find the best treatment options for patients with CLTI, which has led to the merging of these areas [74].

In case of multilevel lesions of lower limb arteries, combined operations consisting in the simultaneous use of open arterial reconstructive surgeries with endovascular procedures (stenting, balloon angioplasty, etc.) have been performed more often [33, 78–80].

The first data on the use of open and endovascular surgery in a patient with critical lower limb ischemia were published in 1973 by J. Porter, who reported on balloon angioplasty of the iliac artery with simultaneous femoral-femoral cross-over bypass [54].

At present, hybrid surgery is a rather promising direction in the treatment of CLTI and accounts for 5 to 21% of lower extremity arterial vessel surgeries in foreign clinics [16, 22, 23].

Some authors mean hybrid surgery as a combined one-stage intervention combining open and endovascular stages within one operating room, while others suggest that these interventions can be separated in time by minutes, hours, or even days [6, 12, 50, 66, 74, 78–80].

There is an opinion that when endovascular and "open" techniques are combined in a single patient, the risk of restenosis and reconstruction occlusions in the distant postoperative period, is much higher than after performing standard open surgery [74, 80].

Hybrid surgery should be used for patients with high surgical risk, with severe concomitant pathology in multilevel

atherosclerotic lesions, but it should be taken into account that in the presence of stage IV limb ischemia, diabetes mellitus, and chronic renal failure, it can negatively affect the remote patency of the reconstruction zones [37, 68, 78].

Considering the fact that the development of critical ischemia in one third of cases is associated with multilevel atherosclerotic lesions of the arterial channel of the lower extremities and the lack of randomized clinical trials in this area is of scientific interest [17, 74, 78, 80]. The accumulated experience of open bypass surgeries, hybrid reconstructions, and endovascular techniques for the treatment of patients with critical ischemia over many years demonstrate positive results. The existing studies comparing the advantages and disadvantages of open, endovascular and hybrid operations in critical ischemia do not consider separately patients with previously performed stenting of lower limb arteries in the clinical picture of critical lower limb ischemia due to disease progression.

CURRENT RANDOMIZED TRIALS INVESTIGATING THE TREATMENT OF PATIENTS WITH CLTI

BASIL is the only randomized controlled trial to date comparing the results of surgical lower extremity arterial reconstruction with those of endovascular revascularization of the lower extremity arteries, in patients with critical lower extremity ischemia. In their original 2005 publication, the BASIL investigators reported that the main clinical outcomes (overall survival and amputation-free survival) at 2 years did not differ between groups. However, after 2 years, open bypass surgery appeared to be advantageous, prompting the continuation of the study [10]. The final analysis of the BASIL results now suggests that patients who initially underwent endovascular interventions have a much worse outcome in the late postoperative period than patients initially treated surgically. Quality of life scores and costs were not significantly different overall. There are many controversies surrounding the BASIL trial and its interpretation. These include the choice of study population, the endpoints considered, and the nature of the procedures performed. The BASIL trial confirms the primacy of open surgical bypass with autovenous for the majority of patients with critical lower extremity ischemia and raises questions about the consequences of failed endovascular interventions. Complications during hybrid operations range from 2–6.5% and are typical complications for endovascular and open interventions [44]. Further multicenter studies are needed to address the large evidence gap for treatment selection in this patient population [14].

BASIL-2 is a multicenter prospective randomized study including patients with critical lower extremity ischemia. The aim of the study was to evaluate the economic and clinical efficacy of treatment of endovascular and femoral-popliteal bypass below the knee joint target with autovenous in patients with critical lower limb ischemia with localization of the lesion at the level and below the popliteal artery. Official recruitment of centers included in the study has been started since July 2014. In total, 600 patients are planned to be included in the study, with a follow-up time of 3 years. As of November 01, 2017, a total of 40 clinical centers are open for participation in the Basil-2 study; 29 in England, 5 in Scotland, 2 in Wales, 3 in Denmark and 1 in Sweden. Thirty-nine of the 40 clinical centers have cumulatively recruited 249 participants [11, 53].

BASIL-3 is a multicenter randomized controlled trial. Comparing the clinical and cost-effectiveness of simple balloon angioplasty with or without metallic stenting, drug-coated balloon angioplasty with or without bare metal stenting, and primary stenting with drug-coated stents secondary to the femoral-popliteal segment. Patients with multilevel atherosclerotic lesions of the lower extremity arteries may receive aorto-iliac and/or popliteal-tibial revascularization at the same time as their randomized femoral-popliteal intervention. The primary clinical outcome is amputation-free survival. The primary outcome in the economic analysis is cost per year. Secondary outcome measures include overall survival, major adverse limb events, major adverse cardiac events, ischemic pain relief, trophic defect healing, and quality of life. The required sample size was calculated for 861 participants (287 at each shoulder). These patients will be recruited over 3 years and followed up for 2 to 5 years [11, 35].

BEST-CLI is a prospective, multicenter, randomized, open comparative study. The primary objective of the study is to compare the efficacy, functional outcomes, and cost of treatment in patients with infrainguinal lesions of lower extremity arteries and the presence of critical lower extremity ischemia who underwent open surgical treatment or endovascular revascularization [27]. The study includes 2100 patients at 140 medical sites in the United States and Canada who are candidates for both revascularization options. This is a 4-year study, ongoing from 2014–2017, with each patient being followed for a minimum of 2 years after treatment [56, 58].

Critical lower extremity ischemia continues to represent a huge public health problem in the developed world. The BEST-CLI study is a timely and necessary study to help identify best practices and provide a framework for thoughtful application of current and future treatment options for critical lower extremity ischemia [28, 41, 43].

Currently, there is no consensus on the prioritized method of surgical treatment for patients with critical lower extremity ischemia. For a long time, open arterial operations remained the “gold standard” in the treatment of CLTI. Since

the advent of endovascular surgery, many positions in the treatment of CLTI began to be reconsidered. Despite the variety of existing methods of surgical treatment, none of them is without disadvantages.

Recently, there has been a rapid increase in the use of minimally invasive technology in revascularization of lower limb arteries in patients with CLTI [38, 74, 78, 80–87]. Repeated surgical interventions on arterial segments are usually technically much more difficult and traumatic [36, 60, 61, 65].

It follows that the problem of choosing the optimal and hybrid surgical tactics for treatment of patients with critical lower limb ischemia or chronic limb threatening ischemia in the presence of extended occlusion of the SFA and lesions of the lower leg arteries is relevant and of scientific and practical interest.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении работу.

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DOI: 10.56871/RBR.2024.68.51.008
UDC 616.31-001.17

PATHOGENETIC TREATMENT OF MECHANICAL BURN SHOCK CAUSED BY EXTENSIVE BURN INJURY AND LONG-TERM COMPRESSION SYNDROME (LITERATURE REVIEW)

© Nikolay K. Sokolov[2], Evgeniy V. Zinoviev[1, 4], Eduard K. Derii[1], Denis V. Kostyakov[1], Stanislav N. Pyatakov[3], Vladimir O. Sidelnikov von Essen[1], Anna V. Kostyakova[1]

[1] Saint Petersburg I.I. Dzhanelidze research institute of emergency medicine. 3 lit. A Budapestskaya str., Saint Petersburg 192242 Russian Federation
[2] City Emergency Hospital. 88/35 Bodraya str., Rostov-on-Don 344068 Russian Federation
[3] City Hospital № 4. 1 Tuapsinskaya str., Sochi 354057 Russian Federation
[4] Saint Petersburg State Pediatric Medical University. 2 Lithuania, Saint Petersburg 194100 Russian Federation

Contact information: Denis V. Kostyakov — Candidate of Medical Sciences, Leading Researcher in the Department of thermal injuries.
E-mail: kosdv@list.ru ORCID: https://orcid.org/0000-0001-5687-7168 SPIN: 9966-5821

For citation: Sokolov NK, Zinoviev EV, Derii EK, Kostyakov DV, Pyatakov SN, Sidelnikov von Essen VO, Kostyakova AV. Pathogenetic treatment of mechanical burn shock caused by extensive burn injury and long-term compression syndrome (literature review). Russian Biomedical Research. 2024;9(3):62–68. DOI: https://doi.org/10.56871/RBR.2024.68.51.008

Received: 27.05.2024 **Revised: 21.06.2024** **Accepted: 16.09.2024**

Abstract. Mechanical burn shock caused by extensive burn injury and prolonged compartment syndrome is a complex and multifaceted problem. A number of pathological processes, such as severe pain, plasma loss, hypovolemia, disseminated intravascular coagulation syndrome, systemic hypoxia, electrolyte imbalance, reperfusion tissue damage, endotoxicosis, and metabolic disorders determine the severity of the pathology in patients with combined trauma. Despite the variety of methods of pathogenetic treatment of mechanical burn shock, mortality among this group of patients still remains at a high level. In accordance with this, the question of a more detailed study of the pathogenesis and improvement of methods of pathogenetic treatment of mechanical burn shock remains relevant.

Keywords: mechanical burn shock, skin burns, prolonged compression syndrome, pathogenesis of shock

ПАТОГЕНЕТИЧЕСКОЕ ЛЕЧЕНИЕ МЕХАНО-ОЖОГОВОГО ШОКА, ВЫЗВАННОГО ОБШИРНОЙ ОЖОГОВОЙ ТРАВМОЙ И СИНДРОМОМ ДЛИТЕЛЬНОГО СДАВЛЕНИЯ (ОБЗОР ЛИТЕРАТУРЫ)

© Николай Константинович Соколов[2], Евгений Владимирович Зиновьев[1, 4], Эдуард Константинович Дерий[1], Денис Валерьевич Костяков[1], Станислав Николаевич Пятаков[3], Владимир Олегович Сидельников фон Эссен[1], Анна Витальевна Костякова[1]

[1] Санкт-Петербургский научно-исследовательский институт скорой помощи имени И.И. Джанелидзе. 192242, г. Санкт-Петербург, Будапештская ул., 3, лит. А
[2] Городская больница скорой медицинской помощи. 344068, г. Ростов-на-Дону, ул. Бодрая, 88/35
[3] Городская больница № 4. 354057, г. Сочи, ул. Туапсинская, 1
[4] Санкт-Петербургский государственный педиатрический медицинский университет. 194100, г. Санкт-Петербург, ул. Литовская, 2

Контактная информация: Денис Валерьевич Костяков — к.м.н., ведущий научный сотрудник отдела термических поражений.
E-mail: kosdv@list.ru ORCID: https://orcid.org/0000-0001-5687-7168 SPIN: 9966-5821

Для цитирования: Соколов Н.К., Зиновьев Е.В., Дерий Э.К., Костяков Д.В., Пятаков С.Н., Сидельников фон Эссен В.О., Костякова А.В. Патогенетическое лечение механо-ожогового шока, вызванного обширной ожоговой травмой и синдромом длительного сдавления (обзор литературы) // Российские биомедицинские исследования. 2024. Т. 9. № 3. С. 62–68. DOI: https://doi.org/10.56871/RBR.2024.68.51.008

Поступила: 27.05.2024 **Одобрена: 21.06.2024** **Принята к печати: 16.09.2024**

Резюме. Механо-ожоговый шок, обусловленный обширной ожоговой травмой и синдромом длительного сдавления, является сложной и многогранной проблемой. Ряд патологических процессов, таких как выраженный

болевой синдром, плазмопотеря, гиповолемия, синдром диссеминированного внутрисосудистого свертывания, системная гипоксия, расстройство электролитного баланса, реперфузионное повреждение тканей, эндотоксикоз, обменные нарушения, обусловливают тяжесть течения патологии у пациентов с комбинированной травмой. Несмотря на разнообразие способов патогенетического лечения механо-ожогового шока, летальность среди этой группы больных по-прежнему остается на высоком уровне. В соответствии с этим актуальным остается вопрос о более детальном изучении патогенеза и усовершенствовании методов патогенетического лечения механо-ожогового шока.

Ключевые слова: механо-ожоговый шок, ожоги кожи, синдром длительного сдавления, патогенез шока

INTRODUCTION

Skin burns occupy the third place among all traumas in the Russian Federation [21]. Despite the high level of health care development, even in some European Union countries the incidence of burn injuries reaches 295 cases per 100,000 population [39]. Annual reports of the Ministry of Health of the Russian Federation state that burn lesions were detected in 220–240 victims in the period 2021–2022, among whom the mortality rate was 6.9–7.3% [33]. Over the last two decades (from 2003 to 2020), the main causes of burns are household injuries — 92%, while industrial injuries account for 8% [13]. Such indicators are primarily associated with the active industrialization of society and an increase in the standard of living.

The main causes of mass burn traumatism are natural and man-made disasters, hostilities, and industrial emergencies [5]. All of the above events increase the risk of not only temperature exposure but also mechanical exposure, which, in turn, may be the cause of the development of long compression syndrome (LSS) [46]. Prolonged compression syndrome is a life-threatening condition resulting from prolonged compression of a body part and its subsequent release, causing a state of shock [37]. Long-term compression syndrome was first described by E. Bywaters in 1941 during World War II. The author analyzed the experience of treating patients affected by massive bombardment [43]. In the following decades, no emergency event in large cities passed without the syndrome of prolonged compression.

The pathogenesis of prolonged compression syndrome is based on ischemic intoxication that develops during decompression. Toxins and products of cytolysis enter the organism from the long-term compressed (ischemic) tissues in the mode of normo- or hypoperfusion [42]. Toxins, in turn, increase the permeability of microcirculatory blood vessel walls, causing plasma effusion into the intercellular space, increasing edema of the injured limb and worsening blood rheology. In addition, an important link in the pathogenesis is pain, especially in the case of limb injury, rich in a large number of nerve endings in the skin, skeletal muscle and periosteum. As a result of complex effects of pain syndrome, toxic lesion, psychological and emotional state, traumatic shock may develop [34].

Due to the steadily increasing process of urbanization and industrialization of society, burn injuries and prolonged compression syndrome are always present in any natural and man-made disasters, and they are closely intertwined with each other. The search for methods to improve the provision of medical care in these conditions is an urgent issue of modern health care.

To optimize the treatment of patients with long compression syndrome in extensive burns, it is important to consider the pathophysiological aspects of this problem. The main cause of severe course and/or lethal outcome due to long compression syndrome with burns is shock. Shock is a state of the organism characterized by a complex of pathological shifts leading to hypoperfusion of organs with the development of subsequent cellular dysfunction [1]. The main pathogenetic factors of shock in these conditions include intoxication, metabolic disorders, hypovolemia, plasma loss, severe pain, cardiac and central nervous system dysfunction [1, 2].

Specialized literature devoted whole sections to the peculiarities of the course and causes of mechanical and burn shock on the background of long compression syndrome [19]. The main cause of unfavorable outcomes in combined lesions is the rapid depletion of homeostasis mechanisms [14]. The pathogenesis of long compression syndrome is characterized by endotoxemia by products of ischemia, tissue decay and reperfusion, the consequence of which is the development of toxic damage to the kidneys, heart and liver.

When a patient suffers from the syndrome of prolonged compression and extensive burns at the same time, a general reaction of the body is formed, which is accompanied by a peculiar clinical picture of mechanical-burn shock [31]. The mechanism of development of such shock is primarily associated with the loss of plasma, including proteins and electrolytes. These patients have systemic disorders due

to hypovolemia, hemoconcentration, increase in peripheral resistance and rheologic disorders in the first hours after injury [45]. These pathological processes are accompanied by a characteristic clinical picture in the form of increased heart rate, decreased stroke volume, and coronary blood flow disorders [8, 45]. In addition to toxic kidney damage by myoglobin due to the development of long compression syndrome, hypocirculation and hypercoagulability with subsequent oligo- or anuria develop under the influence of hemolysis products and tissue necrosis [40].

Generalized hypoxia is one of the leading causes of irreversibility of mechanical and traumatic shock [11]. The term “hypoxia” is understood as oxygen starvation arising from insufficient supply of oxygen to the tissues of the body or disruption of its utilization in the processes of biological oxidation. Hypoxia is a secondary phenomenon arising in the long compression syndrome and often has a significant impact on the outcome of burns, as it increases the existing oxygen deficiency [30].

Mechanical traumatic shock is caused by the syndrome of prolonged compression and extensive deep burns, the concentration of catecholomines in the blood increases 5–7 times, which leads to centralization of blood circulation and redistribution of blood to internal organs [17]. As a result, there is even greater ischemia of the burn area, which, in turn, leads to the formation of zones of secondary necrosis, even in areas where the initial burn was borderline [24].

Thus, a whole range of severe pathological processes such as pronounced pain syndrome, plasma loss, hypovolemia, disseminated intravascular coagulation syndrome, systemic hypoxia, electrolyte balance disorder, reperfusion tissue damage, intoxication, metabolic disorders are realized in the development of mechanical burn shock against the background of burn injury and long compression syndrome. All these pathological processes inevitably lead to multiorgan failure and septic course of traumatic disease in this category of patients.

The main cause of lethal outcomes in this type of shock is the development of multiorgan failure. Therefore, it is necessary to improve the methods of infusion therapy of extensive burns combined with the syndrome of prolonged compression. There are many scientific works in the modern literature, which describe the features of infusion therapy in shock, aimed at different links of the pathological process.

Based on well-known literature data, the conventional boundary of mechanical and burn shock reversibility is widespread blood stasis in metabolic capillaries. Its prevention is the main goal of antishock therapy [9]. The task of infusion therapy in mechanical and burn shock is to maintain the volume of circulating plasma and blood [44]. Infusion and transfusion therapy with crystalloid solutions is used to replenish the volume of circulating blood in shocks of various etiologies. The main preparations of these groups include: physiologic solution 0.9%, Ringer’s solution, ringer-lactate, lactosol, sterofundin, etc. [18]. The infusion rate is also an important parameter. It can be: fast and slow replenishing the deficit of circulating blood volume [28]. When choosing the infusion rate in the acute period of mechanical burn shock, three main parameters serve as a reference point: arterial pressure, central venous pressure and hourly diuresis [28].

One of the most important hemodynamic parameters is oncotic blood pressure. In the phase of circulatory decentralization, special attention should be paid to this parameter, because the increase in oncotic blood pressure will promote the transfer of fluid from the intercellular space into the vascular bed, thus restoring the reduced volume of circulating blood [16]. Native or synthetic colloidal preparations are used for this purpose. Their volume can amount up to 75% of the total infusion volume [10].

The use of infusion therapy with crystalloid solutions without the use of blood products and synthetic colloids can lead to serious complication in the form of hyperhydration with subsequent interstitial pulmonary edema [26]. There is debate in the scientific literature, but most sources cite the opinion that a state of hyperhydration in combined burn injury is less preferable than mild hypohydration [20].

There was performed a comparative evaluation of the efficacy of antishock therapy schemes using synthetic and native colloids in different ratios. It was found that the value of cardiac output in patients who underwent infusion with colloids amounting to more than 50% was significantly higher in the first day after trauma [28].

The use of hydroxyethyl starch solutions with a molar mass of 130 kDa was also quite effective. A group of authors found that the use of this solution in combined burn injuries provides rapid recovery of circulating blood volume, cardiac output, parameters of oxygen delivery and consumption [12].

Sodium lactate is equally important in the treatment of mechanical-burn shock, since severe hypoxia disrupts the processes of lactic acid absorption in the Krebs cycle [38]. In addition to sodium lactate it is reasonable to use such preparations as lactasol and quintasol, where lactate is replaced by acetate [38].

As described above, both systemic and local hypoxia influence the development of mechano-burn shock. As a result, energy deficiency develops at the cellular level, leading to the disruption of a number of important energy-dependent processes in the cell [36]. Accordingly, it is reasonable to add antihypoxic agents [35]. The effect of these drugs is achieved mainly by reducing tissue oxygen demand

and energy potential, blocking calcium channels, inhibiting arachidonic acid metabolism and lipid peroxidation. Such group of drugs includes: amtisol, gutimin, cytochrome C, pyridoxine, sodium oxybutyrate [41]. It has been proved that antihypoxants in crystalloid solutions significantly increase the therapeutic efficacy of antishock infusion therapy when treating mechanical and burn shock [23].

The next group of drugs that improve the efficacy of infusion therapy in burn shock are antioxidants. Their necessity is caused by pathophysiological processes associated with the inevitable development of oxidative stress in burn shock and reperfusion when blood flow is restored in the area of tissue compression [29]. The problem of chain oxidation of cell membrane lipids has been known for a long time and was demonstrated back in the 50–60s of the last century by a group of scientists led by N.N. Semenov. Since then, a vast experience of fundamental and experimental data has been accumulated, confirming the key role of free radicals in physiological and pathological processes in the human body [27]. All antioxidants can be divided into natural and artificial ones. The first group includes vitamin E, which is a classic phenolic antioxidant, vitamin A, carotenoids, ascorbic acid, vitamins of the K group, ubiquinone (coenzyme Q10), flavonoids, melatonin, and estrogens. The second group includes selenium preparations (ebselen), ionol, phenozan, probucol (fenbutol), emoxipin, mexidol, idebenone, neurostrol, thiotriazolin, oliphen, amtisol, dimexide, etc. [27].

It is possible to use ascorbic acid and tocopherol acetate from this wide list of antioxidants in case of patients with burn shock [32]. Their joint administration allows to stabilize cell membranes and prevent excessive vascular permeability, plasma loss, hemolysis [15]. There are also single works on the use of superoxide dismutase and catalase in extensive burns, which allowed to reduce the vascular reaction, the severity of tissue edema and prevent hypoproteinemia [22].

Another pathologic process accompanying mechanical burn shock is the pain syndrome. The problem of pain control has not been completely solved to date [17]. A pain impulse that develops in mechanical-burn shock has a twofold significance. Firstly, it activates excessive defense mechanisms, which often causes energetically disadvantageous strengthening of the most important life-support systems. Secondly, a pain impulse is one of the mechanisms regulating the emergence of inflammatory reaction, which always accompanies traumatic injury and itself can be a source of a pathological impulse, aggravating the patient's condition [4].

To reduce pain syndrome, anesthetics, narcotic and non-narcotic analgesics, hypnotics, tranquilizers, and sedatives are used both as independent therapy and in combination [3]. However, it should be noted that general anesthesia methods cause an additional load on the body and depress many vital systems [6]. Accordingly, they cannot be considered as a specific method of burn shock treatment. Similar problems have been described with the use of narcotic analgesics, which depress the respiratory center, cause hypotension and reduce cardiac output [25]. Currently, modern narcotic analgesics such as buprenorphine and Prosidol are more preferable since they have fewer of the above-described side effect [7].

Thus, mechanical burn shock caused by extensive burns in combination with long compression syndrome is a complex and multifaceted problem. The development of a number of pathological processes, such as pronounced pain syndrome, plasma loss, hypovolemia, DIC, systemic hypoxia, electrolyte balance disorder, reperfusion tissue damage, endotoxemia and metabolic disorders, determine the severity of the pathology in this category of victims. Nowadays there are many variants of solutions, preparations and treatment schemes for infusion therapy of mechanical-burn shock, but lethality still remains high. Accordingly, it is urgent to thoroughly study the possibilities of increasing the effectiveness of infusion therapy in mechanical-burn shock caused by extensive burns in combination with the syndrome of prolonged compression.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении работы.

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DOI: 10.56871/RBR.2024.69.10.009
UDC 616.151.5-072.7+612.115+616.13/.14-005.6-092-084-085+578.834.1

CLINICAL AND BIOCHEMICAL MARKERS FOR EARLY DIAGNOSIS OF SYSTEMIC AMYLOIDOSIS

© Iskander A. Latypov[1], Sarng S. Purveev[1, 2], Kirill V. Chelnyntsev[3], Lev D. Balashov[1]

[1] Saint Petersburg State Pediatric Medical University. 2 Lithuania, Saint Petersburg 194100 Russian Federation
[2] Institute of Experimental Medicine. 12 Academician Pavlov str., Saint Petersburg 19702 Russian Federation
[3] Almazov National Medical Research Centre. 2 Akkuratov str., Saint Petersburg 197341 Russian Federation

Contact information: Sarng S. Pyurveev — Senior Assistant Department of pathological physiology with immunopathology course.
E-mail: dr.purveev@gmail.com ORCID: https://orcid.org/0000-0002-4467-2269 SPIN: 5915-9767

For citation: Latypov IA, Purveev SS, Chelnyntsev KV, Balashov LD. Clinical and biochemical markers for early diagnosis of systemic amyloidosis. Russian Biomedical Research. 2024;9(3):69–75. DOI: https://doi.org/10.56871/RBR.2024.69.10.009

Received: 27.06.2024 **Revised: 06.08.2024** **Accepted: 16.09.2024**

Abstract. Amyloidosis is a group of systemic diseases characterized by the extracellular deposition of pathologic, insoluble fibrillar proteins in tissues and organs, potentially leading to multiple organ failure. In spite of the heterogeneity of systemic amyloidosis etiology, clinical signs and symptoms of various forms of amyloidosis considerably overlap and depend on the affected organs. Signs and symptoms suggestive of amyloidosis are often nonspecific, which makes it difficult for clinicians to diagnose amyloidosis early and prompts them to exercise increased clinical vigilance. In the article, we aimed to determine the most significant clinical and hematologic markers of the most common forms of systemic amyloidosis and to assess the potential of using standard diagnostic manipulations to confirm or rule out amyloidosis in high-risk patients. Amid the backdrop of population aging and an increase in the incidence of neurodegenerative diseases, the adoption of standardized and relatively low-cost methods of early diagnostics will enable clinicians to evaluate disease progression, select treatment strategies, and determine patient prognosis earlier on, thereby minimizing damage to the healthcare system.

Keywords: amyloidosis, modeling of amyloidosis

КЛИНИКО-БИОХИМИЧЕСКИЕ МАРКЕРЫ ДЛЯ РАННЕЙ ДИАГНОСТИКИ СИСТЕМНОГО АМИЛОИДОЗА

© Искандер Альбертович Латыпов[1], Сарнг Саналович Пюрвеев[1, 2], Кирилл Владимирович Челнынцев[3], Лев Дмитриевич Балашов[1]

[1] Санкт-Петербургский государственный педиатрический медицинский университет. 194100, г. Санкт-Петербург, ул. Литовская, 2
[2] Институт экспериментальной медицины. 197022, г. Санкт-Петербург, ул. Академика Павлова, 12
[3] Национальный медицинский исследовательский центр им. В.А. Алмазова. 197341, г. Санкт-Петербург, ул. Аккуратова, 2

Контактная информация: Сарнг Саналович Пюрвеев — ассистент кафедры патологической физиологии с курсом иммунопатологии.
E-mail: dr.purveev@gmail.com ORCID: https://orcid.org/0000-0002-4467-2269 SPIN: 5915-9767

Для цитирования: Латыпов И.А., Пюрвеев С.С., Челнынцев К.В., Балашов Л.Д. Клинико-биохимические маркеры для ранней диагностики системного амилоидоза // Российские биомедицинские исследования. 2024. Т. 9. № 3. С. 69–75. DOI: https://doi.org/10.56871/RBR.2024.69.10.009

Поступила: 27.06.2024 **Одобрена: 06.08.2024** **Принята к печати: 16.09.2024**

Резюме. Амилоидоз — группа системных заболеваний, вызванных внеклеточным депонированием патологических нерастворимых фибриллярных белков в тканях и органах, которые могут привести к полиорганной недостаточности. Несмотря на гетерогенность этиологии системного амилоидоза, клинические проявления различных форм этой нозологической группы во многом пересекаются и зависят от пораженных органов.

Знаки и симптомы, позволяющие заподозрить амилоидоз, чаще всего неспецифичны, поэтому у специалистов возникают трудности в ранней диагностике, что требует усиленного клинического наблюдения. В данной статье мы хотим определить наиболее значимые клинико-гематологические маркеры распространенных форм системного амилоидоза и оценить возможности использования стандартных диагностических манипуляций для подтверждения или исключения амилоидоза у пациентов из групп риска. В связи с активным старением населения и ростом заболеваемости нейродегенеративными заболеваниями внедрение унифицированных и относительно дешевых методов ранней диагностики позволит клиницистам на начальных этапах оценить течение заболевания, подход к лечению и прогноз для пациента, а также позволит минимизировать ущерб для системы здравоохранения.

Ключевые слова: амилоидоз, моделирование амилоидоза

HISTORY

In the XIX century, pathologist R. Virchow, studying the so-called sebaceous disease, discovered that the substance located in the affected organs, when stained with iodine, acquires a purple color, like starch, and called it amyloid (Latin *amylum* — a starch). In the XX century German doctor N.N. Bennhold created one of the first methods of lifetime diagnosis of amyloidosis by intravenous injection of amyloid-specific dye congo-rot and estimation of the rate of reduction of its concentration in the blood. With the development of electron microscopy, A.S. Cohen established that amyloid is a fibrillar protein with β-folded configuration, which is detected in X-ray diffraction and is apparently responsible for the typical coloring of this protein. The discovery was also that in primary amyloidosis fibrils are fragments of immunoglobulin light chains. Later it was found that fibrils consist of different types of protein chains, which was the beginning of the way to the development of etiotropic therapy of amyloidosis.

EPIDEMIOLOGY OF AMYLOIDOSIS

To date, the prevalence of amyloidosis has not been sufficiently studied due to rarely expressed and specific clinical symptoms, difficulties in diagnosis, and low vigilance of specialists. Various sources estimate the prevalence of amyloidosis from 0.1 to 6% in the population based on autopsy data [6, 22].

Because of the lack of documentation, estimates of the prevalence of amyloidosis vary widely depending on the study period, the State and the researchers' methods of estimating incidence. For example, in the United States of America, according to S.Y. Tan, the incidence of amyloidosis ranges from 5.1 to 12.8 cases per 100 thousand population per year [23]. In European countries, the incidence of amyloidosis in chronic diseases ranges from 1.4 to 5%, and in Japan it is 0.1% [7, 23]. Over time and with the development of genetic screening in the Russian Federation, the frequency of occurrence of certain forms of amyloidosis began to increase, and the structure of the detected forms of amyloidosis changed: for example, AA-amyloidosis was detected in 46 patients out of 152 before 2006 and in 90 among 153 patients after 2006, but at the same time the frequency of AL-amyloidosis significantly increased (in 53 out of 153 patients before 2006 and in 80 out of 152 after 2006), which is associated with the increased sensitivity of diagnostic methods [6, 12, 13].

AMYLOIDOSIS MORPHOLOGY

Amyloid fibrils are protein polymers up to 10 nm in diameter and 800 nm in length, having a cross-β conformation, which determines the special polarization ability of amyloid to double beam refraction. Histochemical studies have established that polysaccharides account for no more than 4% of the mass of total amyloid. Nevertheless, the historical name "amyloid" has been retained and is used in the International Classification of Diseases [4, 12].

In addition to fibrillar protein, the so-called P-component, which constitutes 10–15% of the total mass of amyloid, was found in the composition of amyloid. This protein is similar in structure to serum amyloid P-component (SAP), the increase in the amount of which in blood plays its role in the pathogenesis of amyloid accumulation [11, 12]. In addition, P-component protects amyloid fibrils from their lysis by macrophages-amyloidoclasts, which prevents the patient's immune system from effectively destroying the depot of pathological protein and, in turn, also plays an important role in the pathogenesis of amyloidosis [4, 12].

Some types of amyloid have a relationship with neurodegenerative processes such as Alzheimer's disease, Parkinson's disease, hemoblastosis (Rustitzky–Kahler disease), hemodialysis (β_2-microglobulin amyloidosis), chronic inflammatory diseases (tuberculosis, rheumatoid arthritis, gout, bronchiectatic disease, etc.), as well as some genetic defects (Aβ-amyloidosis, familial nephropathic amyloidosis, Finnish-type amyloidosis, American amyloidosis, etc.).

AMYLOIDOSIS CLASSIFICATION

According to the International Classification of Diseases and Related Health Problems (ICD-10), amyloidosis is of the following types:

E85.0 **Non-neuropathic heredofamilial amyloidosis**
Familial Mediterranean fever
Hereditary amyloid nephropathy
E85.1 **Neuropathic heredofamilial amyloidosis**
Amyloid polyneuropathy (Portuguese)
E85.2 **Heredofamilial amyloidosis, unspecified**
E85.3 **Secondary systemic amyloidosis**
Haemodialysis-associated amyloidosis
E85.4 **Organ-limited amyloidosis**
Localized amyloidosis
E85.8 **Other amyloidosis**
E85.9 **Amyloidosis, unspecified** Clinical and biochemical classifications of amyloidosis forms are now widely accepted (Fig. 1).

AA-amyloidosis group: the disease is characterized by extracellular deposition of serum amyloid A (serum amyloid A, SAA) fibrils. SAA is a normal serum acute-phase protein

Table 1

Clinical and biochemical classification of amyloidosis forms

Таблица 1

Клиническая и биохимическая классификации форм амилоидоза

Название амилоидного белка / Name of amyloid protein	Белок-предшественник/ Precursor protein	Клиническая форма / Clinical form
AA	Сывороточный амилоид А (SAA) / Serum amyloid A (SAA)	Вторичный амилоидоз при хронических инфекционных и воспалительных заболеваниях (реактивный), амилоидоз при периодической болезни и синдроме Макла–Уэллса / Secondary amyloidosis in chronic infectious and inflammatory diseases (reactive), amyloidosis in periodic disease and Muckle-Wells syndrome
AL	Λ, κ легкие цепи Ig	Амилоидоз, ассоциированный с плазмоклеточными дискразиями: идиопатический, при миеломной болезни и макроглобулинемии Вальденстрёма / Amyloidosis associated with plasma cell dyscrasias: idiopathic, in multiple myeloma and Waldenström's macroglobulinemia
ATTR	Транстиретин / Transthyretin	Семейные варианты полинейропатического, кардиомиопатического амилоидоза, системный старческий амилоидоз / Familial variants of polyneuropathic, cardiomyopathic amyloidosis, systemic senile amyloidosis
Aβ2M	β_2-микроглобулин / β_2-microglobulin	Диализный амилоидоз / Dialysis amyloidosis
AGel	Гелсолин / Gelsolin	Финская семейная амилоидная нейропатия / Finnish familial amyloid neuropathy
AApoAI	Аполипопротеин / Apolipoprotein	Амилоидная нейропатия (III тип по van Allen, 1956) / Amyloid neuropathy (type III according to van Allen, 1956)
AFib	Фибриноген / Fibrinogen	Амилоидная нефропатия / Amyloid nephropathy
Aβ	β-протеин / β-protein	Болезнь Альцгеймера, синдром Дауна, церебральная амилоидная ангиопатия / Alzheimer's disease, Down syndrome, cerebral amyloid angiopathy
APrPser	Прионный белок / Prion protein	Болезнь Крейтцфельдта–Якоба, болезнь Гертсманна–Штраусслера–Шейнкера / Creutzfeldt–Jakob disease, Gertsmann–Straussler–Scheinker disease
AANF	Предсердный натрийуретический фактор / Atrial natriuretic factor	Изолированный амилоидоз предсердий / Isolated atrial amyloidosis
AIAP	Амилин / Amilin	Изолированный амилоидоз островков Лангерганса при сахарном диабете 2-го типа, инсулиноме / Isolated amyloidosis of the islets of Langerhans in type 2 diabetes mellitus, insulinoma
ACal	Прокальцитонин / Procalcitonin	При медуллярном раке щитовидной железы / For medullary thyroid cancer
ACys	Цистатин С / Cystatin C	Церебральная амилоидная ангиопатия / Cerebral amyloid angiopathy

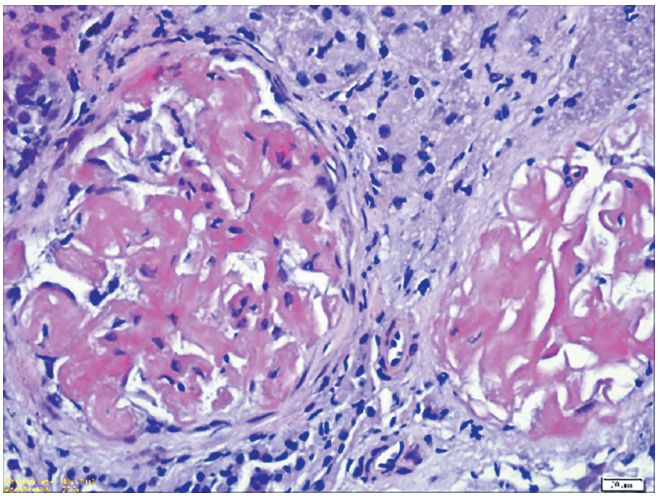

Fig. 1. Glomerular amyloid deposits in secondary amyloidosis. Light microscopia with kongo-rot colouring, ×40 [30]

Рис. 1. Гломерулярные депозиты амилоида при вторичном амилоидозе. Световая микроскопия с окраской конго-рот, ×40 [30]

synthesized by hepatocytes under the influence of pro-inflammatory protein-cytokines [15, 18]. Thus, a consistently high concentration of SAA in blood ensures the development of AA-amyloidosis by folding and stacking protein chains into the β-conformation and binding to glycosaminoglycans (GAGs) and the amyloid P component of serum [8, 21]. This group includes reactive amyloidosis, amyloidosis in periodic disease, and amyloidosis in Muckle-Wells syndrome. SAA levels in plasma have no significant difference according to sex and age and have been variously estimated to be between 5 and 20 mg/L using latex immunoturbidimetry, radioimmunoassay, and rapid quantitative test methods [9].

AL-amyloidosis develops as a result of massive systemic extracellular deposition of monoclonal immunoglobulin light chains secreted by plasmocyte clones [2–4]. It is known that λ-isotype and κ-isotype of light chains are predominantly amyloidogenic [8, 13, 21]. Diagnosis of this type of amyloidosis is based on morphologic examination of biopsy specimens of subcutaneous adipose tissue or salivary glands (at the initial stage), and if it is impossible to isolate it from these organs — from the affected organs: kidneys, liver, gastrointestinal tract organs, myocardium [5, 16, 25]. The presence of extracellular masses positively stained with congo red dye and giving green luminescence during microscopy in polarized light suggests the presence of amyloid deposits. Advanced methods of AL amyloidosis diagnostics may include immunohistochemical study on paraffin sections, immunofluorescence study using highly sensitive and specific anti-λ and anti-κ antibodies [14, 17, 20, 21]. It is necessary to perform differential diagnosis with other types of amyloidosis: for example, in the absence of positive staining of deposits, it is reasonable to analyze the level of serum amyloid A in plasma, β_2-microglobulin in patients on hemodialysis, as well as lysozyme, apolipoproteins, fibrinogen, gelsolin, transthyretin, the level of which may be increased in familial forms of amyloidosis [12, 14].

ATTR-amyloidosis (transthyretin, senile amyloidosis). This type of amyloidosis is an irreversibly progressive and disabling disease characterized by progressive polyneuropathy, as well as the development of heart failure, kidney and other organ damage. It includes familial amyloid polyneuropathy and systemic senile amyloidosis [10, 14, 26, 30].

In familial amyloid polyneuropathy, the amyloid precursor protein is transthyretin. It is a protein that provides transport of thyroxine and retinol and is synthesized in the liver, vascular plexus of the brain ventricles, and retinal epithelium. The development of ATTR-amyloidosis has two pathogenetic variants: genetic mutations associated with amino acid substitution or deletion in the *TTR* gene encoding transthyretin synthesis and located on the long arm of chromosome 18 [1, 24, 25]. Currently, more than 100 types of *TTR* gene mutations are known, but many remain unexplored. The prevalent *TTR* mutations are Val30Met and Val122Ile. Amyloidogenic mutations cause deposition of pathologic protein in the peripheral nervous system, heart, gastrointestinal tract, and lens [13, 22, 26].

ATTR-amyloidosis can be suspected in patients with progressive neuropathy and cardiomyopathy, constipation and diarrhea, and decreased visual acuity. Diagnosis is based on morphologic examination of a biopsy of the affected organ, as well as genetic testing for the presence of *TTR* gene mutations [10, 21, 24].

AN EXPERIMENTAL MODELING OF AMYLOIDOSIS

Many still unsolved problems of etiology, pathogenesis, diagnosis, treatment, and prevention of amyloidosis attract the attention of researchers to experimental models of amyloidosis [27]. Modeling amyloidosis in animals can provide the search for more effective methods of its prevention and treatment. There are many ways of experimental modeling of amyloidosis. Most of them are based on the administration of chemical or biological substances to animals. In the XXI century, the Russian Federation has developed its own methods: for example, for the first time a method was developed to obtain a model of systemic cardiac amyloidosis on the background of a single injection of rats with a mixture containing native egg albumin, complete Freund's adjuvant and rat myocardial homogenate. A method of modeling amyloidosis in white mice consisting in the administration of native egg albumin every other day for 30 days was also patented [3, 5, 7].

However, the disadvantages of these methods are: the small size of animals, the complexity of histological and chemical examination of organs due to their small size, the need to control daily diuresis, tubule reabsorption (by endogenous creatinine clearance) and the content of electrolytes in the urine of animals. The combination of these requirements significantly complicates experimental modeling, as well as increases its cost [3].

As a result of these studies, the authors found out that some pharmacological substances can have a therapeutic effect in amyloidosis: for example, succinic acid administered intragastrically through a probe at a rate of 1.5 mmol/kg for 60 days promoted the recovery of myocardium and stroma vessels and hemodynamics in tissues. Morphological study of the organs of rats treated with acisol (bis-1-vinylimidazole-zincdiacetate) showed a decrease in congophilia, the appearance of individual amyloidoclasts, and foci of revascularization [19].

Since one of the frequent links in the pathogenesis of amyloidosis is chronic inflammation, it is necessary to develop a system of measures allowing mass diagnostics of chronic inflammatory diseases in individuals at risk [6].

Currently, there are no massively implemented therapy protocols capable of inducing a sufficiently rapid process of destruction and excretion of amyloid deposits from tissues, and the available treatment methods are aimed at regulating the metabolism of amyloidogenic substances [29, 30].

The introduction of already available methods of searching for amyloidosis markers, such as C-reactive protein, β_2-microglobulin, serum amyloid A protein, and genetic studies (e.g., exon sequencing of the TTR gene) is feasible due to the possibility of performing such tests at a relatively low cost. Investigation of these markers will allow to detect or exclude the diagnosis of some amyloidoses in patients with unclear clinical picture associated with polyneuropathies, neurological syndromes, and cardiomyopathy of unclear genesis and/or in patients with the above symptoms and a history of chronic inflammatory diseases.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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DOI: 10.56871/RBR.2024.75.27.010
UDC 612.216.3+616-089.5-031.81+612.215

USE OF SPONTANEOUS BREATHING MODES AT VARIOUS STAGES OF GENERAL ANESTHESIA. LITERATURE REVIEW

© Vasiliy A. Pyzhov, Kirill N. Khrapov

Pavlov First Saint Petersburg State Medical University. 6–8 L'va Tolstogo str., Saint Petersburg 197022 Russian Federation

Contact information: Vasiliy A. Pyzhov — Candidate of Medical Sciences, Assistant of Anesthesiology and Intensive Care Department, anesthesiologist and emergency physician of Anesthesiology and intensive care unit No. 2, Research clinical center of anesthesiology and intensive care. E-mail: vasiliy.pyzhov@yandex.ru ORCID: https://orcid.org/0009-0000-7593-4420 SPIN: 7597-5517

For citation: Pyzhov VA, Khrapov KN. Use of spontaneous breathing modes at various stages of general anesthesia. Literature review. Russian Biomedical Research. 2024;9(3):76–86. DOI: https://doi.org/10.56871/RBR.2024.75.27.010

Received: 20.06.2024 **Revised: 26.07.2024** **Accepted: 16.09.2024**

Abstract. Among all the respiratory complications observed in surgical patients in the postoperative period, lung tissue atelectasis is one of the most common. In addition to the use of protective intraoperative ventilation, one of the measures to prevent atelectasis of lung tissue may be to maintain independent breathing throughout, or at certain stages of general anesthesia. Currently, most anesthesia machines have a wide range of ventilation modes, including self-breathing mode with pressure support. When performing respiratory support in this mode, the patient is able to influence all phases of the respiratory cycle, the diaphragm remains functional, which reduces the risk of atelectasis and ventilator-induced dysfunction of the diaphragm. Due to the support pressure applied in response to each breath, the patient does little breathing work, which prevents the development of fatigue of the respiratory muscles. However, anesthesia with preserved spontaneous breathing may be limited by the need to administer high doses of opioids and anesthetics, for example, in highly traumatic surgical interventions, since anesthesia drugs can have a significant effect on the respiratory center. There is sufficient information in the literature regarding the effectiveness of its use at the stage of induction of general anesthesia, in order to better preoxygenation. The use of (PSV, pressure support ventilation) mode in combination with positive end expiratory pressure (PEEP) during preoxygenation improves oxygenation, prevents episodes of desaturation, and lengthens the time of safe apnea. In addition to using this regimen during the induction of general anesthesia, its use may be appropriate at the stage of maintaining anesthesia during operations where the introduction of muscle relaxants is not required, as well as at the final (awakening, extubation) stages of general anesthesia in cases where the main surgical stage requires total myoplegia. The use of pressure support at these stages is less common. However, a number of publications have shown that the use of this regimen during general anesthesia while maintaining independent breathing can lead to improved gas exchange and reduced atelectasis of lung tissue, in addition, make awakening and extubation more comfortable and faster, compared with other approaches to respiratory support during anesthesia.

Keywords: artificial lung ventilation, pressure support ventilation, spontaneous breathing, general anesthesia, awakening

ПРИМЕНЕНИЕ РЕЖИМОВ САМОСТОЯТЕЛЬНОГО ДЫХАНИЯ НА РАЗЛИЧНЫХ ЭТАПАХ ОБЩЕЙ АНЕСТЕЗИИ. ЛИТЕРАТУРНЫЙ ОБЗОР

© Василий Анатольевич Пыжов, Кирилл Николаевич Храпов

Первый Санкт-Петербургский государственный медицинский университет им. академика И.П. Павлова.
197022, г. Санкт-Петербург, ул. Льва Толстого, 6–8

Контактная информация: Василий Анатольевич Пыжов — к.м.н., ассистент кафедры анестезиологии и реаниматологии, врач анестезиолог-реаниматолог отделения анестезиологии и реанимации № 2 научно-клинического центра анестезиологии и реаниматологии. E-mail: vasiliy.pyzhov@yandex.ru ORCID: https://orcid.org/0009-0000-7593-4420 SPIN: 7597-5517

Для цитирования: Пыжов В.А., Храпов К.Н. Применение режимов самостоятельного дыхания на различных этапах общей анестезии. Литературный обзор // Российские биомедицинские исследования. 2024. Т. 9. № 3. С. 76–86. DOI: https://doi.org/10.56871/RBR.2024.75.27.010

Поступила: 20.06.2024 **Одобрена: 26.07.2024** **Принята к печати: 16.09.2024**

Резюме. Среди всех респираторных осложнений, наблюдаемых у хирургических больных в послеоперационном периоде, ателектазирование легочной ткани — одно из наиболее часто встречающихся. Помимо применения протективной интраоперационной вентиляции легких, одной из мер профилактики ателектазирования легочной ткани может являться сохранение самостоятельного дыхания на всем протяжении, либо на отдельных этапах общей анестезии. В настоящий момент на большинстве наркозных аппаратов имеется большой спектр режимов вентиляции, в том числе и режим самостоятельного дыхания с поддержкой давлением (PSV, pressure support ventilation). При проведении респираторной поддержки в данном режиме пациент способен оказывать влияние на все фазы дыхательного цикла, сохраняется работоспособность диафрагмы, что снижает риск возникновения ателектазов и вентилятор-индуцированной дисфункции диафрагмы. За счет подаваемого в ответ на каждый вдох давления поддержки, пациентом проделывается незначительная работа дыхания, что предотвращает развитие усталости дыхательной мускулатуры. Однако проведение анестезии с сохраненным спонтанным дыханием может быть лимитировано необходимостью введения высоких доз опиоидов и анестетиков, например, при высокотравматичных оперативных вмешательствах, поскольку препараты для анестезии могут оказать существенное влияние на дыхательный центр. В литературе имеется достаточно сведений в отношении эффективности использования режима PSV на этапе индукции общей анестезии с целью лучшей преоксигенации. Использование режима PSV в сочетании с положительным давлением в конце выдоха (ПДКВ) во время преоксигенации улучшает оксигенацию, предотвращает появление эпизодов десатурации, удлиняет время безопасного апноэ. Помимо использования данного режима во время индукции общей анестезии, его применение может быть целесообразным и на этапе поддержания анестезии во время операций, где не требуется введение миорелаксантов, а также и на завершающих (пробуждение, экстубация) этапах общей анестезии в тех случаях, когда основной хирургический этап требует тотальной миоплегии. Применение поддержки давлением на этих этапах менее распространено. Однако в ряде публикаций было показано, что применение данного режима во время общей анестезии с сохранением самостоятельного дыхания может привести к улучшению газообмена и уменьшению ателектазирования легочной ткани, помимо этого, сделать пробуждение и экстубацию более комфортными и быстрыми по сравнению с другими подходами к проведению респираторной поддержки во время анестезии.

Ключевые слова: искусственная вентиляция легких, вентиляция с поддержкой давлением, самостоятельное дыхание, общая анестезия, пробуждение

INTRODUCTION

Postoperative pulmonary complications (PPCs) are the most common complications following surgical interventions [23], significantly influencing the course of the postoperative period [25]. The share of pulmonary complications in abdominal and vascular surgery accounts for 10–40% of all postoperative complications [12]. Thus, pulmonary complications are the second most frequent after cardiovascular ones during the postoperative period [19].

Among all respiratory postoperative complications, pulmonary atelectasis is one of the most common in surgical patients. Atelectasis determines the risk of hypoxemia and forms the basis for the development of other postoperative pulmonary complications [27]. Atelectasis can persist for several days after surgery, impairing respiratory function and ultimately increasing the duration of hospitalization [14].

In the early 2000s, a whole range of modes which were previously available in ventilator-assisted resuscitation machines became available on the majority of anesthesia-breathing machines, including modes of independent breathing and primarily pressure-supported independent breathing. Despite this, there are no clear recommendations regarding the use of these modes during anesthesia. As a result, habitual forced ventilation modes are preferred by anesthesiologists in most situations. However, a number of studies have shown that the use of pressure support mode during general anesthesia with preservation of independent breathing can lead to improved gas exchange and reduced atelectasis of lung tissue. In addition, it can make awakening and extubating more comfortable and faster than other approaches to respiratory support during anesthesia [1, 2, 6, 28, 48]. Furthermore, the use of PSV (pressure support ventilation) and preservation of spontaneous breathing can potentially reduce the total anesthetic dose during general

intravenous anesthesia [6, 28]. In addition, anesthesia with preserved spontaneous breathing is limited by the need to administer high doses of opioids and anesthetics, for example, in highly traumatic surgical interventions, because anesthetic drugs can have a significant effect on the respiratory center.

In addition, this mode can be used to maintain anesthesia during operations that do not require the administration of myorelaxants, according to available data, its use may be appropriate at the initial (preoxygenation before induction of general anesthesia) [7] and final (awakening, extubation) [3, 35] stages of general anesthesia in cases where the main surgical stage requires total myoplegia. In the first case, a higher level of oxygen tension in arterial blood and, as a consequence, a longer time of safe apnea compared to classical preoxygenation is provided [7]. In the second case, independent breathing is initiated after the end of the main stage of surgical intervention, which can reduce the time of awakening and extubation, accelerate the transfer of the patient from the operating room, improve gas exchange, reduce the frequency and severity of cough after extubation, and thus make awakening more comfortable than when using forced ventilation [3, 35].

Thus, the use of independent breathing modes at different stages of general anesthesia can potentially reduce the likelihood of postoperative pulmonary complications (PPC) in the early postoperative period.

IMPACT OF FORCED ARTIFICIAL VENTILATION ON THE RESPIRATORY SYSTEM

Effects on lung tissue

It has been shown in both experimental and clinical studies that artificial ventilation (AV) can exacerbate pre-existing lung damage [8, 27, 42] or even induce it in a healthy individual [39]. Several major mechanisms for the development of ventilator-induced lung injury (VILI) have been identified [8, 14]. Increased airway pressure (barotrauma) and the application of high inspiratory volumes (volumotrauma) can cause damage or destruction of alveolar epithelial cells. In addition to baro- and volumotrauma, ventilator-induced lung injury can result from cyclic opening and closing of the alveoli (atelectotrauma) [8]. All three described mechanisms, namely barotrauma, volumotrauma and atelectrauma, can affect both alveolar epithelial cells and pulmonary capillary endothelium [43], as well as cause interstitial damage by disrupting the intercellular matrix [29]. As a consequence of lung tissue injury, surfactant synthesis and barrier function of the alveolo-capillary membrane are impaired, which leads to the development of interstitial pulmonary edema and extensive atelectasis of lung tissue. Ventilator-induced lung injury is one of the causes of postoperative pulmonary complications (PPC).

Heterogeneity of ventilation in different areas of lung tissue may also occur during general anesthesia. This inhomogeneity may be related to extensive atelectasis due to the effects of anesthetics on the respiratory system, to patient positioning (e.g., Trendelenburg position), to increased intra-abdominal pressure (e.g., when carboxyperitoneum is applied during laparoscopic surgeries) [32], and also as a result of alveolar gas resorption [36], which makes the respiratory system even more vulnerable to the negative effects of ventilatory support.

According to current thinking, in order to prevent all types of damaging effects leading to VILI and, consequently, to reduce the risk of postoperative pulmonary complications, a strategy of protective ventilation should be applied in the operating room [11].

Effects on the respiratory musculare

In addition to negative effects on lung tissue, there is also evidence that mechanical ventilation has a negative effect on diaphragm function, which may lead to ventilator-induced diaphragmatic dysfunction (VIDD) [45].

The first evidence that continuous mandatory ventilation can cause respiratory muscle damage was obtained in animal studies [33]. In more recent studies it was shown that mandatory ventilation leads to atrophy of respiratory muscles (diaphragm to a greater extent) [40]. This theory was confirmed in human studies: analysis of histological data of 13 newborns who were on forced ventilation for 12 days revealed diffuse atrophy of diaphragmatic fibers [22]. Diaphragm atrophy may be the result of decreased protein synthesis and/or increased protein degradation [16].

According to other authors, structural transformation of diaphragm muscle fibers occurs as a result of impaired protein synthesis and degradation (especially myosin heavy chain protein) during mandatory ventilation [40].

In addition to global structural rearrangements, an increase in oxidative stress, reflected by increased protein oxidation and lipid peroxidation, was observed in animals undergoing 6-hour forced ventilation [40]. Moreover, according to some studies, structural damage to some cellular organoids was observed after 48 hours of CMV (continuous mandatory ventilation): destruction of myofibrils, abnormal swelling of mitochondria, lipid droplets and vacuoles [4]. The mechanisms of damage are not completely clear, but may include activation of various proteolysis pathways and oxidative stress.

Interestingly, even minimal patient involvement in ventilation can significantly improve the functional status of the diaphragm. According to Sassoon et al., the decrease in

contractility of the rabbit diaphragm after 3 days of artificial ventilation was more pronounced in the group in which CMV was used compared to the group in which assisted continuous mandatory ventilation (AssistCMV) was used and minimal spontaneous respiratory activity was preserved [38].

Taking into account these data, despite the fact that the CMV mode remains the most popular in anesthesia practice, it can be assumed that the use of assisted modes, as well as modes of independent breathing during anesthesia can have a beneficial effect on the respiratory system and reduce the risk of PPC.

INDEPENDENT BREATHING AND GENERAL ANESTHESIA

Numerous studies conducted in the last two decades have led to a better understanding of the pathophysiology of ventilator-induced lung injury that may be responsible for the development of PPC. Consequently, this has resulted in the widespread adoption of protective ventilatory strategies and advanced respiratory monitoring that optimizes ventilation settings [11].

Another, newer area of research related to intraoperative ventilatory support is the study of the association between the use of myorelaxants and the risk of PPC development. The POPULAR research has shown that the use of myorelaxants during general anesthesia leads to an increased risk of PPC. Neither the use of neuromuscular transmission monitoring nor the use of decurarizing agents significantly reduces the risk of these complications [21]. In this regard, it can be assumed that maintaining independent breathing during general anesthesia, where possible, may be one of the options for further improvement of the strategy of protective ventilation.

It is well known that regional distribution of ventilation and perfusion is heterogeneous due to the elastic properties of the lungs, as well as the vertical gradient of pleural, transpulmonary and hydrostatic pressures [41]. The diaphragm displacement is also not homogeneous, and it can be functionally divided into three segments: upper (independent, ventral), middle and lower (dependent, dorsal) ones. The dorsal part makes more movement during spontaneous inspiration than the ventral part, providing better ventilation of dependent lung regions and counteracting the collapse of alveoli due to hydrostatic pressure, leveling the ventilation-perfusion mismatch, and these advantages are maintained even in the supine position [30].

On the contrary, when performing forced ventilation (especially with the use of myorelaxants), a typical redistribution of ventilation occurs: its main part is shifted to the independent and less perfused anterior lung sections, atelectasis formation occurs in the dependent lung regions, which leads to a violation of ventilation-perfusion relations [30]. These effects are primarily associated with changes in diaphragm excursion. During forced ventilation against the background of relaxants, passive displacement of the posterior part of the diaphragm is significantly reduced [5, 6].

The main advantage of maintaining spontaneous breathing during general anesthesia is the preservation of normal work of respiratory muscles and, first of all, the diaphragm. Preservation of tone and active movements of the diaphragm can increase ventilation of the dorsal lung sections, prevent early expiratory airway closure and atelectasis formation, improve ventilation-perfusion relations and gas exchange [37]. The results of the study confirming the benefit of preserving diaphragm performance during general anesthesia with tracheal intubation are indicative. The use of diaphragmatic nerve stimulation, simulating the diaphragm work, accompanied by the use of positive end-expiratory pressure (PEEP) leads to a decrease in the size of atelectasis in dependent parts of the lungs [15].

In addition to the positive effect on pulmonary function, other possible advantages of preserved independent breathing include reduced consumption of anesthetics, as well as reduced time of awakening, extubation and transfer from the operating room [2, 6, 28], no need to use myorelaxants and, consequently, reduced risks associated with their use (postoperative pulmonary complications, allergic reactions) [17, 21].

It should be noted that spontaneous breathing during ventilation also has a number of disadvantages: the possibility of asynchrony, which can lead to baro- or volumotrauma; the need for more careful control of ventilation to ensure timely transfer of a patient to the forced mode due to the effect of narcotic analgesics on respiratory drive, the development of respiratory muscle fatigue and decreased efficiency of independent breathing attempts due to increased breathing [6].

A pressure-supported independent breathing mode can help overcome most of the disadvantages of preserved spontaneous breathing during general anesthesia.

THE USE OF PRESSURE SUPPORT VENTILATION AT DIFFERENT STAGES OF GENERAL ANESTHESIA

Preoxygenation and induction of general anesthesia

The use of pressure support breathing in anesthesia practice is most studied at the stage of induction. Thus, a meta-analysis based on 13 studies performed from 2001 to 2021 showed that the use of noninvasive ventilation

in PSV mode immediately before induction of general anesthesia was more effective than the "traditional" method of preoxygenation [7].

A number of studies have compared the safe apnea time when preoxygenation is performed in PSV mode or with masked oxygen delivery [7]. Although there was a difference in the interpretation of the term "safe apnea" between the authors (the lower limit of saturation in the studies differed), according to the results of all studies, the group of preoxygenation in the PSV mode showed a significantly more favorable result than the group of classical preoxygenation.

One of the studies compared the rate of achieving a 90% end-expiratory oxygen level using the pressure support mode and traditional methods of preoxygenation [10]. Patients of the first group achieved the result significantly earlier than the group in which "classical" preoxygenation was performed.

It is logical that higher PaO_2 [10] and lower $PaCO_2$ [9] were observed during preoxygenation using noninvasive ventilation than in the group of standard preoxygenation.

Separately, we would like to note that this technique is most useful in patients with a potentially large volume of atelectatic lung tissue, which include overweight patients. Thus, a study in morbidly obese patients showed that the use of PSV combined with moderate PEEP during preoxygenation significantly improves oxygenation and prevents desaturation episodes compared with standard preoxygenation in the mode of fully independent breathing [13].

The main stage of general anesthesia

In the last 20 years, modern supraglottic airway devices (SGDs) have been widely introduced into clinical practice: laryngeal masks, I-Gel type supraglottic airway devices, etc. [24]. The placement of these devices, designed to ensure patency of the upper airways, does not require the administration of myorelaxants, respectively, and the use of forced modes of ventilation. The traditional method of ventilation in operations of short duration (less than 1 hour) has become the preservation of spontaneous breathing. However, the use of spontaneous ventilation during longer surgical interventions was limited by a high risk of hypoventilation caused by anesthetics. They influenced the breathing pattern and the development of respiratory muscle fatigue, which required transferring a patient to a controlled mode of ventilation [28].

PSV mode on modern anesthesia and respiratory devices made it possible to perform longer surgical interventions in conditions of preserved independent breathing thanks to control of the respiratory volume and reduction of the patient's work of breathing.

A number of researchers have argued that the use of pressure-support self-respiratory mode offers many advantages over spontaneous breathing without device support or forced ventilation during anesthesia with supraglottic airways. PSV mode significantly reduces work of breathing compared to fully spontaneous breathing and at the same time provides lower airway pressures compared to forced ventilation [6, 28].

When comparing PSV with ventilation in the CPAP mode (continuous positive airway pressure, a mode of independent breathing with constant positive airway pressure), it was found that the former was superior to the latter in terms of respiratory volume, oxygenation indices, and end-expiratory partial pressure of CO_2, which may be associated with improved ventilation and ventilation-perfusion relations in the lungs [46].

However, it should be noted that according to some works, the use of PSV mode, as well as forced ventilation modes, aggravates ventral redistribution of ventilation in comparison with independent breathing without ventilatory support. Such results were obtained in a trial performed using electrical impedance tomography visualizing regional ventilation differences in the lungs [34].

Another study showed that the use of PSV or preservation of spontaneous breathing leads to a shorter time from the moment of anesthetic cessation to awakening, extubation, and transfer from the operating room compared to respiratory support in the mode of volume-controlled mandatory ventilation [6]. Moreover, a significantly higher consumption of anesthetics was noted in the CMV group. However, the group of fully spontaneous breathing showed a significant increase in occlusion pressure 100 ms after the start of inspiration (P0.1), a decrease in minute ventilation, and an increase in end-expiratory carbon dioxide pressure $EtCO_2$ by the end of anesthesia, indicating the development of respiratory muscle fatigue. No such phenomena were observed in the PSV group [6]. The results of the above mentioned research also correspond with the data obtained in a similar research in pediatric patients [28].

A similar research was performed in our clinic. It compared gas exchange parameters by analyzing arterial blood gas composition, airway pressure, and wake-up time in 100 patients who underwent minor traumatic orthopedic interventions on the lower extremities under general combined anesthesia with desflurane. The results of the research demonstrate better indices of arterial blood oxygenation, respiratory mechanics, as well as shorter time intervals before awakening, extubation and transfer to a ward in the group of pressure support mode, which is fully consistent with the above-mentioned foreign researches It

should be noted that in both cases the main hemodynamic parameters as well as the level of anesthesia depth remained normal and did not differ significantly between the groups [2].

In addition to practically healthy patients with physical status ASA I-II, participated in the mentioned studies, the PSV regimen also showed its efficacy in patients with moderate obesity (body mass index (BMI) 25–35 kg/m^2) and physical status II–III according to ASA. This category of patients underwent PSV respiratory support, as a result there were observed intraoperative improvement in oxygenation index (PaO_2/FiO_2) and higher values of SpO_2 in the early postoperative period compared to a group receiving pressure-controlled forced ventilation (CMV-PC) [48].

A number of studies have shown that besides general anesthesia with supraglottic airways, PSV may also be useful during anesthesia with tracheal intubation. The use of a pressure-supported independent breathing mode during general anesthesia accompanied by tracheal intubation may also reduce wake-up and extubation time. Interestingly, the level of depth of anesthesia according to BIS monitoring in this study remained normal and did not differ between groups (using PSV and CMV-VC) [1].

When comparing PSV and CPAP modes during anesthesia with tracheal intubation, it was shown that the use of pressure support provides a lower respiratory rate and lower end-expiratory carbon dioxide level, as well as stable respiratory volume [5].

Among other things, the mode of independent breathing with pressure support can be useful for patients coming to an operating room from intensive care units. This category of patients is initially in severe condition and requires pressure assisted ventilation. Thus, it is possible to ventilate these patients in the same mode as in the intensive care unit. This can help prevent deleterious effects of forced ventilation on the compromised respiratory and cardiovascular systems [44].

It should be stated that pressure support regimen during the maintenance phase of anesthesia is evaluated in significantly fewer studies than during the induction phase of anesthesia. Apparently, it seems that using this mode during the maintenance of general anesthesia is less common in clinical practice. In addition, the majority of trials that evaluated the intraoperative use of PSV mode used total intravenous anesthesia, the possibility of such ventilation against the background of inhalation anesthetics was evaluated much less frequently.

Completion of general anesthesia, awakening

The main purpose of using protective intraoperative ventilation is to make intraoperative ventilation safer by reducing the probability of postoperative pulmonary complications; however, it has been shown that all the positive aspects achieved by improving the methods of respiratory support at the initial and main stages of general anesthesia can be lost during awakening and extubation [47]. There are works [18, 31] that demonstrated that atelectasis of lung tissue occurs at the final stage of general anesthesia, despite the protective strategy of artificial ventilation at the main stage. Thus, it was revealed that pulmonary atelectasis occurs in 39% of patients at the time of extubation and full awakening of a patient [31]. In this regard, a study devoted to the influence of ventilation mode on the severity of pulmonary atelectasis after extubation at the end of anesthesia should be noted. According to the data presented, the incidence of postoperative atelectasis in patients who received PSV ventilation before awakening was much lower than in patients breathing independently without device support [18].

Some authors have demonstrated that the pressure support mode used at the end of general anesthesia, at the stage of extubation and awakening can both potentially prevent postoperative pulmonary complications and improve intraoperative gas exchange, as well as significantly improve patient comfort in comparison with other approaches to respiratory support at this stage of general anesthesia [1, 6, 28, 48]. First of all, we are talking about reducing the severity of the cough reflex during extubation. Despite the fact that coughing is a necessary physiological reflex, its severe and prolonged character may cause a whole set of adverse effects, including increased intracranial, intraocular, and intra-abdominal pressures [26]. In addition, severe repetitive coughing leads to a significant increase in blood pressure, depleting coronary blood flow [20].

Many influences can trigger the cough reflex. However, in the case of postextubation cough, it is certain that the main trigger is a mechanical impact of an intubation tube on the airway [26]. Extubation itself is often causes bronchospasm or laryngospasm, which may lead to the development of hypoxemia, directly threatening patient's life.

In recent decades, a considerable amount of studies have been conducted aimed at selecting pharmacologic methods to reduce airway irritation under caused by intubation tubes. These include irrigation of the vocal folds with local anesthetic solution during direct laryngoscopy, its intravenous administration and even injection of local anesthetic solution into the cuff of the intubation tube. Some authors suggest using beta-blockers, calcium channel antagonists, and opioids for this purpose. At the same time, a study by Richardson et al. showed that the use of PSV mode on awakening, immediately before extubation, significantly reduces the severity of the cough reflex caused

by the endotracheal tube than the mode of forced ventilation or independent breathing without device support [35].

Our clinic has conducted a study on a similar topic. We evaluated the frequency and severity of postextubation cough, as well as the time of awakening and extubation in patients who underwent routine general surgical interventions under general combined anesthesia with desflurane with tracheal intubation and myorelaxation at the main stage of intervention. Patients who underwent independent breathing with further transfer to the pressure support mode after completion of the main stage of surgical intervention, had severe and moderate coughs much less frequently than patients on forced ventilation during the whole duration of general anesthesia. At the same time, the independent breathing group had shorter time intervals from inhalation anesthetic switch-off to awakening, extubation, and transfer to a ward [3].

Thus, the use of PSV at the final stage of anesthesia can potentially reduce the severity of periextubation irritation of the airways by the endotracheal tube, prevent the occurrence of severe and recurrent cough. This approach to respiratory support at the end of general anesthesia can make this stage more comfortable for the patient, which is an extremely important aspect of modern medicine. However, there is no evidence in the literature whether a pressure support regimen can improve gas exchange in the early postoperative period, reduce the time of awakening, extubation and transfer from the operating room.

CONCLUSION

In summary, the use of pressure support mode in an operating room has quite a few positive effects, which include improved oxygenation, faster awakening, transfer of a patient out of the operating room, and greater comfort of the peri-extubation period. However, we should not forget about some limiting factors that require special attention from the anesthesiologist. First of all, it is the dose of narcotic analgesic, obviously individualized for each patient, at which the respiratory drive capable of maintaining normal ventilation will be preserved.

It is also worth noting that the use of PSV mode in an operating room is not limited to the preoxygenation and induction phase of general anesthesia, which is the subject of most available articles. Such tactics of respiratory support can be successfully and beneficially used at the main stage of general anesthesia. Supraglottic airways can be used if the surgical technique does not require the introduction of myorelaxants, as well as at the final stage of general anesthesia, accompanied by total myoplegia at the main stage.

Obviously, it is necessary to continue studying this approach to intraoperative ventilation and its effect on postoperative pulmonary complications, especially in patients with existing respiratory pathology. In addition, further research of this topic may allow to determine more precisely the limiting doses of narcotic analgesics and anesthetics, to develop additional requirements for intraoperative monitoring. It also seems important to study this approach in more traumatic surgical interventions, taking into account the multimodal approach to intraoperative anesthesia (use of non-opioid analgesics, combined anesthesia).

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data of the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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DOI: 10.56871/RBR.2024.20.71.011
UDC 616.993.1+616-022+614.8.027.1+616.24-002+577.18+615.33

INFECTIONS AND THEIR CAUSATIVE AGENTS IN INTENSIVE CARE UNITS (LITERATURE REVIEW)

© Lyubov M. Tsentsiper[1, 2, 3], Anna M. Tihomirova[1], Ilya N. Leyderman[1]

[1] Almazov National Medical Research Centre. 2 Akkuratov str., Saint Petersburg 197341 Russian Federation
[2] Russian Research Neurosurgical Institute named after A.L. Polenov at V.A. Almazov National Medical Research Centre. 12 Mayakovsky str., Saint Petersburg 191014 Russian Federation
[3] Saint Petersburg State Pediatric Medical University. 2 Lithuania, Saint Petersburg 194100 Russian Federation

Contact information: Lyubov M. Tsentsiper — Doctor of Medical Sciences, Professor of the Department of Anesthesiology and Reanimatology with the Clinic of the IMO Almazov National Medical Research Centre; Professor of the Department of Anesthesiology, Reanimatology and Emergency Pediatrics, Faculty of Postgraduate and Additional Professional Education SPbSPMU.
E-mail: lmt1971@yandex.ru ORCID: https://orcid.org/0000-0001-7527-7707 SPIN: 3320-4209

For citation: Tsentsiper LM, Tihomirova AM, Leyderman IN. Infections and their causative agents in intensive care units (literature review). Russian Biomedical Research. 2024;9(3):87–97. DOI: https://doi.org/10.56871/RBR.2024.20.71.011

Received: 02.07.2024 **Revised: 12.08.2024** **Accepted: 16.09.2024**

Abstract. Pathogens of nosocomial infections are formed in hospitals in conditions of close contact between individual patients, as well as between patients and staff, which leads to the exchange of strains of microorganisms. In parallel, the formation of antibiotic-resistant strains occurs against the background of intensive use of antimicrobial drugs. The purpose of the review is to summarize the available modern literature data on the most common infectious pathogens in intensive care units (ICU). The review presents data on the most frequently developing infectious complications in the ICU and their causative agents. Data on the similarities and differences of the microbial spectrum depending on the ICU profile are presented. Conclusion. Nosocomial infection of patients in intensive care units is characterized by complex epidemiological and pathophysiological mechanisms of occurrence and development. An increase in the frequency of release of multidrug-resistant microorganisms complicates the implementation of adequate antibiotic therapy, including initial empirical antibiotic therapy, which significantly increases the role of preventive measures.

Keywords: infections, risk factors, pneumonia, angiogenic infections, antibiotic resistance, intensive care units

ИНФЕКЦИИ И ИХ ВОЗБУДИТЕЛИ В ОТДЕЛЕНИЯХ РЕАНИМАЦИИ И ИНТЕНСИВНОЙ ТЕРАПИИ (ОБЗОР ЛИТЕРАТУРЫ)

© Любовь МарковнаЦенципер[1, 2, 3], Анна Максимовна Тихомирова[1], Илья Наумович Лейдерман[1]

[1] Национальный медицинский исследовательский центр им. В.А. Алмазова. 197341, г. Санкт-Петербург, ул. Аккуратова, 2
[2] Российский научно-исследовательский нейрохирургический институт имени профессора А.Л. Поленова, филиал НМИЦ им. В.А. Алмазова. 191014, г. Санкт-Петербург, ул. Маяковского, 12
[3] Санкт-Петербургский государственный педиатрический медицинский университет. 194100, г. Санкт-Петербург, ул. Литовская, 2

Контактная информация: Любовь Марковна Ценципер — д.м.н., профессор кафедры анестезиологии и реаниматологии с клиникой ИМО НМИЦ им. В.А. Алмазова; профессор кафедры анестезиологии, реаниматологии и неотложной педиатрии факультета послевузовского и дополнительного профессионального образования СПбГПМУ. E-mail: lmt1971@yandex.ru
ORCID: https://orcid.org/0000-0001-7527-7707 SPIN: 3320-4209

Для цитирования: Ценципер Л.М., Тихомирова А.М., Лейдерман И.Н. Инфекции и их возбудители в отделениях реанимации и интенсивной терапии (обзор литературы)// Российские биомедицинские исследования. 2024. Т. 9. № 3. С. 87–97. DOI: https://doi.org/10.56871/RBR.2024.20.71.011

Поступила: 02.07.2024 **Одобрена: 12.08.2024** **Принята к печати: 16.09.2024**

Резюме. Возбудители внутрибольничных инфекций формируются в стационарах в условиях тесного контакта между отдельными пациентами, а также между больными и персоналом, что приводит к обмену штаммами

микроорганизмов. Параллельно на фоне интенсивного применения антимикробных препаратов происходит формирование антибиотикорезистентных штаммов. Цель обзора — обобщить имеющиеся современные литературные данные о наиболее часто встречающихся в отделениях реанимации и интенсивной терапии (ОРИТ) инфекционных возбудителях. В обзоре представлен обзор исследований, посвященных микробному профилю ОРИТ и нозокомиальным инфекциям. Приведены данные о сходствах и различиях микробного спектра в зависимости от профиля ОРИТ. Внутрибольничное инфицирование пациентов отделений реанимации и интенсивной терапии характеризуется сложными эпидемиологическими и патофизиологическими механизмами возникновения и развития. Увеличение частоты выделения микроорганизмов с множественной лекарственной устойчивостью усложняет проведение адекватной антибиотикотерапии, в том числе и стартовой эмпирической антибиотикотерапии, что значительно увеличивает роль проведения профилактических мероприятий.

Ключевые слова: инфекции, факторы риска, пневмония, ангиогенные инфекции, антибиотикорезистентность, отделения интенсивной терапии

INTRODUCTION. CONCEPT OF HOSPITAL STRAINS

Rapid introduction of infection control measures and rules of asepsis and antiseptics in modern hospitals has led to evolution of both pathogenic and opportunistic microorganisms, resulting in the selection of new, so-called hospital strains.

A hospital strain is a microorganism that has changed its genetic properties circulating in the department. As a result of mutations or gene transfer (plasmids), it has acquired some characteristic features that are not peculiar to the "wild" strain, allowing it to survive in hospital conditions. Studies indicate that, as a rule, typical characteristics of a hospital strain include resistance to antimicrobial agents (antibiotics, disinfectants, antiseptics, etc.), increased virulence, resistance in the external environment, the ability to circulate for a long time in hospital conditions, enhanced colonization and adhesive properties, competitive activity and genetic uniformity [8]. Hospital-acquired infections (HAIs) are formed in hospitals in close contact between patients, as well as between patients and staff. Thus, there is an exchange of microorganism strains. Simultaneously, intensive and sometimes excessive use of antimicrobial drugs leads to the selection of antibiotic-resistant strains. As a result, a microecological situation characterized by the dominance of certain strains of microorganisms and the prevalence of antibiotic-resistant strains among them is formed in medical institutions. Microbiological studies show that the "landscape" of HAI pathogens dynamically changes even within one intensive care unit (ICU), which is associated with changes of operation mode in the clinic, contingent of patients, intensity of the treatment process, modes of antibiotic prevention and therapy [1, 3].

The most severe cases of healthcare-associated infections (HCAIs) are connected with hospital strains. The risk of mortality in patients infected with resistant microorganisms is two to three times higher than in patients with strains that are sensitive to antibacterial drugs. As the duration of stay in a hospital lengthens, the likelihood of patient's own microflora being replaced by hospital microflora increases, and consequently, infections caused by hospital microflora develop.

There are endogenous and exogenous sources of healthcare-associated infections which are relevant for ICU patients.

Endogenous sources of HCAIs are: obligate patients' microflora of skin, urogenital system (UGS), gastrointestinal tract (GIT), as well as foci of chronic infection that a patient had prior to hospitalization. Endogenous infection can occur in critically ill patients by translocation of intestinal flora into the bloodstream and then into the area of surgical intervention due to deep tissue hypoxia. Tissues can also be contaminated by normal microflora of organs when their integrity is violated during surgical intervention and migration of microflora from the focus of chronic infection resulting in purulent-septic process in the area of surgical intervention.

Exogenous sources of HCAIs in ICU include hands of medical personnel, invasive devices, medical equipment, air, water and foodstuffs. The spread of infection may be caused by a pathogen itself: there is evidence that *Enterococcus* spp. is more likely to be transmitted by contact through hands of personnel. Sources of *P. aeruginosa* can be ventilators and other equipment, and infection with *S. aureus* and *K. pneumoniae* is more often airborne, through air ducts and staff hands. Hidden carriage of Staphylococcus aureus among medical personnel plays a major role in pathogenesis of HCAI. Literature also contains data pointing to staff cell phones and stethoscopes as sources of nosocomial infection [14].

In general, it is possible to identify a number of factors associated with a high level of nosocomial infection in

intensive care units: stay in ICU for more than 48 hours; a large number of therapeutic and diagnostic manipulations; emergency manipulations during resuscitation; duration of ventilator support; intravascular and urinary catheters, parenteral nutrition; frequency and duration of antimicrobial drugs use; crowdedness of resuscitation beds in wards; number of patients assigned to one medical worker; staff turnover; unfair passing/conducting of periodic medical check-ups; neglect of aseptic and antiseptic rules by the staff when performing therapeutic and diagnostic manipulations; inadequate disinfection and sterilization of medical instruments and equipment; non-compliance with isolation and restriction measures, if necessary; inadequate delimitation of "clean" and "dirty" areas due to insufficient space in the department; insufficient amount of sanitary and technical equipment, consumables and disinfectants; deterioration of medical equipment, non-compliance with operating conditions.

AIM

The aim of the review is to summarize available current literature on the most common infectious agents in intensive care units.

STRUCTURE OF HEALTHCARE-ASSOCIATED INFECTIONS IN INTENSIVE CARE UNITS

According to the EPIC (European Prevalence of Infection in Intensive Care) multicenter survey conducted in 17 European countries (1417 ICUs and 9565 patients participated in the survey), catheter-related bloodstream infections (CRBSIs) are among the top three leading ICU-associated infections, along with catheter-associated urinary tract infection and ventilator-associated pneumonia (VAP).

Angiogenic infections, or catheter-related bloodstream infections, are the third most common among all UTIs and the first among the causes of primary bacteremia (up to 87%). The number of CRBSIs varies in different departments and hospitals by structure and profile and, according to various studies, ranges from 2.9 cases per 1000 days of catheterization in specialized ICUs and up to 7.7 cases in general ICU patients [39]. Risks of CRBSIs increase in direct proportion to the duration of catheterization — at catheterization periods up to 7 days, the development of infection is observed in 5% of patients, and in 36% of patients if catheterization lasts for more than 1 month. The association of sepsis with an infected catheter, according to different data, ranges from 20 to 55% [44].

The greatest etiologic role in the development of CRBSIs belongs to *coagulase-negative staphylococci* (34–49.1%) and *S. aureus* (11.9–17%). Infections caused by *Enterococcus* spp. (5.9–6%), *Candida* spp. (7.2–9%) and *Pseudomonas* spp. (4.9-6%) are less common [7].

Two types of infection are possible in CRBSIs. The first is extraluminal, when normal microflora of patient's skin enters a bloodstream along an outer surface of a catheter. This type of infection is typical (up to 60% of cases) for short-term catheters and develops, as a rule, within the first 10 days. If catheterization is prolonged and asepsis is violated during catheter use or infusion solution preparation, intraluminal infection is possible.

There are certain etiologic differences for extra- and intraluminal CRBSIs. Extraluminal infections are more often caused by *coagulase-negative staphylococci, S. epidermidis, S. aureus, Corynebacterium* spp., and *Bacillus* spp. Extraluminal infection with *P. aeruginosa, Acinetobacter* spp. and *Candida albicans* is also possible in case it is brought from the skin of medical personnel's hands. Intraluminal CRBSIs are more often caused by *Enterobacter* spp. and *Citrobacter* spp. [21, 29].

Ventilator-associated pneumonia (VAP) is a specific for intensive care units, which is an inflammatory lung lesion that develops not earlier than 48 h from the moment of intubation and initiation of ventilatory support in the absence of signs of pulmonary infection when ventilator support is initiated [15]. During the first two days of ventilatory support the risk of VAP is low (0.5%), after 72 h — already 50%, and by 8–10 days — 80%. Each subsequent day of ventilator over the third day increases the number of cases by 1–4%.

VAP is the most common CRBSI in ICU — it accounts for up to 86% of all cases of nosocomial pneumonia in surgical ICU patients. According to a number of studies, the average incidence of VAP reaches 27% of all cases of prolonged ventilation and remains practically unchanged over the last 20 years [33, 45].

VAP can develop due to exogenous or endogenous infection. Exogenous sources of infection include endotracheal tubes, tracheostomy cannulas, breathing circuits, valves and humidifiers of ventilators, inhalers, catheters used for sanitation, and contaminated air. Endogenous infection occurs via patient's own microflora — skin, nasopharynx, oropharynx, sinuses, esophagus, stomach and intestines, urinary tract and foci of chronic infection.

The most important risk factors for the development of VAP are: prolonged ventilation (more than 72 h), the severity of a patient's condition, repeated surgical interventions, inadequacy of previous antibiotic therapy, abdominal sepsis, chronic lung diseases, emergency

surgery, unconsciousness of the patient, aspiration and emergency intubation.

The incidence and nature of VAP caused by a particular pathogen depends on the microbiologic landscape of a particular ward. Microbial spectrum of possible pathogens includes Gram-positive (*S. aureus* — 15–35%, *S. pneumoniae* — 10–20%) and Gram-negative flora (*P. aeruginosa, Enterobacteriacae* spp., *A. baumanii, H. influenzae, E. coli, K. pneumoniae*), to which a leading etiologic role belongs. 17–40% of VAP are polymicrobial [25].

Early and late forms of VAP are usually distinguished according to terms of VAP development. Early VAP develops during the first 5 days of hospitalization and is associated with antimicrobial-sensitive pathogens and favorable prognosis. Late VAP does not develop before the 6th day of hospitalization and is associated with a high risk of multidrug-resistant pathogens [18].

Catheter-associated urinary tract infections (UTIs). According to the Russian multicenter ERGINI study (2013), urinary tract infections rank second in the structure of nosocomial infections with a frequency of 16.7%. According to the EPIC II study (Vincent J.-L., 2009), UTIs account for 19.7% of all cases of CRBSI in ICUs of Eastern Europe. It was found that 79–97% of UTIs in ICU are associated with urethral catheter placement [38, 41].

Urinary tract infections may be the cause of secondary bacteremia or sepsis, risk factors for which include male gender, immunosuppression, neutropenia, renal disease, and malignancy. It has also been found that bacteremia is significantly more frequent in nosocomial urinary infection caused by enterococci and fungi of the genus *Candida.*

Urogenital pathogenic microorganisms causing urinary tract infections in ORIT include gram-negative bacteria of the *Enterobacteriaceae* family (primarily *E. coli, K. pneumoniae, Proteus* spp.), *A. baumanii*, and *P. aeruginosa*; the group of Gram-positive bacteria is represented by *E. faecalis, E. faecium, Staphylococcus aureus* and coagulase-negative staphylococci; fungi of the genus *Candida* have a definite etiologic role in the development of urinary tract infections. Anaerobic and atypical microorganisms are not etiologically significant [16, 22].

ETIOLOGY OF HEALTHCARE-ASSOCIATED INFECTIONS

The most clinically significant and common causative agents of all types of HCAIs in ICU are a limited group of microorganisms called ESKAPE — *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, representatives of the order *Enterobacteriales*.

This statement is true both for the entire structure of nosocomial infections and for infections registered in intensive care units in particular [11]. According to the data for 2020, the share of *Enterobacteriaceae* in the etiology of HCAIs is 53.2%, the most frequent species are *K. pneumoniae* (26.7%) and *E. coli* (14.6%), the share of infection with *P. aeruginosa* and *A. baumannii* was 21.9 and 16.7% of all bacterial pathogens, respectively, *S. aureus* — 7.7% [3, 5].

Hospital biovars produced by HCAI pathogens may include: *Enterobacteriaceae (K. pneumoniae, E. cloacae, E. coli)* producing extended-spectrum β-lactamases (ESBL) or carbapenemases; *Pseudomonas aeruginosa* which are resistant to carbapenems and/or ceftazidime and/or ciprofloxacin; *Acinetobacter* spp. resistant to carbapenems; *Staphylococcus aureus, Staphylococcus epidermidis* resistant to methicillin (MRSA — methicillin-resistant strain of *S. aureus*) and/or vancomycin and/or ciprofloxacin and/or β-lactamase-producing; Vancomycin resistant *Enterococcus* spp. (VRE) — the main role belongs to *E. faecalis* and *E. faecium; Streptococcus pneumoniae* resistant to β-lactam antibiotics; *Candida* spp. resistant to fluconazole [20, 23, 26, 32].

In recent years, Enterobacteriaceae have been the most frequent causative agents of HCAIs in Russian hospitals. Microorganisms of this order demonstrate high levels of resistance to antimicrobials, with resistance to cephalosporins and carbapenems being of the greatest clinical significance. Resistance of hospital-acquired *Enterobacteriaceae* to cephalosporins reaches >80%, mainly due to the spread of ESBL-producing strains [38]. According to 2020 data, the resistance of *K. pneumoniae* and *E. coli* to ceftazidime amounted to 85.3% and 45.1%, respectively. There is also an increase in resistance to carbapenems, including those mediated by carbapenemase production by hospital strains of *Enterobacteriaceae.* By 2020, 50.4 and 68.7% of *K. pneumoniae* strains and 4.7 and 5.8% of *E. coli* strains, were resistant to meropenem and ertapenem respectively [19, 23].

In addition to antibiotic resistance of hospitalized strains, increasing resistance of out-of-hospital strains of *Enterobacteriaceae* is also a problem. According to the 2018-2019 data, *E. coli* out-of-hospital isolates were resistant to amoxicillin/clavulanate (41.4%) and ciprofloxacin (37.2%), as well as to cefotaxime (32.2%), cefepime (19.7%) and ceftolozane/tazobactam (3.8%) mainly due to the production of ESBL [19].

Pseudomonas aeruginosa is the second or third most frequent species after *Klebsiella pneumoniae,* followed by *Acinetobacter* spp. in some hospitals. Genes of acquired carbapenemases were detected in 42.4% of hospital-acquired isolates of this microorganism, including: metallo-

β-lactamases (MBL) of VIM and IMP groups — 83.2 and 0.8%, respectively; serine carbapenemases of GES-5 group — 15.2%; both MBL and serine carbapenemases were produced simultaneously by 0.8% of isolates. MBL producers were characterized by resistance to all antimicrobials except aztreonam and polymyxins; GES-5 producers were resistant to most drugs except ceftazidime/avibactam and polymyxins [23]. *Pseudomonas aeruginosa* showed the greatest resistance to meropenem — 52.5%, cefepime — 52.8%, ceftazidime — 55.0%, imipenem — 57.9%, piperacillin/tazobactam — 61.1%, ciprofloxacin — 63.2%. In 2020, *Acinetobacter* spp. (mainly Acinetobacter baumannii) was the fourth most frequent species (14.3%) after *K. pneumoniae* (26.7%), *P. aeruginosa* (16.5%) and *E. coli* (14.6%). *A. baumannii* and related species have significantly lower natural sensitivity to most β-lactam antibiotics, including penicillins and cephalosporins, which limits the choice of drugs with potential applicability for therapy of infections caused by *Acinetobacter* spp. [23]. 90.5% of *A. baumannii* isolates were found to have genes for acquired carbapenemases, mostly belonging to molecular class D (98.6%), which mediates resistance to imipenem and meropenem. The vast majority of isolates were also resistant to ciprofloxacin (98.1%), amikacin (91.8%) and gentamicin (82.7%). The frequency of resistance to tobramycin and trimetho-prim/sulfamethoxazole was 64.5 and 52.8%, respectively.

The proportion of HCAIs caused by *Staphylococcus aureus* is 7.7%. In comparison with the earlier period of observation, this can be characterized as a decrease. The main problem of *S. aureus* resistance is resistance to β-lactam antibiotics acquired through the production of β-lactamases. According to multicenter Russian studies, MRSA accounted for 24.9 to 66.9% of all infections caused by *S. aureus*. The most effective antibiotics against this pathogen are glycopeptides and lipopeptides (vancomycin, telavancin, daptomycin), oxazolidinones (linezolid, tedizolid), anti-MRSA cephalosporins (ceftaroline) and glycylcyclines (tigecycline). All studied strains were sensitive to these antimicrobials [19].

According to the guidelines "Diagnosis and antimicrobial therapy of infections caused by multidrug-resistant strains of microorganisms", issued by the Association of Anesthesiologists and Resuscitators, there are specific risk factors for the development of multidrug-resistant infections [8].

Risk factors for infections caused by Enterobacteriaceae — ELBS producers are: hospitalization during prior 3 months or current hospitalization; intake of antibiotics (III–IV generation cephalosporins, fluoroquinolones) for any reason during previous 3 months; staying in long-term care facilities (nursing home, orphanage, hospice); hemodialysis; comorbidity: Diabetes mellitus, liver cirrhosis, chronic kidney disease (CKD) [17, 27, 35, 43].

Risk factors for infections caused by MRSA: known high prevalence of MRSA in the ward where the patient is located; previous (within 3 months) hospitalization with surgical interventions and invasive procedures (especially implantation of artificial materials and/or devices); taking broad-spectrum antibiotics (fluoroquinolones, to a lesser extent III–IV generation cephalosporins) for any reason within the previous 3 months; presence of an intravascular catheter; nasal carriage of MRSA; intravenous drug abuse; presence of trophic ulcers or pressure sores [17, 30, 36, 37].

Risk factors for infections caused by multidrug-resistant P. aeruginosa are: prior therapy with cephalosporins, fluoroquinolones, and carbapenems; prolonged stay in ICU; ventilatory support >4 days; sternotomy; presence of bronchiectasis, cystic fibrosis; and presence of urethral catheter [17, 28, 31, 34].

Risk factors for infections caused by carbapenem-resistant Enterobacteriaceae are: known high prevalence of carbapenem-resistant Enterobacteriaceae in a certain department; previous carbapenem therapy; colonization of the patient's gut by carbapenem-resistant Enterobacteriaceae [17, 40, 42].

Assessment of these factors is necessary when empirical antimicrobial therapy is initiated, since the choice of the optimal antimicrobial agent is directly related to probable infection of a patient with multidrug-resistant strains [6].

REVIEW OF MICROBIAL LANDSCAPE STUDIES IN INTENSIVE CARE UNITS OF DIFFERENT PROFILES

The share of each pathogen in the structure of HCAIs in ICUs is determined by the nature of the most frequent forms of HCAIs, the profile of a hospital and a particular ICU. Each medical institution is characterized by its own microbial landscape: in surgical hospitals, *S. aureus et epidermidis, Streptococcus* spp., *P. aeruginosa, Enterobacter* spp. are more likely to cause HCAIs; *P. aeruginosa and* S. *aureus* play a major etiological role in burn centers; herpes viruses, cytomegaloviruses, *Candida fungi* and pneumocysts are particularly dangerous in wards for haematology and HIV-infected patients due to their immunosuppression [10].

Literature data also demonstrate differences in etiological structure of HCAIs in intensive care units of different profiles.

According to a survey on the HCAIs etiology in neurosurgical ICUs conducted in 2017, Gram-positive flora was responsible for 46.75% of HCAIs, Gram-negative flora — for 48.05%, and fungi — for 5.19% of cases.

The most frequently isolated Gram-negative pathogens were *K. pneumoniae* (14.29%), *A. baumannii* (15.58%), *P. aeruginosa* (11.69%), and among Gram-positive patho-

gens — *S. aureus, E. faecalis* and *S. epidermidis*; the total share of these six microorganisms accounted for 80.51% of all reported HCAIs during the observation period. The *Enterococcus spp.* bacteria isolated were mainly represented by *E. faecalis* (6.49%) and *E. faecium* [24].

A 2019 survey compares microbial landscapes of neurological and surgical ICUs. *Pseudomonas aeruginosa* and *Proteus* spp. were most frequently isolated in neurological ICUs — 25.3% of cases for each strain. The proportion of *Enterobacter spp.* was 16.3%, *Staphylococcus* spp. — 10%, *E. coli* — 7.7%, *Streptococcus* spp. — 5,4%. In total, Gram-negative flora caused HCAIs in neurological ICUs in 84.6% of cases. The most frequent flora isolated from surgical ICU patients and environmental objects were *Pseudomonas aeruginosa* — 21.7%, *Enterobacter* spp. — 16.5%, *Staphylococcus* spp. — 15.2% and *Proteus vulgaris* — 14.83%. The proportion of gram-negative microorganisms was 78.3%.

Thus, a surgical ICU profile was associated with a higher proportion of cefoperazone-resistant Gram-positive flora (*Staphylococcus* spp., *Streptococcus* spp.).

In 2020–2021 there were performed a survey studying etiological structures of HCAIs in surgical and therapeutic ICUs,. However, the association between an increased proportion of Gram-positive pathogens in surgical ICUs was not confirmed. In both observation years, the proportion of Gram-positive flora was higher in the therapeutic ICU — 39.4 and 31.5% versus 34.7 and 21.2% in the surgical ICU, respectively. The dominant pathogens were representatives of 4 families: *Moraxellaceae* (15.6–33.3%), *Enterobacteriaceae* (26.8–32.6%), *Staphylococcaceae* (17.7–23.5%), *Pseudomonadaceae* (4.9–11.9%). A significantly lower proportion of infections caused by *Pseudomonas aeruginosa* (up to 11.9%) draws attention in comparison with the previous survey [2].

Analysis of the microbial landscapes of general intensive care units in two multidisciplinary hospitals also demonstrates significant differences in Gram-positive flora prevalence. A research performed in Omsk town in 2011 testifies to the equal role of Gram-negative and Gram-positive microbiota in the etiology of HCAIs. However, a similar study in Tula town in 2014 revealed the predominance of Gram-negative flora in the structure of HCAIs (75% of cases). The leading etiological role also belonged to different microorganisms: in the first study, *Klebsiella spp.* (46%), *E. coli* (22%) and *Enterobacter* spp. (17%) caused the largest number of cases, while in the second study — *P. aeruginosa* (50%) and equal proportions of *E. coli* and *S. epidermidis* — 17% of cases each [9, 12].

CONCLUSION

Nosocomial infection in ICU patients is characterized by complex epidemiological and pathophysiological mechanisms of emergence and development. The increasing frequency of multidrug-resistant microorganisms complicates the adequate antibiotic therapy of HCAIs, including the initial empirical antibiotic therapy, which significantly increases the role of preventive measures. The analysis of microbiological monitoring data from different intensive care units revealed significant differences in both the species structure and sensitivity to antimicrobials of isolated microorganisms. There were no specific microbial landscape features which would be specific to certain ICU profiles. Thus, it is necessary to develop internal protocols for empirical antimicrobial therapy and perioperative antibiotic prevention individually for each ward/hospital. Therefore, regular analysis of the microbial landscape and drug susceptibility profiles of detected microorganisms is important. It should be noted that an individual and comprehensive approach to ICU nosocomial infection is needed. This approach, which should take into account local characteristics of the microflora species composition, can provide a reliable reduction in overall and attributable mortality, as well as reduce the length of stay of patients in these departments.

ADDITIONAL INFORMATION

Disclosure. The authors declare that they have no competing interests.

Author contribution. All authors according to the ICMJE criteria participated in the development of the concept of the article, obtaining and analyzing factual data, writing and editing the text of the article, checking and approving the text of the article.

Ethics approval. Not required.

Funding source. This study was not supported by any external sources of funding.

Data Availability Statement. Data sharing not applicable — not new data generated.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

Вклад авторов. Все авторы в равной степени участвовали в разработке концепции статьи, получении и анализе фактических данных, написании и редактировании текста статьи, проверке и утверждении текста статьи.

Этическое утверждение. Не требуется.

Информация о финансировании. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Декларация о наличии данных. Условие доступа к данным неприменимо — новые данные не генерируются.

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DOI: 10.56871/RBR.2024.76.11.012
UDC 616.12-008.3-073.96+612.172.4+82-5

24-HOUR ECG MONITORING (LECTURE)

© Marina Yu. Erina[1, 2], Ksenia A. Gafiatulina[2], Linard Yu. Artyukh[1, 2], Larisa V. Shcheglova[1, 2]

[1] Saint Petersburg State Pediatric Medical University. 2 Lithuania, Saint Petersburg 194100 Russian Federation
[2] City Mariinsky Hospital. 56 Liteyny ave., Saint Petersburg 191014 Russian Federation

Contact information: Ksenia A. Gafiatulina — the Medical doctor is a functional diagnostician. E-mail: zgbv00@mail.ru
ORCID: https://orcid.org/0000-0002-6527-3347 SPIN: 4466-9583

For citation: Erina MYu, Gafiatulina KA, Artyukh LYu, Shcheglova LV. 24-hour ECG monitoring (lecture). Russian Biomedical Research. 2024;9(3):98–109. DOI: https://doi.org/10.56871/RBR.2024.76.11.012

Received: 28.06.2024 **Revised: 08.08.2024** **Accepted: 16.09.2024**

Abstract. This lecture material was created to familiarize future functional diagnostic doctors with the basics of the Holter monitoring (HM) method — not only resident doctors, but also experienced doctors of other specialties during retraining. This article provides a biography of the founder of this method, Norman Holter; methodology and sequence of examination; sections such as indications for chemotherapy, the main parts of the analysis of daily monitoring are noted: heart rate, circadian index, rhythm and its disorders, myocardial ischemia, *T* wave alternans, as well as the *Q*–*T* interval. The lecture also presents historical drawings and examples from HM protocols.

Keywords: Holter monitoring, Norman Holter, 24-hour ECG monitoring

СУТОЧНОЕ МОНИТОРИРОВАНИЕ ЭКГ (ЛЕКЦИЯ)

© Марина Юрьевна Ерина[1, 2], Ксения Александровна Гафиатулина[2],
Линард Юрьевич Артюх[1, 2], Лариса Васильевна Щеглова[1, 2]

[1] Санкт-Петербургский государственный педиатрический медицинский университет. 194100, г. Санкт-Петербург, Литовская ул., 2
[2] Городская Мариинская больница. 191014, г. Санкт-Петербург, Литейный пр., 56

Контактная информация: Ксения Александровна Гафиатулина — врач функциональной диагностики. E-mail: zgbv00@mail.ru
ORCID: https://orcid.org/0000-0002-6527-3347 SPIN: 4466-9583

Для цитирования: Ерина М.Ю., Гафиатулина К.А., Артюх Л.Ю., Щеглова Л.В. Суточное мониторирование ЭКГ (лекция) // Российские биомедицинские исследования. 2024. Т. 9. № 3. С. 98–109. DOI: https://doi.org/10.56871/RBR.2024.76.11.012

Поступила: 28.06.2024 **Одобрена: 08.08.2024** **Принята к печати: 16.09.2024**

Резюме. Данный лекционный материал создан для ознакомления будущих врачей функциональной диагностики с основами метода холтеровского мониторирования (ХМ) — не только врачей-ординаторов, но и уже опытных докторов других специальностей при прохождении переподготовки. В статье приводится биография основоположника данного метода Нормана Холтера, методика и последовательность проведения обследования. Отмечены такие разделы, как показания к ХМ, основные части анализа суточного мониторинга: частота сердечных сокращений, циркадный индекс, ритм и его нарушения, ишемия миокарда, альтернация зубца *T*, а также интервал *Q*–*T*. В лекции представлены исторические рисунки и примеры из протоколов по ХМ.

Ключевые слова: холтеровское мониторирование, Норман Холтер, суточное мониторирование ЭКГ

One thing no one can take away from you is what you know.

The tombstone inscription on the monument to N. Holter

Holter monitoring (HM) has gained wide popularity in clinical practice — today HM is used in almost 100% of cardiac patients and very widely in other clinical entities. HM is one of the electrocardiography (ECG) techniques. However, the interpretation of ECG by means of HM has a number of significant features and limits, compared to the traditional 12-channel resting ECG. Therefore, separate attention and lecture material is required to improve educational, therapeutic and preventive processes.

BIOGRAPHY OF NORMAN HOLTER

Norman Holter was known as an inventive engineer, physicist, chemist. He had a passion for photography, biotelemetry, but what is most valuable — he made an invaluable contribution to the development of medicine (Fig. 1).

Norman's grandfather and father were entrepreneurs, they owned mines. The scientist's mother suffered from rheumatoid arthritis and often travelled long distances in search of an effective cure for her disease. This may have encouraged N. Holter to develop his talent in the field of medicine.

Fig. 1. Norman Jeff Holter [1]

Рис. 1. Норман Джефф Холтер [1]

Norman Holter attended Carroll College, the University of California, Los Angeles, where he received a master's degree in physics in 1937 and a master's degree in chemistry in 1938, after graduating from the University of Southern California. Before defending his thesis, his supervisor Emil Starz said: "I know you will make discoveries in your chosen profession, conscious of the fact that science will still hear from you in the years to come. I wish you success and fortitude to definitively prove your knowledge". Holter later graduated from the University of Heidelberg in Germany, the University of Chicago, the Oak Ridge Institute for Nuclear Research and Oregon Medical School. During World War II, Holter served as a senior physicist in the U.S. Navy, studying the physical characteristics of ocean waves.

Fig. 2. The original Holter biotelemetric apparatus, manufactured in 1947. It was used to broadcast electroencephalograms and electrocardiograms using coarse heavy battery equipment of almost 40 kg [1]

Рис. 2. Оригинальный биотелеметрический аппарат Холтера 1947 г. выпуска. Использовался для трансляции электроэнцефалограммы и электрокардиограммы с использованием грубого тяжелого аккумуляторного оборудования весом почти 40 кг [1]

Fig. 3. Visual use of one of the first XM ECG devices [2]

Рис. 3. Наглядное использование одного из первых приборов ХМ ЭКГ [2]

In 1946, he led a government research team testing an atomic bomb at Bikini Atoll. Upon returning home, Norman began mapping radioactive fallout of nuclear tests carried out by the United States and the Soviet Union. The Atomic Energy Commission subsequently engaged Holter to research the hydrogen bomb at Eniwetok Atoll.

In 1956 the development of nuclear medicine began — radioisotope diagnostic methods were used for the first time. N. Holter was one of the first to realize the therapeutic possibilities of radiation. He believed that radioactive substances should be used in medicine. Probably, that is why he decided to organize the Montana Nuclear Medicine Society, where nuclear medicine began. Holter was the president of the Society for nearly 13 years.

In 1939, Holter began working with Joseph E. Gengerelli. The idea behind the work was to induce muscle contraction without mechanical or electrical contacts. The scientists reproduced muscle contraction by applying an alternating electric field to a nerve. After confirming their idea, they came to the conclusion that an electric field excites a nerve, and the nerve itself creates a magnetic field that can be registered. In 1961, it became technically possible to confirm their theory. J.E. Gengerelli and N. Holter conducted their experiments on rats, stimulating their brains at a distance: they implanted electrodes in the skull and attached a miniature radio receiver, and then observed the behaviors of the test animals when playing with the radio at different frequencies.

The out-of-the-box thinking led Holter to develop a method for long-term recording of electrocardiograms with data storage and the ability to analyze them in the future (Fig. 2).

In 1947, Norman established the Holter Research Foundation with his own funds.

Officially, HM was created in 1961, when the American journal Science published an article by Holter entitled “A New Method of Cardiac Research. Practical use of prolonged electrocardiography in patients in the active period”. The cassettes and batteries used at that time made it possible to record one ECG channel continuously for 10 hours.

In 1962, joint work with Dr Eliot Corday began at Cedars-Sinai Hospital (Los Angeles), where the first clinical prototype of the Holter monitor was tested. The device was tested on 200 patients with ischemic changes and extrasystole.

The result was a classic publication in the Journal of the American Medical Association (JAMA) issued in 1965 “Detection of Hidden Arrhythmias and Transient Electrocardiographic Abnormalities” (Fig. 3).

The method has been actively used in clinical practice since 1963.

METHOD DEFINITION AND USED TERMINOLOGY

In Russia, the terms “Holter monitoring” (HM) or “daily monitoring” (DM ECG) are used.

In the USA and Europe, the method is more commonly referred to as “outpatient ECG monitoring”, “dynamic electrocardiography”, “daily ECG monitoring”, “Holter monitoring”.

WORK SEQUENCE

1. Preparation of a monitor for work (installation of accumulators, batteries, checking their charge and cable suitability, preventive maintenance of the monitor).
2. Preparation of a patient, explanations, selection of a research protocol.
3. HM ECG examination.
4. Receipt of data, their processing, evaluation by a doctor of functional diagnostics, drawing a conclusion.
5. Data archiving (if necessary), data erasure.

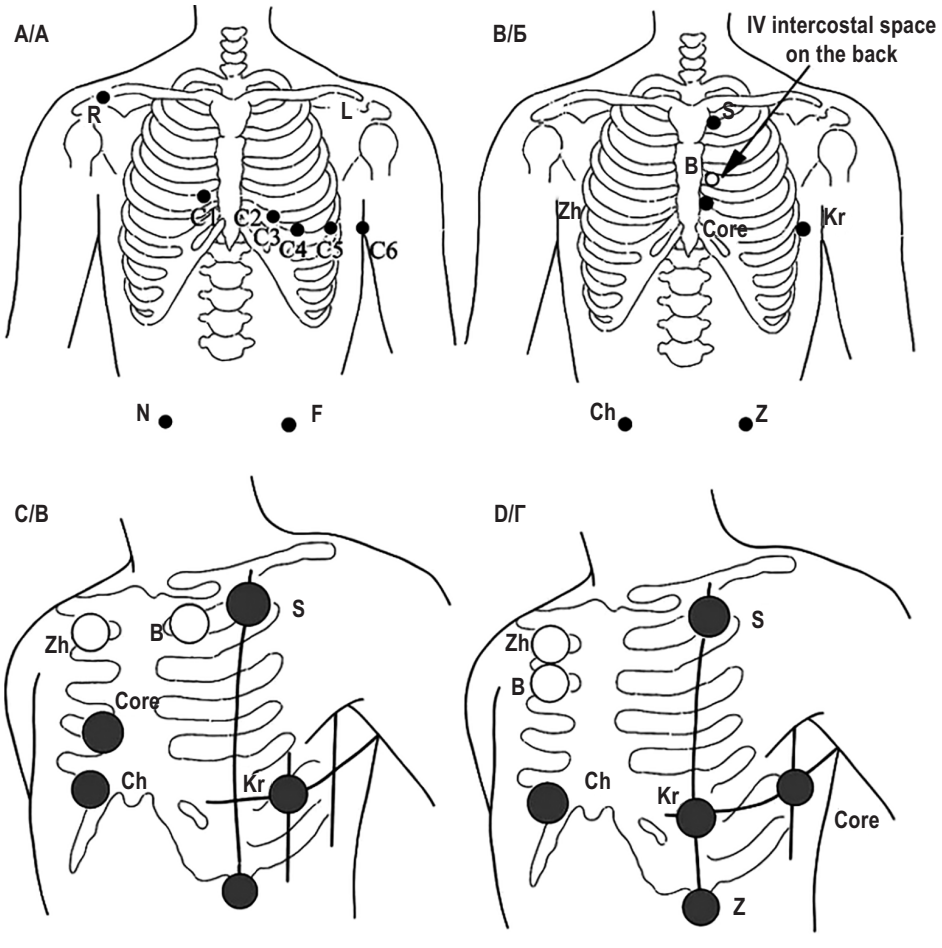

Fig. 4. **Twelve standard ECG leads (chest electrodes are located at standard points C1–C6, and electrodes from the limbs are transferred to the ends of the clavicles and to the iliac crests) (A); three orthogonal leads for recording late ventricular potentials according to Simpson (Б); system of monitor leads Vim, V5m, Y, most suitable for diagnosing rhythm disturbances (B); the V4m, V6m, Y system is most suitable for diagnosing myocardial ischemia (D). The colors of the electrodes are indicated: Zh — yellow; B — white; Ch — black; S — blue; Z — green; Core — brown; Kr — red**

Рис. 4. **Двенадцать стандартных отведений ЭКГ (грудные электроды располагаются в стандартных точках С1–С6, а электроды с конечностей переносятся на окончания ключиц и на гребни подвздошных костей) (А); три ортогональных отведения для регистрации поздних желудочковых потенциалов по Симпсону (Б); система мониторных отведений Vim, V5m, Y, максимально пригодная для диагностики нарушений ритма (В); система V4m, V6m, Y максимально пригодна для диагностики ишемии миокарда (Г). Обозначены цвета электродов: Ж — желтый; Б — белый; Ч — черный; С — синий; З — зеленый; Кор — коричневый; Кр — красный**

VARIANTS OF THE EQUIPMENT USED

1. **Monitors with permanent recording.**

2. **Monitors with intermittent recording** (*event recorder),* including implantable loop heart rate recorders that can monitor ECG rhythm for months with wireless transmission to a service centre.

LEAD SYSTEMS USED

Two or three-channel ECG recording: two bipolar modified leads VI and V5 or three leads such as V5, AVF and II standard leads, which are close to the cardiac orthogonal axis directions.

1. The most orthogonal system of 7 electrodes with formation of three leads: type V5, AVF and V3, reflecting three axes — horizontal, vertical and sagittal ones.

2. Systems of three ECG leads formed by seven electrodes are increasingly used and are the closest to Frank's orthogonal system.

3. In recent years, almost all manufacturers have marketed monitors with the ability to record 12 ECG channels, identical to the 12 channels on the resting ECG or stress test (Fig. 4) [3].

INDICATIONS FOR DAILY ECG MONITORING

The indications for daily ECG monitoring are as follows [3].

Class I

1) Patients with unexplained syncopal and presyncopal states or episodic dizziness (with no identified noncardiac cause).

2) Patients with unexplained recurrent heart palpitations.

Class II

1) Patients with episodic dyspnoea, chest pain or unexplained weakness.

2) Patients with neurological pathology if transient atrial fibrillation/atrial flutter is suspected.

3) Patients with symptoms such as syncopal and presyncopal states, episodic dizziness or palpitations for which a different (non-arrhythmic) cause has been identified but symptoms persist despite receiving aetiotropic treatment.

Class III

1) Patients with symptoms such as syncopal and presyncopal states, episodic dizziness or palpitations who are determined to have another cause on examination.

2) Patients with cerebrovascular disorders without other evidence of arrhythmia.

AIM

1. Heart rate (HR) per day, daytime and nighttime, their ratios.
2. Variability of R-R intervals (analysis of autonomic regulation and adaptation mechanisms of circulatory system regulation) and *Q*–*T* interval.
3. Rhythm and conduction disorders (calculation of their number and characteristics).
4. Adequacy of antiarrhythmic therapy (if arrhythmia is reduced by 75% — the treatment is adequate), control of other types of treatment.
5. Changes in repolarization (ischemic, dystrophic ones).
6. Evaluation of the effectiveness of electrocardiostimulation (ECS).
7. Evaluation of ventricular late potentials.
8. Assessment of exercise tolerance.

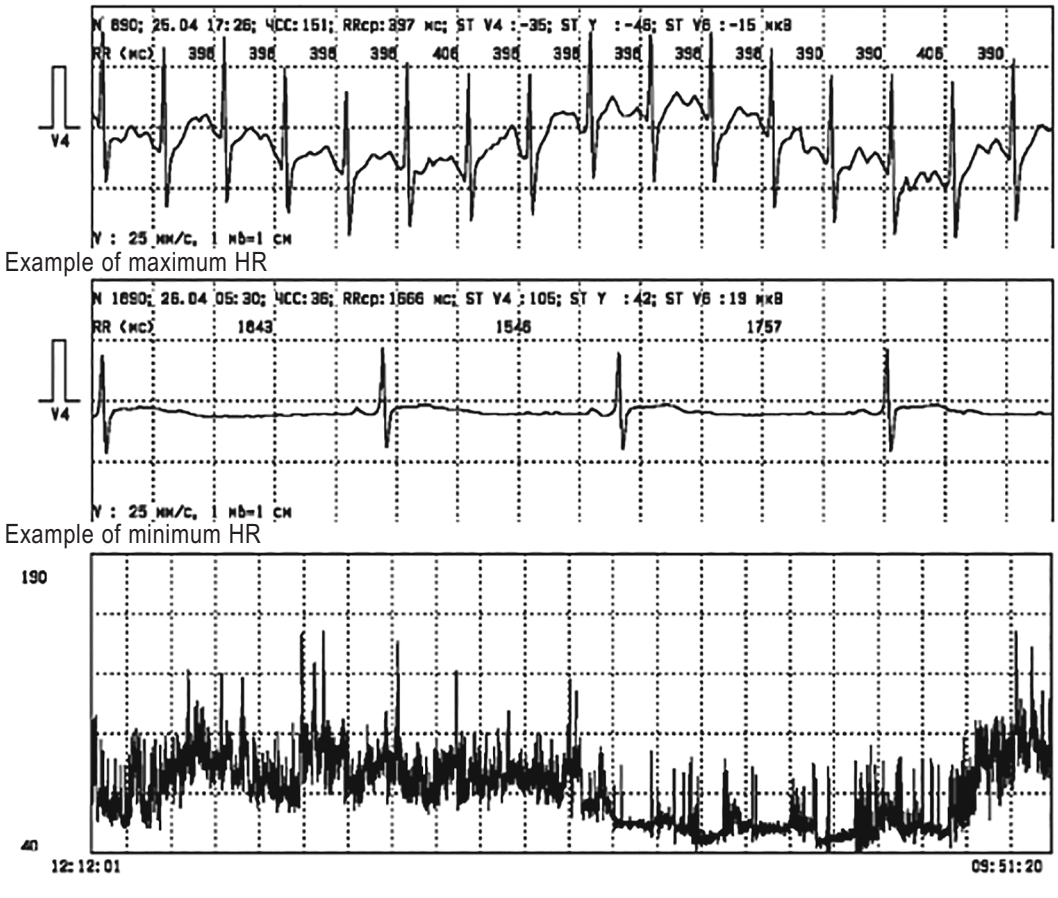

Fig. 5. Graph of heart rate values [40]

Рис. 5. График значений ЧСС [40]

RHYTHM AND ITS ABNORMALITIES IN HEALTHY INDIVIDUALS

Assessment of HM results begins with the estimation of the HR [3]. Average daily parameters, as well as maximum and minimum values of HR per day are distinguished (Fig. 5).

Note that the rhythm in HM ECG differs from the standard ECG throughout the day.

Average daily HR reaches 70–100 beats per minute (in women — 83–86, in men — 79–86). There is also a correlation with age (Table 1) [4–6].

The average overnight HR varies between 55–70 beats per minute (64–70 in women, 56–62 in men), nocturnal HR reflects the "baseline rhythm" and is little affected by age.

Table 1

The average daily values of the percentile (%) distribution of heart rate (bpm) in XM in healthy individuals aged 20–90 years [3]

Таблица 1

Среднесуточные значения процентильного (%) распределения ЧСС (уд./мин) при ХМ у здоровых лиц 20–90 лет [3]

Возраст (лет) / Age (years)	ЧСС (уд./мин) / Heart rate (bpm)		
	50%	5%	95%
20–29	79	56	104
30–39	78	55	103
40–49	78	54	102
50–59	76	53	100
60–69	77	52	99
70–79	72	51	98
80–89	73	49	97

CIRCADIAN INDEX

The circadian index (CI) is defined as the ratio of daytime HR to nighttime HR.

There is no significant sex-age difference in healthy individuals, and this index is 1.24–1.44 [7].

An increase in CI is observed in the following conditions: pronounced vagotonia in the evening and at night, persistent sinus tachycardia during the day (emotional, physical stress, vagotonic sinus node dysfunction). Reduced CI: persistent sinus tachy-, bradycardia, rigid rhythm (sinus node weakness syndrome, diabetic cardiovascular autonomic neuropathy, tetraplegia, heart transplantation, etc.).

NB! A functional diagnostician should check sleep time in an HR chart.

Depending on the obtained CI, a circadian profile of a patient is derived. In a normal circadian profile, the CI corresponds to 1.24–1.44. Rigid circadian HR profile (signs of "autonomic denervation") corresponds to CI <1,2. Enhanced circadian profile or increased sensitivity of heart rhythm to sympathetic influences corresponds to CI >1.45 [3].

SINUS ARRHYTHMIA

In contrast to standard ECG, the variation of adjacent *R–R* intervals is higher. Possible variants of sinus arrhythmia in DM ECG are: mild — *RR* fluctuations up to 15% (more often in the elderly), moderate — with *RR* fluctuations of 50–100%; severe — fluctuations of more than 100%, which makes it almost impossible to detect sinoauricular blockade.

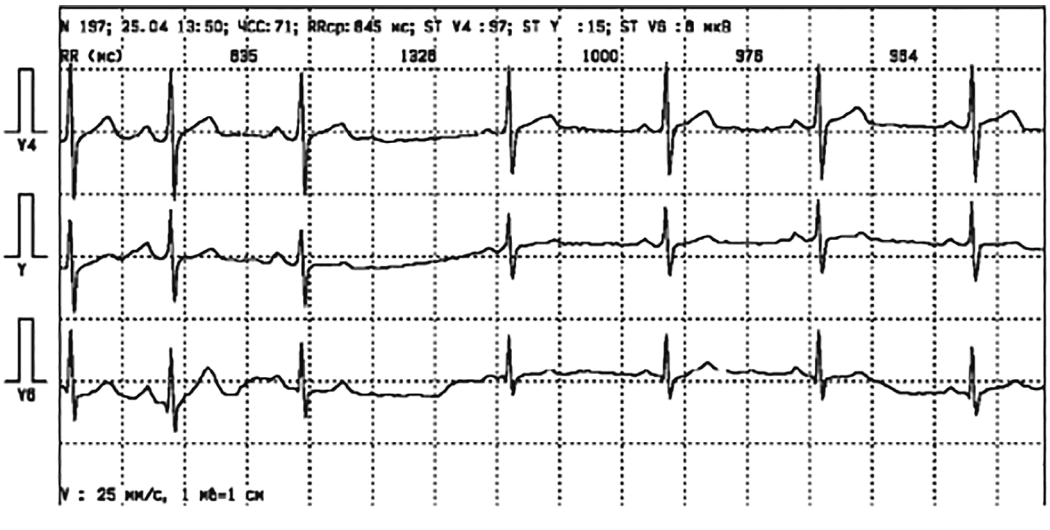

Fig. 6. Migration of the rhythm driver [40]

Рис. 6. Миграция водителя ритма [40]

NB! It is more correct to use the term "pauses on the background of sinus arrhythmia" and to take into account their duration: up to 1.5 s — in 31–68% of healthy people, 1.5–2 s — in 25% of young men, over 2 s — in 1–2% [3, 7, 8].

When detecting prolonged pauses, it is necessary to distinguish clinically significant pauses from clinically insignificant ones. Thus, pauses over 2 s are considered pathologic and require further follow-up examination. Pauses of 1.5 s or more should be treated with caution in elderly patients.

PACEMAKER MIGRATION

Rhythm driver migration across the atria is detected at night in the majority of healthy people (54%), and is more characteristic for young people. Rhythm driver migration to the AV junction ("nodal" rhythm) is rare in healthy people — 2–9% and is a reason for further examination (Fig. 6) [9, 10, 40].

AV CONDUCTION AND ITS DISORDERS

AV conduction disorders occur in healthy patients in 2–8% of cases, they are usually asymptomatic (at night — on the background of bradycardia). AV-blockade of the I degree is the most frequent, II degree AV-blockade of the Mobitz 1 type is less frequent.

NB! Increase of *P–Q* interval on the background of bradycardia (HR less than 50 per minute) up to 240–260 ms is natural and should not be interpreted as AV conduction disorder.

RHYTHM DISTURBANCES

Special software decodes a 24-hour recording and presents a total number of complexes as "normal", "ventricular", "artifactual" and "unknown" (other variants are possible), as well as arrhythmia classes [3]. All arrhythmia classes should be assessed and confirmed visually by an experienced clinician who is familiar with features of arrhythmia assessment in HM. It is important to keep in mind possible false-negative and false-positive detections of arrhythmias.

According to the ACC/AHA guidelines, the following reasons for such identifications are emphasized [11]:

1) inadequate algorithm of computerized detection and identification of *QRS* complexes;
2) "noise" and flooding, electrode displacement, artifacts;
3) low recording voltages;
4) recording defects due to violation of recording speed or recording to another carrier;
5) physiologic variability of *QRS* complex shape and voltages;
6) incomplete deletion or erasure of a previous recording from the carrier;
7) inadequate or incorrect technical interpretation during the analysis;
8) incorrectly time labeled [3].

Arrhythmia analysis

According to the results of various studies, supraventricular extrasystole (SVE) is registered in adults in 56% of cases during HM in healthy individuals [3, 12–15]. In healthy individuals, ventricular extrasystole (VES) is recorded in 70% of adult patients in the same studies [16, 17]. In healthy individuals, single paired extrasystoles and volleys of ventricular tachycardia of no more than three consecutive contractions are also registered (Fig. 7, 8). It is important to take into account that no more than four consecutive complexes will be considered as group extrasystole. If there are 5 or more complexes, it is legitimate to speak about a tachycardia paroxysm [7]. It should also be noted that identification of SVE and LES from each other seems obvious, but in practice it is not so simple, although it is very important.

ST SEGMENT ANALYSIS IN HOLTER MONITORING

It is important that the rhythm is sinus rhythm. Initial *ST* segment displacement should not exceed 0.1 mV, in morphology

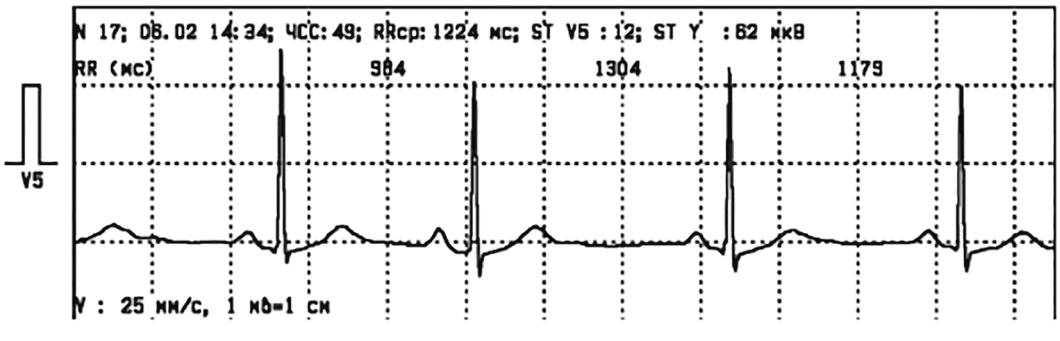

Fig. 7. Single supraventricular extrasystole [40]

Рис. 7. Единичная суправентрикулярная экстрасистола [40]

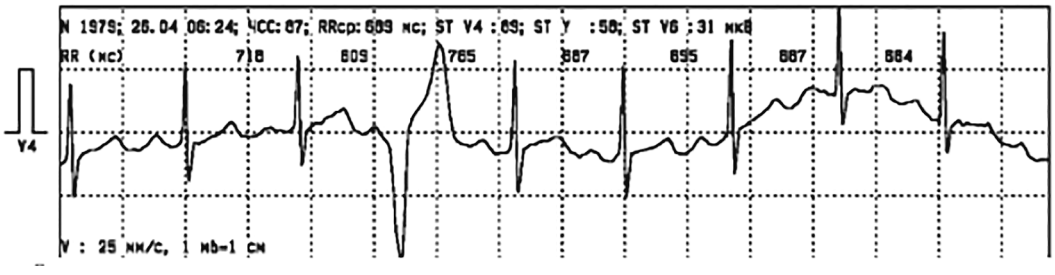

Fig. 8. Single ventricular extrasystole [40]

Рис. 8. Единичная желудочковая экстрасистола [40]

it should be with a positive T tooth. For adequate assessment of the *ST* segment, the height of the *R* tooth in the monitored lead should be ≥10 mV. Patients with evidence of left ventricular hypertrophy (LVH), signs of preexcitation, left bundle branch block (LBBB), or nonspecific intraventricular conduction abnormalities with a delay of ≥0.10 s are not suitable for assessment of myocardial ischemia by CM. The leads selected for ischemia monitoring with CM should not have *Q* teeth of ≥0.04 s duration and a pronounced baseline *ST* segment shift. It is necessary to exclude the influence of drug therapy on the study period (cardiac glycosides, antiarrhythmics, antidepressants).

Ischemia is identified as a sequence of the following ECG changes: horizontal or oblique *ST* segment depression ≥0.1 mV with gradual onset and termination that lasts for at least 1 minute.

Kodama classification [18] is most commonly used in practice in order to confirm and describe myocardial ischemia during HM:

1. Horizontal or descending *ST* segment decrease of 0.1 mV at a point 80 ms from the *J* point and lasting at least 1 minute. The sensitivity of the criteria for men is 93.3% and specificity is 55.6%; for women it is 66.7% and 37.5%, respectively.
2. *ST* segment elevation of 0.1 mV lasting 80 ms from the point *J*.
3. Episodes of *ST* elevation and *ST* segment depression.
4. *ST*/HR index that is equal to 1.4 mV/ud/min. Sensitivity of ischemia detection — 80%, specificity — 64.7%.

Ellestad criteria [19] for describing an episode of myocardial ischemia during HN are also used:

1. Horizontal or oblique *ST* segment depression that lasts 80 ms after the end of the *QRS* complex. *J* point depression should reach at least 1 mV.
2. Oblique slow *ST* segment depression that lasts at least 80 ms from the *J* point, the *ST* segment that is 80 ms away from it should be reduced by at least 2 mV.

The *ST* segment, as well as HR, is subject to circadian influences. Thus, during daytime and morning hours, the *ST* segment may have a slanting shape with *J* point depression under increased sympathetic influence. At night hours, saddle-shaped *ST* segment elevation may be registered as a result of vagus influence [3].

In practice, it is very important to distinguish true myocardial ischemia from false-positive or false-negative myocardial ischemia. According to ACC/AHA (American College of Cardiology / American Heart Association) guidelines, the following causes of false identifications are distinguished [3]:

1) *ST* segment positional changes;
2) hyperventilation;
3) sudden significant *ST* segment changes at the peak of physical activity;
4) vasoregulatory or vagus (Valsalva) induced *ST* segment changes;
5) intraventricular conduction disorders;
6) undiagnosed left ventricular hypertrophy;
7) *ST* segment changes due to tachycardia;
8) false-positive *ST* segment changes on the background of atrial fibrillation;
9) *ST* segment changes due to electrolyte disorders;
10) inadequate formation of leads for recording;
11) incorrect calibration of leads;
12) signal recording system that changes *ST* segment.

All these reasons must be taken into account during medical interpretation of HM. It is not allowed to rely blindly on machine identification!

A marked oblique *ST* depression with a *J* point decrease of more than 1 mV is absolutely normal in tachycardia. Moreover, *ST* elevations over 1 mV may be recorded in severe bradycardia and early repolarization syndrome/phenomenon.

It is important to remember that changes in the *T* wave (final ventricular deflection) are often nonspecific. Visual alternation phenomenon is also interesting. It is an alternation of positive and negative *T* wave, and it indicates a high degree of myocardial electrical instability [3]. International Recommendations for the Prevention of Sudden Cardiac Death (SCD) [20, 21] include the assessment of *Q–T* interval and visual alternation of the *T* wave during HM (A of evidence) in the first class of indications in risk groups.

There are two methods of estimating the MAT (microvolt alternation of the *T* wave) — these are spectral and temporal ones. The spectral (Conventional Spectral based method or Cambridge Heart method) method can be used only in stress test and transesophageal stimulation when a certain HR is reached [22] and is not suitable for analysis during HM [23]. The temporal method of MMA (Modified Moving Average) can also be used in HM [24]. Studies [25, 26] have shown that a cut-off point value of MMA above 65 microvolts (μV) is associated with a risk of high mortality in the adult population [23]. MMA values should not exceed 55 μV in healthy individuals in all age groups [27]. In case MMA values are higher than 65 μV in adults and 55 μV in children, they can be reflected in the HM report as a manifestation of myocardial electrical instability and can be interpreted as a risk factor for the development of life-threatening arrhythmias [3].

EVALUATION OF THE *Q–T* INTERVAL DURING HOLTER MONITORING

Q–T interval estimation is an extremely important element in the analysis of HM. According to international guidelines for the prevention of sudden cardiac death (SCD) [20], assessment of the *Q–T* interval during HM is a 1A grade indication to perform HM in individuals with a high risk of developing life-threatening rhythm disturbances [3].

The range of normal values of the *Q–T* interval during HM is still debatable. It is known [3] that the clinical standard for resting ECG is the calculation of corrected *Q–T* interval (*Q–Tc*) using the Bazett formula (*Q–T*/the square root of the preceding *RR* interval) or (much less frequently) the Fredericia formula (*Q–T*/cubic root of the preceding interval) *R–R* [3]. However, only maximum absolute *Q–T* interval can be determined during manual analysis of HM, which is measured at the minimum HR. According to different data [3, 28–38], it can be concluded that the maximum values of the mean daily *Q–Ts* in healthy individuals at automatic calculation in different HM systems do not exceed 450 ms in adults and 480 ms in children. Sex differences are presented in Table 2.

Table 2

Sex differences between *Q–T* and *Q–Tc* in HM [3]

Таблица 2

Половые различия *Q–T* и *Q–Tc* при ХМ [3]

Интервал, мс/ Interval, ms	В целом по группе / Total	Женщины / Females (n=28)	Мужчины / Males (n=29)
Q–T	367±18	368±18	367±17
Q–Tc	409±15	417±12	401±13

Dynamic evaluation of daily adaptation parameters of *Q–T* interval to HR also deserves attention. The so-called *QT*-dynamics is performed to identify the parameters of daily adaptation of the *Q–T* interval to HR, i.e. the higher the slope *QT*/*RR* (slope *QT* is a method of manual calculation of *Q–T* interval duration), the more the *Q–T* interval shortens during tachycardia and lengthens during bradycardia, and vice versa [3]. Based on this approach, the concept of "hyper- and hypoadaptation" of *Q–T* to HR was proposed, which defines "hyperadaptation" at values of daily slope *QT*/*RR* greater than 0.24 and "hypoadaptation" at its values less than 0.13 [34]. "*Q–T* hyperadaptation" is characteristic for patients with heart failure, myocardial infarction and the third type of *Q–T* prolongation syndrome, "*Q–T* hypoadaptation" — for patients with Brugada syndrome and the first type of *Q–T* prolongation syndrome.

ANALYSIS OF VENTRICULAR LATE POTENTIALS

This technique is based on the analysis of low-amplitude (less than 20 μV), high-frequency (over 20–50 Hz) signals at the end of the QRS complex — ventricular late potentials (VLPs), reflecting delayed, fragmented activity occurring in heterogeneously changed myocardium. The program automatically processes the *QRS* complex with the help of time-domain analysis. On the basis of the latter, a conclusion is made if there are signs of VLPs. It is worth mentioning that the method was supposed to be used in HM for complex analysis of heart rhythm. However, a certain number of technical difficulties, such as the presence of artifacts and variability of adhesion, do not allow to introduce the technique into standard programs in HM. Even now, according to our experience, qualitative analysis of VLP is possible only when using the most modern computer algorithms of decoders in commercial HM systems.

Thus, according to the automatic analysis of VLP in HM, we can distinguish two groups of patients: with or without late potentials [39]. The following parameters served as a criterion for late potentials in HM:

1) tot*QRS* (*QRS* duration) ≥120 ms;
2) rMS40 (*QRS* amplitude of last 40 ms) ≤25 μV;
3) LAS40 (duration <40mV) ≥39 ms. Patients with myocardial infarction appeared to have a circadian rhythm of LAS registration [3].

DRAWING A CONCLUSION

The main task of a functional diagnostics doctor is to provide a treating physician with the most objective document which must reflect all parameters of the examination.

The conclusion should reflect:

1) the rhythm registered during the observation period, rhythm change (in hours and minutes);
2) HR dynamics (according to CI), max and min HR during the day and night;
3) heart rate variability indices (reflection of VNS activity);
4) detected rhythm and conduction disturbances (quantitative and qualitative assessment) not only in the report itself, but also in the arrhythmia graph (distribution per day), as well as in the protocol with visual examples;
5) *ST* segment changes (ischemic, dysmetabolic, mixed type);
6) assessment of *Q*–*T* interval variability, VLP (if possible);
7) assessment of exercise tolerance.

NB! The purpose is to relate these indices to each other, to correlate them with subjective feelings of a patient according to his diar

CONCLUSION

This lecture contains basics required to analyze the results of Holter ECG monitoring. Holter monitoring provides information that cannot be obtained by analyzing an electrocardiogram recording of a few seconds. It is a flexible and informative tool in talented and professional hands.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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ПРАВИЛА ДЛЯ АВТОРОВ

Утв. приказом и.о. ректора
ФГБОУ ВО СПбГПМУ Минздрава России от 05.04.24

НАСТОЯЩИЕ ПРАВИЛА ДЛЯ АВТОРОВ ЯВЛЯЮТСЯ ИЗДАТЕЛЬСКИМ ДОГОВОРОМ

Условия настоящего Договора (далее «Договор») являются публичной офертой в соответствии с п. 2 ст. 437 Гражданского кодекса Российской Федерации. Данный Договор определяет взаимоотношения между редакцией журнала «**Russian Biomedical Research»** (далее по тексту «Журнал»), зарегистрированного Федеральной службой по надзору в сфере связи, информационных технологий и массовых коммуникаций (РОСКОМНАДЗОР), свидетельство: ПИ № ФС77-74228 от 02 ноября 2018 г. (ранее ПИ № ТУ78-01869 от 17 мая 2016 г.), именуемой в дальнейшем «Редакция» и являющейся структурным подразделением ФГБОУ ВО СПбГПМУ Минздрава России, и автором и/или авторским коллективом (или иным правообладателем), именуемым в дальнейшем «Автор», принявшим публичное предложение (оферту) о заключении Договора.

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  Авторское резюме к статье является основным источником информации в отечественных и зарубежных информационных системах и базах данных, индексирующих журнал. Резюме доступно на сайте журнала «Russian Biomedical Research» и индексируется сетевыми поисковыми системами. Из аннотации должна быть понятна суть исследования, нужно ли обращаться к полному тексту статьи для получения более подробной, интересующей его информации. Резюме должно излагать только существенные факты работы.

  Рекомендуемая структура как аннотации, так и самой статьи IMRAD (для оригинальных исследований структура обязательна): введение (Introduction), материалы и методы (Materials and methods), результаты (Results), обсуждение (Discussion), выводы (Conclusion). Предмет, тему, цель работы нужно указывать, если они не ясны из заглавия статьи; метод или методологию проведения работы целесообразно описывать, если они отличаются новизной или представляют интерес с точки зрения данной работы. **Объем текста авторского резюме** определяется содержанием публикации (объемом сведений, их научной ценностью и/или практическим значением) и должен быть в пределах **200–250 слов (1500–2000 знаков)**.
- Ключевые слова (Keywords) от 3 до 10 ключевых слов или словосочетаний из 2–4 слов, которые будут способствовать правильному перекрестному индексированию статьи, помещаются под резюме с подзаголовком «Ключевые слова». Используйте термины из списка медицинских предметных заголовков (Medical Subject Headings), приведенного в Index Medicus (если в этом списке еще отсутствуют подходящие обозначения для недавно введенных терминов, подберите наиболее близкие из имеющихся). Ключевые слова разделяются запятой.
- Текст статьи может быть написан либо на русском, либо на английском языке, также возможна публикация статьи с полным переводом. На русском и английском языках необходимо предоставить все рисунки и таблицы (заголовки, все надписи, а также текст таблиц должны иметь перевод).

  В разделе «Методика» обязательно указываются сведения о статистической обработке экспериментального или клинического материала. Единицы измерения даются в соответствии с Международной системой единиц — СИ. Фамилии иностранных авторов, цитируемые в тексте рукописи, приводятся в оригинальной транскрипции.

  Таблицы и рисунки приводятся непосредственно в теле статьи, каждый из которых имеет номер и название с обязательными ссылками на них в тексте статьи — в контексте предложения (например: «…как показано на рисунке 1…») или в конце предложения в круглых скобках (например: «...выявлена положительная корреляционная связь умеренной степени (r=0,41) между уровнем ТТГ матери и новорожденного (рис. 2)»; просьба учитывать, что в печатной версии журнала рисунки будут воспроизводиться в черно-белом варианте.
- Список литературы обязательно приводится в порядке упоминания.

Текст статьи должен быть подготовлен в строгом соответствии с настоящими правилами и тщательно выверен автором. В случае обнаружения значительного количества опечаток, небрежностей, пунктуационных и орфографических ошибок, нерасшифрованных сокращений, отсутствия основных компонентов, переводов заголовков таблиц, подрисуночных подписей, надписей на рисунках,

текста таблиц и других технических дефектов оформления статей редакция возвращает статью автору для доработки. Небольшие погрешности редакция может исправить сама без согласования с автором. Редакция оставляет за собой право осуществления литературного и технического редактирования статей.

Сокращений, кроме общеупотребительных, следует избегать. Сокращения в названии статьи, названиях таблиц и рисунков, в выводах недопустимы. Если аббревиатуры используются, то все они должны быть непременно расшифрованы полностью при первом их упоминании в тексте (например: «Наряду с данными о РОН (резидуально-органической недостаточности), обусловливающей развитие ГКС (гиперкинетического синдрома), расширен диапазон исследований по эндогенной природе данного синдрома».

Все цитирования производятся следующим образом:

ФИО автора, год издания и прочая информация не упоминаются в тексте. Вместо этого указывается ссылка на источник литературы в виде номера в квадратных скобках (пример: «Ряд исследователей отмечает различные нарушения речевых функций при эпилепсии в детском возрасте [17, 21, 22].»), который включен в расставленный в порядке упоминания (1, 2, 3 и т.д.) список источников в конце статьи.

Все ссылки должны иметь соответствующий источник в списке, а каждый источник в списке — ссылку в тексте.

В виде исключения в тексте могут приводиться ФИО конкретных авторов в формате И.О. Фамилия, год и даже название источника, но при этом все равно обязательна ссылка (в квадратных скобках в конце предложения) на источник, включенный в список литературы. (Например: «В 1892 году великий Эраст Гамильтонский описал в своем бессмертном труде «Об открытии третьего уха у человека» третье (непарное) ухо» [34].)

Литература (References)

Учитывая требования международных систем цитирования, список литературы приводится не только в обычном виде, но также и дополнительно в переведенном на английский язык (References).

В статье приводятся ссылки на все упоминаемые в тексте источники.

Фамилии и инициалы авторов в пристатейном списке приводятся в порядке упоминания.

В описании указываются все авторы публикации.

Библиографические ссылки в тексте статьи даются в квадратных скобках.

Ссылки на неопубликованные работы не допускаются.

Список литературы комплектуется в следующем порядке:

Нормативные акты

Приказы, нормативные акты, методические письма и прочие законные акты, патенты, полезные модели не вносятся в список литературы, оформляются в виде сносок. Сноска — примечание, помещаемое внизу страницы (постраничная сноска). Знак сноски ставят цифрой после фрагмента основного текста, где есть упоминание об этих источниках. Рекомендуется сквозная нумерация сносок по тексту.

Интернет-ресурс

1. Интернет-ресурс, где есть название источника, автор, вносится в список литературы (в порядке алфавита) с указанием даты обращения (см. ниже пример оформления).

2. Если есть только ссылка на сайт, оформляется подстрочное примечание (сноска), с указанием даты обращения.

Щеглов И. Насколько велика роль микрофлоры в биологии вида-хозяина? Живые системы: научный электронный журнал. Доступен по: http://www.biorf.ru/catalog.aspx?cat_id=396&d_no=3576 (дата обращения 02.07.2012).

Kealy M. A., Small R. E., Liamputtong P. Recovery after caesarean birth: a qualitative study of women's accounts in Victoria, Australia. BMC Pregnancy and Childbirth. 2010. Available at: http://www.biomedcentral.com/1471–2393/10/47/ (accessed 11.09.2013).

Примеры оформления литературы

Книга:

Юрьев В.К., Моисеева К.Е., Глущенко В.А. Основы общественного здоровья и здравоохранения. Учебник. СПб.: СпецЛит; 2019.

Никифоров О.Н., ред. Санкт-Петербург в 2021 году. СПб.: Петростат; 2022.

Brandenburg J.H., Ponti G.S., Worring A.F. eds. Vocal cord injection with autogenous fat. 3 rd ed. NY:Mosby; 1998.

Domeika M. Diagnosis of genital chlamydial infection in humans as well as in cattle. Uppsala; 1994.

Глава из книги:

Тутельян В.А., Никитюк Д.Б., Шарафетдинов Х.Х. Здоровое питание — основа здорового образа жизни и профилактики хронических неинфекционных заболеваний. В кн.: Здоровье молодежи: новые вызовы и перспективы. Т. 3. М.; 2019: 203–227.

Статья из журнала:

Карсанов А.М., Полунина Н.В., Гогичаев Т.К. Безопасность пациентов в хирургии. Часть 2: Программа менеджмента качества хирургического лечения. Медицинские технологии. Оценка и выбор. 2019;1(35):56–65. DOI: 10.31556/2219-0678.2019.35.1.056-065.

Brandenburg J.H., Ponti G.S., Worring A.F. Vocal cord injection with autogenous fat: a long-term magnetic resona. Laryngoscope. 1996;l06(2,pt l):174–80.

Deb S., Campbell B.K., Pincott-Allen C. et al. Quantifying effect of combined oral contraceptive pill on functional ovarian reserve as measured by serum anti-Müllerian hormone and small antral follicle count using three-dimensional ultrasound. Ultrasound Obstet Gynecol. 2012;39(5):574–580.

Тезисы докладов, материалы научных конференций:

Марковская И.Н., Завьялова А.Н., Кузнецова Ю.В. Микробный пейзаж пациента первого года жизни с дисфагией, длительно находящегося в ОРИТ. XXX Конгресс детских гастроэнтерологов России и стран СНГ: тез. докл. М.; 2023: 29–31.

Салов И.А., Маринушкин Д.Н. Акушерская тактика при внутриутробной гибели плода. В кн.: Материалы IV Российского форума «Мать и дитя». Ч. 1. М.; 2000; 516–519.

Авторефераты:

Авилов А.Ю. Девиации полоролевой идентичности мужчин с умственной отсталостью в условиях психоневрологического интерната. Автореф. дис. … канд. психол. наук. СПб.; 2021.

Описание интернет-ресурса:

Естественное движение населения. Москва: Росстат. Доступен по: https://rosstat.gov.ru/folder/12781 (дата обращения: 23.10.2023).

World Health Organization. Prevalence and incidence of selected sexually transmitted infections — 2008. Geneva: World Health Organization; 2012. Available at: https://aefsg.ch/wp-content/uploads/who-9789241503839_eng.pdf (accessed 11.04.2024)

Перевод и транслитерация

В зависимости от ситуации следует либо проводить транслитерацию (писать исходные неанглоязычные слова буквами романского алфавита), либо указывать перевод неанглоязычной информации о первоисточниках в References.

Если цитируемая статья написана **на латинице** (на английском, немецком, испанском, итальянском, финском, датском и других языках, использующих романский алфавит), ссылку на нее следует привести на оригинальном языке опубликования. Пример (статья в норвежском журнале на норвежском языке):

Ellingsen A.E., Wilhelmsen I. Sykdomsangst blant medisinog jusstudenter. Tidsskr Nor Laegeforen. 2002;122(8):785–787. (In Norwegian).

Если статья написана **не на латинице** (на кириллице, в том числе на русском), нужно привести официальный перевод или выполнить транслитерацию в романский алфавит. Для книг необходимо в этом случае привести транслитерацию на латиницу. В конце описания в скобках указать язык издания.

Ссылка на источник литературы в References может состоять одновременно и из транслитерированных элементов (например, ФИО авторов, названия журналов), и из переводных (название публикации).

Стандарт транслитерации. При транслитерации рекомендуется использовать стандарт BSI (British Standard Institute, UK). Для транслитерации текста в соответствии со стандартом BSI можно воспользоваться ссылкой http://ru.translit.ru/?account=bsi.

ФИО авторов, редакторов. Фамилии и инициалы всех авторов на латинице следует приводить в ссылке так, как они даны в оригинальной публикации. Если в оригинальной публикации уже были приведены на латинице ФИО авторов, в ссылке на статью следует указывать именно этот вариант (независимо от использованной системы транслитерации в первоисточнике). Если в официальных источниках (на сайте журнала, в базах данных, в том числе в eLIBRARY) ФИО авторов на латинице не приведены, следует транслитерировать их самостоятельно по стандарту BSI.

Название публикации. Если у цитируемой Вами работы существует официальный перевод на английский язык или англоязычный вариант названия (его следует искать на сайте журнала, в базах данных, в том числе в eLIBRARY), следует указать именно его. Если в официальных источниках название публикации на латинице не приведено, следует выполнить транслитерацию в романский алфавит по стандарту BSI.

Название издания (журнала). Некоторые не англоязычные научные издания (журналы) имеют кроме названия на родном языке официальное «параллельное» название на английском (например, у журнала «Сахарный диабет» есть официальное англоязычное название «Diabetes Mellitus»). Таким образом, для списка References в ссылке на статью из русскоязычного журнала следует указать либо транслитерированное название журнала, либо переводное. Переводное название журнала можно взять либо с официального сайта журнала (или использовать данные о правильном написании англоязычного названия из цитируемой статьи), либо проверить его наличие в базе данных, например в CAS Source Index, библиотеке WorldCat или каталоге Web of Science (ISI), каталоге названий базы данных MedLine (NLM Catalog). В случае, когда у журнала нет официального названия на английском языке, в References нужно приводить транслитерацию по системе BSI. Не следует самостоятельно переводить названия журналов.

Место издания. Место издания в ссылках всегда следует указывать на английском языке и полностью — не в транслитерации и без сокращений. То есть Moscow, а не «Moskva» и не «M.:», Saint Petersburg, а не «Sankt Peterburg» и не «SPb».

Название издательства/издателя. В отличие от места издания, название издательства для ссылок в References следует только транслитерировать (за исключением крайне редких случаев наличия у издателя параллельного официального англоязычного названия).

Примеры перевода русскоязычных источников литературы для англоязычного блока статьи

Книга:

Yuriev V.K., Moiseeva K.E., Glushchenko V.A. Fundamentals of public health and healthcare. Textbook. Saint Petersburg: SpetsLit; 2019. (In Russian).

Nikiforov O.N., ed. Saint Petersburg in 2021. Saint Petersburg: Petrostat; 2022. (In Russian).

Глава из книги:

Tutelyan V.A., Nikityuk D.B., Sharafetdinov Kh.Kh. Healthy nutrition is the basis of a healthy lifestyle and the prevention of chronic non-communicable diseases. In: Youth health: new challenges and prospects. T. 3. Moscow; 2019: 203–227. (In Russian).

Статья из журнала:

Karsanov A.M., Polunina N.V., Gogichaev T.K. Patient safety in surgery. Part 2: Quality management program for surgical treatment. Medical technologies. Evaluation and selection. 2019;1(35):56–65. DOI: 10.31556/2219-0678.2019.35.1.056-065. (In Russian).

Тезисы докладов, материалы научных конференций:

Markovskaya I.N., Zavyalova A.N., Kuznetsova Yu.V. Microbial landscape of a patient in the first year of life with dysphagia who has been in the ICU for a long time. XXX Congress of pediatric gastroenterologists of Russia and the CIS countries: abstract. report. Moscow; 2023: 29–31.

Salov I.A., Marinushkin D.N. Obstetric tactics in intrauterine fetal death. In: Materialy IV Rossiyskogo foruma “Mat’ i ditya”. Part 1: Moscow; 2000; 516–519. (In Russian).

Авторефераты:

Avilov A.Yu. Deviations of gender role identity of men with mental retardation in a psychoneurological boarding school. PhD thesis. Saint Petersburg; 2021. (In Russian).

Описание интернет-ресурса:

Natural population movement. Moscow: Rosstat. Available at: https://rosstat.gov.ru/folder/12781 (accessed: 10/23/2023). (In Russian).

Kealy M.A., Small R.E., Liamputtong P. Recovery after caesarean birth: a qualitative study of women’s accounts in Victoria,

Australia. BMC Pregnancy and Childbirth. 2010. Available at: http://www.biomedcentral.com/1471-2393/10/47/ (accessed: 11.09.2013).

Пример списка литературы (References):

ЛИТЕРАТУРА

1. Криворученко В.К. Жестокое обращение с ребенком. Проявление и меры предотвращения. Информационный гуманитарный портал Знание. Понимание. Умение. 2012; 3. Доступен по: http://www.zpu-journal.ru/e-zpu/2012/3/Krivoruchenko_Child-Abuse (дата обращения: 27.12.2023).
2. Jacobi G., Dettmeyer R., Banaschak S., Brosig B., Herrmann B. Child abuse and neglect: diagnosis and management. Dtsch Arztebl Int. 2010;107(13):231-239. DOI: 10.3238/arztebl.2010.0231.

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1. Krivoruchenko V.K. Child abuse. Manifestation and prevention measures. Informatsionnyy gumanitarnyy portal Znaniye. Ponimaniye. Umeniye. 2012; 3. Available at: http://www.zpu-journal.ru/e-zpu/2012/3/Krivoruchenko_Child-Abuse (accessed: 27.12.2023) (In Russian).
2. Jacobi G., Dettmeyer R., Banaschak S., Brosig B., Herrmann B. Child abuse and neglect: diagnosis and management. Dtsch Arztebl Int. 2010;107(13):231-239. DOI: 10.3238/arztebl.2010.0231.

Для всех статей необходимо указывать индекс DOI в конце библиографического описания, а также EDN при его наличии.

Примеры:

Саттаров А.Э., Карелина Н.Р. Особенности ростовых процессов у мальчиков и юношей различных пропорций и телосложения, проживающих в южной части Кыргызстана. Педиатр. 2018;9(5):47–52. DOI: 10.17816/PED9547-52. EDN: YRAEPZ.

Voropaeva E.E., Khaidukova Yu.V., Kazachkova E.A., et al. Perinatal outcomes and morphological examination of placentas in pregnant women with critical lung lesions in new COVID-19 coronavirus infection. Ural Medical Journal. 2023;22(2):109–121. DOI: 10.52420/2071-5943-2023-22-2-109-121. EDN: CXRCMN. (In Russian).

ОТВЕТСТВЕННОСТЬ ЗА ПРАВИЛЬНОСТЬ БИБЛИОГРАФИЧЕСКИХ ДАННЫХ НЕСЕТ АВТОР.

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АДРЕС РЕДАКЦИИ

194100, Санкт-Петербург, Литовская ул., 2

e-mail: scrcenter@mail.ru

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ИЗДАТЕЛЬСТВО ПЕДИАТРИЧЕСКОГО УНИВЕРСИТЕТА ПРЕДСТАВЛЯЕТ

Руководство по педиатрии. ОФТАЛЬМОЛОГИЯ ДЕТСКОГО ВОЗРАСТА

Редакционная коллегия тома: Д.О. Иванов, В.В. Бржеский

Том 11 «Руководства по педиатрии» отражает современный уровень развития офтальмологии детского возраста. Книга содержит актуальную информацию о современных методах диагностики и лечения заболеваний глаз у детей. Отдельные разделы посвящены клиническим рекомендациям по основным синдромам и заболеваниям.

Издание предназначено офтальмологам, педиатрам и представителям других медицинских дисциплин, а также студентам старших курсов медицинских вузов.

Твердый переплет, цветные иллюстрации, 344 страницы.

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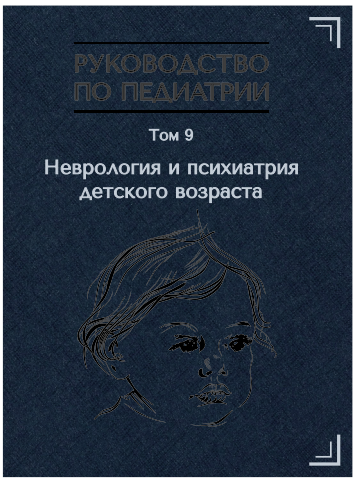
Редакционная коллегия тома: Д.О. Иванов, В.И. Гузева, С.В. Гречаный



Том 9 «Руководства по педиатрии» отражает современный уровень развития неврологии и психиатрии детского возраста. Книга содержит актуальную информацию о современных методах диагностики и лечения заболеваний нервной системы и психических расстройствах. Отдельные разделы посвящены клиническим рекомендациям по основным синдромам и заболеваниям.

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ИЗДАТЕЛЬСТВО ПЕДИАТРИЧЕСКОГО УНИВЕРСИТЕТА ПРЕДСТАВЛЯЕТ

ОРТОПЕДИЧЕСКАЯ СТОМАТОЛОГИЯ. ПРОТЕЗИРОВАНИЕ НЕСЪЁМНЫМИ КОНСТРУКЦИЯМИ ЗУБНЫХ ПРОТЕЗОВ

М. Ф. Сухарев, С. Б. Фищев, М. Г. Рожкова

Учебник соответствует программе Министерства здравоохранения Российской Федерации по ортопедической стоматологии, предназначен и будет полезным для преподавателей курсов и стоматологических кафедр, студентов стоматологических факультетов, ординаторов, аспирантов, врачей-стоматологов.

Авторы будут признательны за критические замечания и дополнения.

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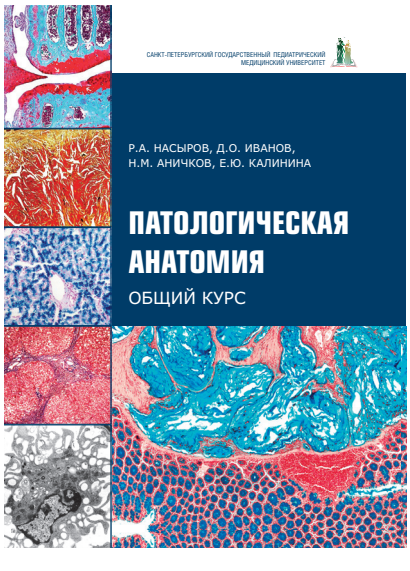
ПАТОЛОГИЧЕСКАЯ АНАТОМИЯ. ОБЩИЙ КУРС

Р.А. Насыров, Д.О. Иванов, Н.М. Аничков, Е.Ю. Калинина



В общем курсе патологической анатомии (клинической патоморфологии) рассмотрены вопросы общей патологической анатомии: методы исследования в патоморфологии, повреждение и гибель клеток и тканей, в том числе старение; нарушения кровообращения и иных сред организма, воспаление, репарация и регенерация, заживление ран, иммунная патология, адаптация, патология роста клеток и их дифференцировки, опухоли, генетические заболевания, учение о диагнозе в патологической анатомии, патология и факторы окружающей среды, патология, вызванная питанием, констатация смерти и др.

Учебник рассчитан на студентов-медиков всех факультетов, а также на врачей, интересующихся вопросами общей патологической анатомии.

Твердый переплет, цветные иллюстрации, 280 страниц.

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