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107076, Москва, ул. Короленко, д.3А, офис 18Б
Тел.: (495) 777-41-17
E-mail: info@medarhive.ru

ГЕНЕРАЛЬНЫЙ ДИРЕКТОР
Чернова Ольга Александровна
o_chernova@medarhive.ru

АДРЕС РЕДАКЦИИ
107076, Москва, ул. Короленко, д.3А, офис 18Б
Тел.: (495) 777-41-17

Медицинский редактор
Ефремова Елена Владимировна, *д.м.н., доцент кафедры терапии и профессиональных болезней ФГБОУ ВО «Ульяновский государственный университет» (Ульяновск, Россия)*
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Верстка
Виталий Котов

Отдел распространения и рекламы
Бабяк Алина
reklama@medarhive.ru

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«SYNAPSE» LLC
107076, Moscow, Korolenko str., 3A, of. 18B
info@medarhive.ru

CHIEF EXECUTIVE OFFICER
Olga A. Chernova
o_chernova@medarhive.ru

JOURNAL EDITORIAL OFFICE
107076, Moscow, Korolenko str., 3A, of. 18B
Phone: +7(495)777-41-17

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PAGE-PROOFS
Kotov Vitaly

ADVERTISING
Babiak Alina
reklama@medarhive.ru

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Г.А. Игнатенко, А.Э. Багрий, Т.С. Игнатенко, В.А. Толстой, И.С. Евтушенко, Е.С. Михайличенко*

ГОО ВПО «Донецкий национальный медицинский университет им. М. Горького», Донецк, Россия

ВОЗМОЖНОСТИ И ПЕРСПЕКТИВЫ ПРИМЕНЕНИЯ ГИПОКСИТЕРАПИИ В КАРДИОЛОГИИ

G.A. Ignatenko, A.E. Bagriy, T.S. Ignatenko, V.A. Tolstoy, I.S. Evtushenko, E.S. Mykhailichenko*

SEI HPE State Donetsk State Medical University named after M. Gorky, Donetsk, Russia

Possibilities and Prospects of Hypoxytherapy Application in Cardiology

Резюме

Несмотря на достижения современной кардиологии, заболеваемость и смертность от кардиоваскулярной патологии в большинстве стран мира остается высокой, что мотивирует более широкое использование дополнительных (альтернативных) профилактических и лечебных подходов, одним из которых является гипокситерапия. За несколько десятилетий использования этого метода накоплен обширный объем информации, позволяющий констатировать благоприятное воздействие различных режимов гипокситерапии на выраженность клинической картины сердечно-сосудистых заболеваний, что потенциально может улучшать их прогноз. Применение гипокситерапии ассоциируется с улучшением циркадного ритма артериального давления, поток-зависимой вазодилатации, со снижением инсулинорезистентности, уменьшением жесткости сосудистой стенки, улучшением реологии крови, функции эндотелия и системы оксида азота, снижением уровней провоспалительных и протромботических цитокинов. Ряд авторитетных экспертов рассматривают гипокситерапию в качестве доступного и перспективного метода профилактики и лечения сердечно-сосудистой патологии, эффективно дополняющего традиционные немедикаментозные и медикаментозные подходы. Накопленные данные свидетельствуют о серьезных перспективах расширенного изучения возможностей применения гипокситерапии у кардиологических больных, в том числе в рамках крупных государственных исследовательских программ. Настоящий обзор посвящен рассмотрению физиологических эффектов гипокситерапии, возможностей ее применения в кардиологической практике, в том числе с анализом собственных данных, а также мер предосторожности при ее проведении.

Ключевые слова: *гипокситерапия, сердечно-сосудистые заболевания, ишемическое прекондиционирование тканей, артериальная гипертония, ишемическая болезнь сердца*

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Abstract

Despite the achievements of modern cardiology, the cardiovascular morbidity and mortality in most countries of the world remains high, which motivates the wider use of additional (alternative) preventive and therapeutic approaches, one of which is hypoxytherapy. Over several decades of

*Контакты: Евгения Сергеевна Михайличенко, e-mail: klassiki@inbox.ru
*Contacts: Eugenia S. Mykhailichenko, e-mail: klassiki@inbox.ru
ORCID ID: https://orcid.org/0000-0001-8625-1406

using this method, a large amount of data has been accumulated that allows us to state the beneficial effect of various hypoxytherapy regimens on the clinical course of cardiovascular diseases and can potentially improve prognosis of them. The use of hypoxytherapy is associated with an improvement in blood pressure circadian rhythm, flow-dependent vasodilation, an insulin resistance decrease, a vascular wall stiffness redaction, an improvement in blood rheology, endothelial function and nitric oxide system, a decrease of proinflammatory and prothrombotic cytokines levels. A number of modern experts consider hypoxytherapy as an affordable and perspective method of prevention and treatment of cardiovascular disease, effectively supporting traditional non-drug and drug-based approaches. Contemporary data indicate serious future perspectives for an expanded study of the hypoxytherapy possibilities in cardiac patients, including through the State research programmes. This review is devoted to the discussion of the physiological effects of hypoxytherapy, the possibilities of its application in cardiological practice, including with the analysis of own data, as well as precautions during its implementation.

Key words: *hypoxytherapy, cardiovascular diseases, ischemic tissue preconditioning, arterial hypertension, ischemic heart disease*

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AH — arterial hypertension, BP — blood pressure, HOT — hypoxytherapy, CAD — coronary artery disease, CVD — cardiovascular diseases, CHF — congestive heart failure, NO — nitrogen oxide

Arterial hypertesion (AH), coronary artery disease (CAD), congestive heart failure (CHF), cerebrovascular and peripheral vascular disorders are a cause of at least one third of all deaths globally, and their rate in mortality in developed countries is even higher [1, 2]. The leading role of these cardiovascular diseases (CVD) in the structure of causes of deaths globally forces to constantly improve the methods of prevention and treatment [2, 3].

An important achievement in cardiology and internal medicine in general is the widespread understanding of the need in adherence to recommendations to change the lifestyle, including low-salt healthy food, smoking cessation and cutting down on alcohol, moderate physical exercises, reduction of overweight, good sleeping habits and prevention of excessive emotional stress, regular monitoring and correction of blood pressure, blood sugar and lipids [3-6]. Solid achievements in cardiology during the past two decades also include introduction of advanced invasive and minimally invasive approaches (coronary revascularization, implants to control arrythmias and heart blocks, etc.), approval and wide use of statins for CVD, advances in anti-thrombotic therapy (dual anti-platelet therapy, novel oral anticoagulants), wider use of mineralocorticoid receptor antagonists in AH, use of dual neurohumoral blockade (valsartan plus sacubitril) and gliflozin in CHF [1, 3].

Unfortunately, despite impressive achievements in modern cardiology, desired reduction in CVD mortality and mortality has not yet been observed in a majority of countries all over the world [2]. Therefore, the interest in the use of additional (alternative) preventive and therapeutic approaches has been growing; one of such approaches is exposure to dosed and controlled hypoxia, commonly called hypoxytherapy (HOT). HOT variants (hypobaric, normobaric oxygenation with or without physical exercises, of various intensity and duration) have bee studied for decades [7–10]. Over this period, a lot of information has been gathered allowing to state that HOT has a number of favourable effects, which can reduce the intensity of clinical signs of CVD and has potential for improving the CVD prognosis [11–14]. A number of respectable experts see HOT as a convenient and promising approach to prevent and treat CVD, which is an efficient addition to conservative non-drug and drug methods [8, 15–17]. This literature review is dedicated to discussion of physiological effects of HOT, possible use of various HOT variants in CVD, and precautions for HOT procedures.

Physical Responses to Hypoxia

Exposure to controlled hypoxia causes formation of a complex of various physiological changes in the body [7, 12, 18-20]. A short period of hypoxia, especially intermittent, leads to development of a number of compensatory changes in respiratory and cardiovascular systems. They are designed to maintain sufficient oxygenation of peripheral tissues during hypoxia and potentially have cardiovascular protective effect [7, 10]. Respiratory changes are associated with exposure of carotid chemoreceptors to hypoxia and include hyperventilation, increase in the diffusive capacity of lungs (with an increase in the aero-hematic barrier permeability for respiratory gases — oxygen and carbon dioxide), increase in respiratory minute volume and ventilatory lung capacity, increase in respiratory response to physical activities [7, 12, 21]. Changes in the cardiovascular

system during hypoxia are caused by sympathic nervous system activation and include increase in the heart rate at rest and during physical activities, increased cardiac output, increased endothelium-dependent and NO-mediated vasodilation, including arteriolar and venous vasodilation, improved endothelium function, reduced blood viscosity, reduced blood pressure (BP), increased hemoglobin oxygen affinity, increased expression of hypoxia-induced factor 1-α (HIF-α) and vascular endothelial growth factor (VEGF), as well as increased angiogenesis [7, 22]. These processes are closely associated with metabolic changes induced by short-term intermittent hypoxia, including reduced appetite (caused by a shift in hormones regulating food intake and energy balance, including leptin, ghrelin, glucagon-like peptide-1 (GLP-1), pancreatic polypeptide (PP), peptide YY (PYY), serotonin), increased activity of glycolysis enzymes and transmembrane glucose transporter GLUT4, reduced insulin resistance, body weight loss [11, 18, 19]. It was demonstrated that at least some of the above favourable effects of intermittent hypoxia can persist for 3 months after hypoxia termination [10, 21]. From the pathophysiological point of view, a number of authors believe that HOT variants that involve procedures of 20 to 60 minutes/day in sessions of at least 5 days (preferably 10–15 days), repeated once every 3–6 months, are optimal for steady cardiovascular protection [7, 8, 16, 21].

For some pathophysiologists and clinicians, intermittent hypoxia is a variant of hypoxic/ ischemic tissue preconditioning [7, 18]. This phenomenon comprises a set of biological reactions (changes in regulation of ion channels, ATP-sensitive potassium channels of mitochondria, mitochondria membrane permeability, formation of active oxygen radicals) to increase tissue resistance to effects of hypoxia and ischemia by means of hypoxic training [17]. Metabolic adaptation to mild intermittent ischemic events has been studied mostly for myocardium (and is used for its protection against ischemic/reperfused events during revascularisation); there are some evidences of this phenomenon in brain tissue as well (later it can be useful for brain protection against ischemia) [17, 20, 22]. Interpretation of effects of HOT as a variant of hypoxic/ischemic tissue preconditioning seems promising for the assessment of perspective clinical use of this metod, especially in cardiology and neurology [8, 12, 13, 20].

Stable and long-term exposure to hypoxia (e.g., living in high mountain regions) is associated with increased erythropoiesis and reduced cardiac output to the level close to the normoxia [23].

Available hypoxia variants used in clinical settings, including intermittent variants of exposure to normobaric and hypobaric dosed hypoxia as well as physical activities during controlled hypoxia lead to similar positive respiratory, cardiovascular and metabolic changes; and it is assumed that their intensity can be higher in hypobaric HOT as compared to normobaric conditions and in HOT with physical activities as compared to HOT without any exercises [19, 23]. Favourable HOT-associated effects can be used for CVD both for prevention and treatment [9, 14, 21, 24].

Clinical Effects of HOT

HOT is promoted as a method of alternative medicine, the advantage of which adds to the possibilities of conventional methods of CVD prevention and treatment [22, 24]. Two HOT variants are worth noting — these are procedures with exposure to various types of dosed hypoxia and physical activities during controlled hypoxia. Both these variants demonstrate a number of positive effects for cardiovascular system and CVD pathophysiology. Let's discuss the possibilities of both these variants of HOT in CVD.

Exposure to dosed hypoxia. The assumption of possible favourable effect of oxygen-deficient air inhalation on CVD is based on the information from epidemiological studies comparing cardiovascular characteristics of those living in high mountain regions and flat-bottom land. The information in such analyses is often ambiguous because of significant diversity of the studied populations in ethnicity, race, gender, physical activity and diet. At the same time, the largest and most respected epidemiological papers evidence reduction in the cardiovascular risk in people living in high mountain regions vs. those living in flat-bottom land. A series of papers by Faeh D. et al. (2009, 2016) assessed the impact of the altitude above sea level on CVD first in 1.64 million, then in 4.2 million of people from various regions in Germany and Switzerland (using the Swiss National Cohort Study Group register) [25, 26]. Results of such large studies quite definitely demonstrated (1) marked favourable effect of living in mountain regions on the risk and progression of CAD; (2) independent protective effect of being born in a high mountain region regarding the risk of CAD; (3) linear dependence of the cardiovascular mortality on the increase of the altitude above sea level. Similar evidence of positive effects of living in a mountain region on the cardiovascular risk was observed in other population studies (Ezzati M. et al., 2012), where analysis was performed by such respected epidemiological sources in the USA as the National Center for Health Statistics, he National Elevation Dataset and the U.S. Census Estimates [27]. The paper by Winkelmayer W.C. et al. (2012) which analysed a US dialysis population also showed

a significantly lower rate of myocardial infarction, cerebral strokes and cardiovascular complications among people living in mountains as compared to people living in flat regions [28].

These promising information from epidemiological registers was used to plan a number of studies where exposure to dosed hypoxia was used for prevention and therapy in various categories of people — healthy people and CVD patients [29-34]. Vedam H. et al. (2009) evaluated the cardiovascular effects of hypoxia with controlled reduction in oxygen saturation to 80 % for 20 minutes in a group of healthy male volunteers [29]. The authors proved that inhalation of an oxygen-deficient air mix results in endothelium-dependent and NO-mediated arterial vasodilation with increased blood flow in skeletal muscles. Leuenberger U.A., et al. (2008) created hypobaric hypoxia conditions in a group of healthy male volunteers; these conditions were similar to those at an altitude of 2438–4877 m above sea level during 20 minutes [30]. They demonstrated that this hypoxia regimen is associated with increased NO production in venous endothelium of skeleton muscles and development of marked hypoxia-induced vasodilation in this blood flow. Another study by Tremblay J.C., et al. (2020) confirmed favourable effects of hypobaric hypoxia on endothelial function in healthy males, including after induced increased in circulating plasma during this study [31].

Cardiovascular effects of HOT were assessed in a number of studies in patients with various CVD. Patients with stage 1 AH demonstrated favourable clinical and pathophysiological effects from 20-day use of intermittent normobaric HOT, presenting as BP reduction and increased NO production [32]. It is worth mentioning that the achieved BP reduction was maintained for over 3 months in 28 out of 33 studied patients. A double-blind study by Burtscher M., et al. (2004) assessed effects of 3-week intermittent HOT (with inspired oxygen fraction (FiO_2) = 0.10–0.14) in 16 males aged 50–70 years, including 8 post-infarct patients and the other 8 patients who did not have myocardial infarction [33]. The authors demonstrated that the use of HOT was associated with improved aerobic capacity and improved tolerance to physical activities in elderly people, both post-infarction patients and those who did not have myocardial infarction. According to another report by del Pilar Valle M., et al. (2006), intermittent hypobaric HOT in patients with severe chronic coronary disorders was associated with marked improvement in miocardial perfusion [34]. The authors used this information to conclude that this method can be a useful addition to conventional management of patients with chronic CAD.

A lot of studies with various HOT variants in CVD (mostly intermittent normobaric HOT) were published in Russian sources [8, 20, 24, 35]. These papers are based on relatively small cohorts of patients with CVD and generally positive HOT effects and good tolerability. At the same time, patients with arterial hypertension and chronic CAD demonstrated favourable effects of HOT on BP and NO-dependent vasodilation of arterial and venous blood flows. Besides, there were positive effects of HOT on insulin resistance, pro-inflammatory and prothrombotic cytokines, as well as clinical parameters (better physical activity tolerability, reduction in angina functional class) [8, 20, 24, 35].

Numerous studies led by Prof. G. A. Ignatenko are dedicated to the use of normobaric hypoxytherapy as a part of therapy and prevention of arterial hypertension, chronic heart disease, microvascular angina, metabolic syndrome, ischemic pre-conditioning, etc. [24, 36, 37]. Hypoxytherapy addition to a comprehensive therapeutic program for young patients with genetically induced hypertension vs. patients who were treated only with medications allowed reducing the number of complaints (headache, palpitation, irregular heart rate), the rate of uncomplicated and complicated hypertensic crises, extrasystolic arrhythmia and paroxysmal atrial fibrillation, daily average systolic and diastolic blood pressure (BP), total peripheral vascular resistance. Reduction in night-peacker circadian variability with a corresponding increase in the dipper type makes it possible to bring daily pressure fluctuations to physiological values and to minimise night risks associated with cardiac and cerebral blood flow disorders [37]. High efficiency of hypoxytherapy was observed in comorbidities (cardiac pathology and bronchopulmonary, endocrine, renal, prostate gland diseases, etc.). The results of the use of hypoxytherapy in cardiopulmonary disorders observed by the authors make it possible to treat hypoxytherapy as a universal pathogenic therapy which can optimise coronary blood flow, reduce manifestations of bronchial obstruction, cardiac and respiratory insufficiency and improve physical activity tolerability [38]. Hypoxytherapy, a non-drug component of a long-term comprehensive treatment program, can help in improving some parameters that characterise the quality of life (physical functioning, viability, social functioning, role emotional functioning) to the level of healthy people [39].

Physical Activities During Controlled Hypoxia. A combination of dosed physical activity with exposure to hypoxia leads to the development of marked compensatory arterial vasodilation aimed at maintenance of sufficient oxygen supply to skeletal muscles during oxyhemoglobin deficiency in blood [23, 41]. Physical activities themselves are a potent factor affecting metabolism [16, 40, 41]. During hypoxia, physical activities are associated with reduced oxygen supply to skeletal muscles and

increased oxygen demand, resulting in marked reduction of partial oxygen pressure in mitochondria of engaged muscles [42]. In turn, it is associated with increased NO production by vascular endothelial cells and compensatory vasodilation mobilisation [9, 40, 42]. This process underlines potential vaso- and cardioprotection by load HOT in CVD prevention and treatment.

Cardiovascular effects of a combination of physical activity and hypoxia were studied both in healthy volunteers and patients with CVD. The population of healthy female volunteers studied by Jung K., et al. (2020) demonstrated that pilates during hypobaric hypoxia (FiO_2 = 0.145) vs. normoxia was associated with development of more marked metabolic response (carbon dioxide excretion, carbohydrates oxidation) and more significant vasodilation [43]. Similarly, in the study by Katayama K., et al. (2013), physical activity during hypoxia (FiO_2 = 0.12) in healthy male subjects resulted in more marked endothelium-dependent vasodilation as compared to similar activities during normoxia [44].

There are numerous reports where load HOT was used in post-menopausal women (Nishiwaki M., et al. (2011), hypobaric hypoxia similar to an altitude of approx. 2000 m above sea level [45]), elderly men (Park H., et al. (2019), normobaric hypoxia, FiO_2 = 0.145 [46]), obese women (Jung K., et al. (2020), hypobaric hypoxia [47]), in sportsmen (Zembron-Lacny A., et al. (2020), intermittent hypoxia for 6 days at FiO_2 = 0.135–0.12 in combination with intensive physical activities [48]). These and some other similar papers (Wee J., et al. (2015) demonstrated that physical activities in combination with HOT are associated with vasodilation, BP reduction, improved functioning of vegetative nervous system, blood rheology, functions of endothelium, lipid profile and glucose tolerability, as well as reduced levels of pro-inflammatory mediators; and all these valuable biological effects were much more marked compared to absence of hypoxia [15].

Effects of load HOT on cardiovascular parameters were studied also in persons with CVD. Muangritdech N., et al. (2020), who analysed the results of the use of intermittent normobaric hypoxia (FiO_2 = 0.14) in combination with dosed physical load in patients with AH and found out that this method results in marked reduction of arterial hypertension, presumably due to such favourable metabolic effects as increased NO metabolite levels and increased HIF-α production [17]. Significant contribution to the study of effects of HOT in patients with CVD was made by outstanding Russian specialists, in particular by the study team led by Academician O. V. Korkushko [49]. These studies demonstrated that, in elderly persons with CAD, intermittent normobaric hypoxia in combination with dosed physical activities resulted in reduction in angina intensity; according to the authors, this positive effect is due to an improved function of coronary artery endothelium, normalised miocardial microcirculation and optimised oxygen consumption by myocardium. In a series of papers dedicated to HOT and in an analysis summarising data from numerous sources published over the last 50 years, T. V. Serebrovskaya et al. (2014, 2016) defend for a good reason the viewpoint that load HOT can be a very useful therapy complementing modern treatments of most common CVD, including AH, CAD and CHF [8, 35].

Precautions for HOT

For HOT, there are some evidence of a certain favourable potential for the clinical manifestation and course of CVD [29, 31, 33-35, 63]. The two recent decades are remarkable for active studies of the therapeutic effects of HOT, which allowed confirming a number of useful pathophysiological and clinical characteristics of this method and its good tolerability. However, the development of HOT is hindered by the lack of standardisation of the equipment used and hypoxia regimens; therefore, it is not possible to conduct large multicenter studies under an advanced protocol (preferably randomised controlled studies) and this method cannot be added to the Russian and international guidelines for the management of CVD [8, 9, 22].

HOT procedures in persons with CVD require certain precautions [9]. Experts claim that persons undergoing HOT should have stable CVD, without exacerbations and decompensation, because otherwise clinical signs of CVD can increase even in dosed and controlled hypoxia [8, 9]. According to some authors, before HOT a number of tests should be conducted with dosed physical activity with normoxia in order to assess HOT safety [8, 9]. It is essential to keep taking all medications prescribed by the attending physician during HOT, especially statins and antithrombotic agents, without any breaks. During therapy with HOT, it is advised to avoid such potentially unfavourable factors as physical overwork, dehydration, marked changes in the diet and temperature regimen (including overheating, e.g., baths, or hypothermia, e.g., cold training); it is also important to reduce emotional stress (at home, at work, including stress from smoking cessation, etc.). For an optimal result, it is useful to create positive motivation for the patient and their relatives for HOT, to explain positive effects of the procedure and precautions and make sure they comply with a course of at least 5 days long [50]. A decision to initiate HOT should be taken by the doctor; the room where the procedure is performed should be equipped with a CVD first aid kit.

Conclusion

HOT including procedures with exposure to dosed intermittent hypoxia ans physical activities during controlled hypoxia are characterised by the development of various favourable pathophysiological and clinical effects in chronic CVD and can be a valuable component of a comprehensive therapy. Positive effects of HOT demonstrated in healthy subjects and CVD patients include improved circadian AH rhythm and flow-associated vasodilation, reduced insulin resistance, reduced vascular wall rigidity, improved blood rheology, endothelial and NO system function, reduced levels of pro-inflammatory and prothrombotic cytokines. This information shows sound perspectives of a deeper study of HOT capabilities in CVD patients, including during large state research programs.

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Игнатенко Г.А. (ORCID ID: https://orcid.org/0000-0003-3611-1186): создание идеи и концепции рукописи, утверждение окончательного варианта

Багрий А.Э. (ORCID ID: https://orcid.org/0000-0003-2592-0906): написание актуальности, раздела, посвященного физиологическим эффектам гипокситерапии, критический обзор материала, окончательное редактирование рукописи

Игнатенко Т.С. (ORCID ID: https://orcid.org/0009–0001–2138–2277): сбор и анализ литературных данных, написание раздела о клинических эффектах гипокситерапии, редактирование рукописи

Толстой В.А. (ORCID ID: https://orcid.org/0009–0002–4586-3718): сбор и анализ литературных данных, написание раздела «Физические нагрузки в условиях контролируемой гипоксии»

Евтушенко И.С. (ORCID ID: https://orcid.org/0009-0008–5989–7891): сбор и анализ литературных данных, написание заключения, редактирование рукописи

Михайличенко Е.С. (ORCID ID: https://orcid.org/0000-0001-8625-1406): сбор, анализ и обобщение литературных данных, написание резюме, подготовка рукописи к публикации

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Ignatenko G.A. (ORCID ID: https://orcid.org/0000-0003–3611–1186): generating the idea and the concept of the manuscript, approval of the final version

Bagriy A.E. (ORCID ID: https://orcid.org/0000-0003-2592-0906): writing the relevance, the section devoted to the physiological effects of hypoxytherapy, critical review of the material, final editing of the manuscript.

Ignatenko T.S. (ORCID ID: https://orcid.org/0009-0001–2138–2277): collection and analysis of literature data, writing a section devoted to the clinical effects of hypoxytherapy, editing the manuscript.

Tolstoy V.A. (ORCID ID: https://orcid.org/0009–0002–4586–3718): collection and analysis of literature data, writing the section "Physical activity in conditions of controlled hypoxia".

Evtushenko I.S. (ORCID ID: https://orcid.org/0009–0008–5989–7891): collection and analysis of literary data, writing a conclusion, editing a manuscript.

Mykhailichenko E.S. (ORCID ID: https://orcid.org/0000-0001-8625-1406): collection, analysis and generalization of literary data, writing a summary, manuscript preparation

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Л.А. Камышникова*, К.С. Горбачевская, О.А. Ефремова, Н.И. Оболонкова, О.А. Болховитина

Белгородский государственный национальный исследовательский университет, Белгород, Россия

БИОМАРКЕРЫ РАЗВИТИЯ НЕЖЕЛАТЕЛЬНЫХ СЕРДЕЧНО-СОСУДИСТЫХ СОБЫТИЙ ПРИ ЗАБОЛЕВАНИЯХ ПОЧЕК

L.A. Kamyshnikova*, K.S. Gorbachevskaya, O.A. Efremova, N.I. Obolonkova, O.A. Bolkhovitina

Belgorod State National Research University, Belgorod, Russia

Biomarkers of Adverse Cardiovascular Events in Kidney Disease

Резюме

В обзоре представлена информация по анализу научно-исследовательских сведений в отечественных и международных источниках литературы о факторах риска и биомаркерах развития неблагоприятных сердечно-сосудистых событий у пациентов с хронической болезнью почек и острым повреждением почек. Исследования биомаркеров имеют важное значение, особенно на ранних стадиях хронической болезни почек, когда профилактические и лечебные мероприятия работают более эффективно. В обзоре рассматриваются такие предикторы сердечно-сосудистых событий при хронической болезни почек как биомаркеры: окислительного стресса (малоновый диальдегид, ишемически-модифицированный альбумин; супероксид дисмутаза), воспаления (интерлейкин-6, интерлейкин-18), острого повреждения почек (молекула повреждения почек 1; нейтрофильный желатиназа-ассоциированный липокалин), кардиоспецифические биомаркеры (высокочувствительный тропонин) и циркулирующие микрорибонуклеиновые кислоты: 133a и 21, а также обсуждаются перспективы дальнейшего изучения биомаркеров. Отдельный акцент сделан на необходимости установления пороговых значений для различных биомаркеров при хронической болезни почек в зависимости от степени снижения функции почек, что позволит эффективно использовать эти показатели в клинической практике сердечно-сосудистых заболеваний, поскольку обычные референсные значения, используемые в общей популяции, будут выше при заболеваниях почек. В настоящее время известны референсные значения для тропонина и натрийуретических пептидов, которые в популяции с хронической болезни почек не достаточно изучены, по сравнению с общей популяцией.

Ключевые слова: *хроническая болезнь почек, острое повреждение почек, предикторы, сердечно-сосудистая система, биомаркеры*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Based on domestic and international literature the review refers to the analysis of the research data on risk factors and biomarkers for the development of adverse cardiovascular events in patients with chronic kidney disease and acute kidney injury. Biomarker studies are important, especially in the early stages of chronic kidney disease, that is, in patients with creatinine clearance above 60 ml/min/1.73 m2, when preventive and therapeutic measures work more effectively. Among the potential predictors of adverse cardiovascular events, the biomarkers related to the following pathological processes

*Контакты: Людмила Александровна Камышникова, e-mail: kamyshnikova@bsu.edu.ru
*Contacts: Lyudmila A. Kamyshnikova, e-mail: kamyshnikova@bsu.edu.ru
ORCID ID: https://orcid.org/0000-0002-6129-0625

(conditions) should be noted: oxidative stress (malondialdehyde, ischemic-modified albumin; superoxide dismutase), inflammation (interleukin-6, interleukin-18), acute kidney injury (kidney injury molecule 1; neutrophil gelatinase-associated lipocalin), cardiospecific biomarkers (highly sensitive troponin) and circulating microribonucleic acids (specific miRNA-133a, miRNA-21), as well as the prospects for further study of some biomarkers in cardionephrology are discussed. A separate emphasis is placed on the need to establish threshold values for various molecules in chronic kidney disease, depending on the degree of decline in kidney function, which will allow these indicators to be effectively used in clinical practice as diagnostic and prognostic biomarkers for cardiovascular diseases, since their usual reference values are used in the general population, will be higher in kidney disease. Currently, only for troponin and natriuretic peptides, certain reference values are established, which are less clear-cut in the population with chronic kidney disease than in the general population, and for all other biomarkers, cut-off values are not yet known.

Key words: *chronic kidney disease, acute kidney injury, predictors, cardiovascular system, biomarkers*

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AVP — arginine-vasopressin, hsTnT — highly sensitive troponin T, LVH — left ventricular hypertrophy, CAD — coronary artery disease, IL — interleukin, KIM-1 — kidney injury molecule 1, MMP — matrix metalloproteinase, microRNA — microribonucleic acid, MPO — myeloperoxidase, NUP — natriuretic peptides, AMI — acute myocardial infarction, AKI — acute kidney injury, GFR — glomerular filtration rate, HF — heart failure, SOD — superoxide dismutase, CRP — C-reactive protein, CVD — cardiovascular diseases, CVE — cardiovascular events, CKD — chronic kidney disease, Gal 3 — galectin 3, NGAL — neutrophil gelatinase-associated lipocalin

Introduction

Chronic kidney disease (CKD) is an independent risk factor of cardiovascular diseases (CVD) affecting the overall and cardiovascular mortality [1, 2]. CVD are one of the main causes of morbidity and mortality in patients with CKD [3]. In patients on chronic dialysis the level of cardiovascular mortality is 10-20-fold higher than in the general population [4, 5].

Timely CVD diagnosis and treatment will improve CKD outcomes and the patient's quality of life, leading to decreased number of hospitalizations and consumption of medical resources. Overall, this will result in general direct and indirect treatment cost reduction [6]. Lately more and more cardionephrology investigators actively study various biomarkers of cardiovascular lesions both as CVD risk factors in patients with CKD and as a target for early detection and prevention of life-threatening conditions [4, 7, 8].

Cardiovascular risk factors

The causes of significant increase in the number of cardiovascular events (CVE) in CKD progression are still analyzed; however, it is considered that they are related to the complex mode of action of traditional and non-traditional CVD risk factors.

Traditional risk factors are well-known and widely presented both in the general population and the CKD population. They have been studied and identified in a well-known Framingham study, including the age, male sex, hypertension, diabetes mellitus, hyperlipidemia, family history, and smoking [7]. In later studies the following CVD factors and mechanisms typical for CKD have been added: inflammation, oxidative stress, impaired metabolism in uremic cells, malnutrition, hyperhomocystinemia, hyperuricemia, increased leptin levels, carnitine deficiency, vascular calcification, hypertriglyceridemia, anemia, endothelial dysfunction, quick changes of the circulatory volume and electrolytes on dialysis, impaired blood coagulation, immunosuppressive treatment after renal transplant, sympathetic hyperactivity, cardiac microvascular diseases, high levels of final glycolysis products, impaired nitrogen oxide balance, left ventricular hypertrophy (LVH) [4, 7–9].

Tawfik A.M. et al. (2022) describe not only traditional risk factors associated with CKD progression, but also divide them into several categories: inflammation, oxidative stress, anemia, uremia, endothelial dysfunction, impaired calcium-phosphorus metabolism and secondary hyperparathyroidism, etc. [7]; specific molecules participating in the pathogenesis of CVD in CKD may be analyzed as biomarkers in each of those categories.

Biomarkers of cardiovascular diseases in chronic kidney disease

It is well-known that approximately 10 % of adults in the general population suffer from some form of CKD, and up to 50 % of them die from CVD not reaching final CKD stage, the necessity of detecting CVD biomarkers in CKD is quite understandable [3, 4] (Table 1). The complexity of biomarker tests lies in their reference values,

Table 1. *Some biomarkers of cardiovascular disease in kidney disease*

Группа маркеров/ Markers group	Биомаркеры/ Biomarkers
Oxidative stress biomarkers	Superoxide dismutase Myeloperoxidase Ischemic modified albumin Malondialdehyde Asymmetric dimethylarginine Glycolysis end products
Biomarkers of acute kidney injury	KIM-1 (Kidney injury molecule-1) NGAL (Neutrophil gelatinase–associated lipocalin)
Cardiospecific biomarkers	High-sensitive troponin
Neurohormones	Natriuretic peptides Endothelin Arginine-Vasopressin
Inflammation biomarkers	C-reactive protein Interleukin-1 (IL-1) Interleukin-6 (IL-6) Interleukin-18 (IL-18)
Biomarkers of mineral metabolism disorders	Osteoprotegerin Fetuin-A Fibroblast growth factor-23 Vitamin D Parathyroid hormone
Biomarkers associated with the matrix	Galectin 3
Microribonucleic acids (microRNA)	MicroRNA-133a MicroRNA-21
Biomarkers of endothelial dysfunction	Matrix metalloproteinase (MMP-2, MMP-9)
Biomarkers of hypoxia	Hypoxia-inducible factor 1 (HIF-1α) Endogenous erythropoietin (EPO)

accounting for the fact that the concentration depends on the excretory and metabolic renal function. Higher target levels are used currently — these have a diagnostic and prognostic value for the CKD population [7, 8].

Below are the data on CVD biomarkers in CKD divided into groups based on the pathogenesis.

Oxidative stress biomarkers

Due to the fact that oxidative stress plays one of the dominating roles in the pathogenesis of atherosclerosis, it is important to analyze biomarkers which could become CVE predictors in patients with CKD. The following biomarkers are the ones studied most extensively: myeloperoxidase, malondialdehyde, asymmetric dimethylarginine, as well as other molecules of lipid or protein peroxidation [10].

Myeloperoxidase (MPO) is the main source of oxidative stress. Uncontrollable MPO hyperexpression is related to negative cardiovascular outcomes and increased cardiovascular mortality risks [10, 11].

Protection from increased oxidative stress has several barrier lines, the first of which being superoxide dismutase (SOD). SOD is the most effective intracellular enzyme available for analysis as a biomarker [12]. Some data have been discovered about the potential role of SOD in the development of vascular calcification, which is deleterious to the cardiovascular system and promotes CKD progression [13]. However, separate studies aimed at analyzing SOD levels as a biomarker were not arranged in patients with CVD and CKD. The ischemia-modified albumin (IMA) is also one of the newer CVE biomarkers associated with ischemic conditions and enhanced oxidative stress. The biomarker is very well-studied in CVD [14]; its levels have been analyzed in single studies in CKD [15]. CKD enhances the oxidative stress; besides, hemodialysis additionally promotes its increase. Authors demonstrate IMA levels increasing as the glomerular filtration rate (GFR) drops and conclude that this biomarker is suitable to determine oxidative stress in CKD [15].

Acute kidney injury biomarkers

Studies of acute kidney injury (AKI) biomarkers in CVD are currently studied extensively. The neutrophil gelatinase-associated lipocalin (NGAL) and the kidney injury molecule 1 (KIM-1) are one of the most analyzed AKI biomarkers which can potentially participate in the pathogenesis of CKD and prediction of cardiovascular events (CVE).

It is known that NGAL values are increased in atherosclerotic plaques, while its expression increases in ischemic, hypoxic conditions, and in myocardial infarction. The NGAL level is regulated by the vascular inflammation response to ischemia [16]. The association between NGAL and coronary artery diseases has been studied lately. The article of Freitas I.A. et al. (2020) analyzes 8 new prediction biomarkers in patients with atherosclerotic coronary artery disease. The main results confirmed that increased NGAL levels were associated with the better prognosis after cardiac arrest and concomitant kidney damage [17]. Some data demonstrate that NGAL may be a new biomarker that can help to stratify the risk in patients with coronary artery disease [18]. It should be noted that this biomarker monitoring may be significantly important for early disease diagnosis and course not only in CKD patients, but also in those with the cardiorenal syndrome, heart failure, cardiopulmonary bypass, and cardiothoracic surgeries [19].

In CKD patients, increased plasma NGAL levels may also be an independent predictor of future CVE [20]. It should be noted that elevated urine NGAL levels increase the rate of ischemic atherosclerotic events in patients with CKD and does not depend on GFR, albuminuria, and concomitant diseases [21].

KIM-1 is released with ischemic and toxic effects of causative agents on proximal kidney tubules. The studies show that elevated KIM-1 urine levels may be associated with increased risks of the coronary artery disease (CAD), heart failure (HF), and all-cause mortality in CKD patients. New data are expected regarding the use of this molecule as a potential biomarker of cardiovascular events [22]. Feldreich T. et al. (2019) analyzed the group of patients with terminal renal failure and detected that plasma KIM-1 was a biomarker of coronary calcification, increasing the CVD mortality risk [23].

Cardiospecific biomarkers

The highly sensitive troponin T (hsTnT) has turned out to be the best biomarker for cardiovascular outcome prediction and acute CVE biomarker in the group of patients with CKD [24]. The authors of the meta-analysis (2022) concluded that increased troponin levels were associated with severe diffuse CAD in dialysis and pre-dialysis patients [25]. In their study Ledwoch J. et al. (2022) detected weak negative correlation between the estimated glomerular filtration rate (eGFR) and hsTnT (Pearson r = -0.16; p<0.001), with eGFR being the only variable to be independently associated with hsTnT [24]. Authors defined the threshold hsTnT value of 40 ng/L for acute HF in patients with eGFR ≥45 mL/min/1.73 m^2 (sensitivity 73 %, specificity 71 %) and 55 ng/L with eGFR <45 mL/min/1.73 m^2 (sensitivity 63 %, specificity 62 %). The prognostic hsTnT accuracy in patients hospitalized with acute HF was lower in patients with the decreased renal function regarding the 30-day mortality [24]. Thus, threshold hsTnT values used to predict acute HF in patients with decreased eGFR require further studies in real clinical practice.

Some data demonstrate various threshold troponin levels in acute myocardial infarction (AMI) among patients with CKD versus the general population. According to Russian clinical cardiology guidelines [26], a 10-fold troponin increase with its increasing trend are used for AIM diagnosis in Russian medical institutions. The recent meta-analysis of Kampmann et al. (2022) discusses threshold troponin levels in patients with AIM and impaired renal function, proposing the following values for AIM diagnosis in CKD — 42 ng/L for troponin I, 48 ng/L for troponin T. For patients on dialysis, the troponin T threshold is significantly higher (over 239 ng/L). Specific troponin I levels for dialysis patients have not been established yet due to missing study results [27].

Neurohormones

B-type brain natriuretic peptide (BNP) and its N-terminal fragment (NT-proBNP) are well-known indicators of decompensated HF, which may also be used in CVD diagnosis and prediction in patients with CKD. However, their common standard reference values used in the general population increase in CKD [16]. This is related to decreased clearance of natriuretic peptides in CKD, which should be accounted for in patients with creatinine clearance below 60 mL/min/1.73 m^2. Studies among dialysis patients have confirmed the prognostic NT-proBNP value regarding the lower survival and increased cardiovascular mortality risks [28].

Arginine-vasopressin (AVP) is an antidiuretic and vasoconstrictive peptide hormone released in response to hyperosmolality and hypovolemia. Key AVP functions include water reabsorption in kidney tubules, increased peripheral vascular resistance, and subsequent blood pressure increase [29]. Due to poor stability and short AVP half-elimination for diagnostic purposes, copeptin (C-terminal provasopressin fragment, CT-proAVP) has been introduced into clinical practice as a robust AVP equivalent [30]. The literature contains evidence of AVP increase in patients with HF [29]. Among patients with HF with preserved ejection fraction (HFpEF), AVP was independently associated with left ventricular hypertrophy (LVH) and higher mortality risk or recurrent HF-related hospitalizations. Copeptin has also been confirmed to be a significant predictor of poor prognosis in the HF population [30].

Circulating plasma levels of endothelin-1 and related peptides formed during endothelin-1 synthesis have

been studied widely as potential CVE risk biomarkers. Jankowich M. (2020) describes the association of endothelin-1 with aging and CKD, as well as the association between endothelin-1 levels and cardiac remodeling signs, including increased left atrial diameter and increased left ventricular mass [31]. Some data confirm increased endothelin-1 levels as eGFR decreases in CKD stages 1–4 [32].

Inflammatory biomarkers

Accounting for the importance of inflammation as a factor affecting the development of atherosclerosis, individual inflammatory biomarkers for CVE prediction have been studied in CKD patients in a large number of studies.

C-reactive protein (CRP) is the most well-known and widely used biomarker of acute-phase systemic inflammation in the general population and CKD patients. Tawfik A.M. et al. (2022) [7] discovered inverse correlation between creatinine clearance and highly sensitive CRP (p = 0.0174). Increased highly sensitive CRP levels were detected not only in patients on hemodialysis, but also in elderly patients with CKD [7].

Interleukin 6 (IL-6) is a protein/inflammation biomarker produced in the liver; it is a potential predictor of all-cause or CVD mortality in the population of CKD patients with various renal injury stages [33]. The STABILITY study included 14,611 patients with known baseline IL-6 levels. During the follow-up, CVE developed in 1,459 people (10.0 %). Higher IL-6 levels were independently associated with the CVE risk (p<0.001) in CKD. Elevated IL-6 levels (≥2.0 vs. <2.0 ng/L) was associated with increased CVE risk both with preserved renal function and in CKD of various stages: 2.9 % events/year with preserved renal function (GFR ≥90 mL/min/1.73 m^2) [risk ratio (RR), 1.35; 95 % confidence interval (CI), 1.02–1.78], 3.3 % with mild CKD (GFR 60–90 mL/min/1.73 m^2) [RR, 1.57; 95 % CI, 1.35–1.83], 5.0 % with moderate or severe CKD (GFR <60 mL/min/1.73 m^2) [RR, 1.60; 95 % CI, 1.28–1.99]). In patients with chronic coronary syndrome, higher IL-6 levels were associated with the CVE risk in all CKD groups. The authors concluded that IL-6 and CKD stage could be the predictors for the administration of anti-inflammatory treatment in patients with the chronic coronary syndrome [33]. Russian investigators also detected inverse correlation between IL-6 and eGFR (r = -0.42, p = 0.0001) in patients with CHF and CKD [34].

Experimental data confirm the role of IL-1 in the development of kidney diseases and essential hypertension. IL-1 studies as a cardiovascular risk biomarker have demonstrated promising results in patients on hemodialysis and those after renal transplant. The study of Schunk et al. (2021) demonstrated that IL-1α was a central regulator of leukocyte-endothelial adhesion in myocardial infarction and CKD; thus, IL-1α inhibition may serve a new strategy of anti-inflammatory treatment in this population [35].

Interleukin 18 (IL-18) is an increasingly mentioned and tested inflammation biomarker for CVE prediction in CKD patients. IL-18 initiates the cascade of other pro-inflammatory cytokines which activate the lymphocytic response of T-helpers (1 or 2). This lymphocytic activation triggers the immune response and accelerates the atherosclerotic process. Elevated serum IL-18 levels are an important indicator of cardiovascular mortality in CKD patients [36].

Biomarkers of mineral metabolism disorders

Serum phosphorus, calcium, and magnesium imbalance, elevated levels of vascular calcification inducers (alkaline phosphatase, osteocalcin, osteonectin, bone morphogenic protein, fibroblast growth factor 23), decreased levels of vascular calficication inhibitors (fetuin A, osteopontin, Gla and α-Klotho matrix protein) are among common mineral metabolism disorders in CKD patients [37]. Thus, KDIGO (Kidney Disease Improving Global Outcome) guidelines recommend those biomarkers in the CKD patient population [38]. Target parathyroid hormone (PTH) levels change as CKD progresses, reaching 9-fold values compared to reference values in the general population [38].

Serum phosphorus, calcium, and magnesium imbalance are associated with increased HF risk, development of vascular calcification and subsequent complications, while hyperphosphatemia is widely prevalent at the terminal CKD stage [39]. Elevated serum phosphate and calcium levels promote the increased cardiovascular morbidity and mortality due to vascular calcification and endothelial dysfunction [40]. As vascular calficiation promotes significantly increased cardiovascular morbidity and mortality in CKD, it is important to study the calcification, related biomarkers, and approaches to its correction [38].

Fibroblast growth factor 23 (FGF-23) is a biomarker stimulating the vascular calcification. Elevated biomarker levels are associated with the progression of CKD, atherosclerotic CVD, and increased cardiovascular mortality [41, 42].

The group of endogenous vascular calcification inhibitors includes specific molecules which have also been tested as biomarkers of resistance to cardiovascular diseases in CKD [43]. Fetuin A, osteopontin, osteoprotegerin, Gla and α-Klotho matrix protein are only several inhibitors analyzed among CKD patients [8]. The association between serum osteoprotegerin and cardiovascular risk factors has been confirmed in CKD [44].

Biomarkers of the extracellular matrix condition

Galectin 3 (Gal-3) is a protein from the family of galectins (b-galactoside-binding lectins) which has important functions in many biological processes, including cardiac and renal fibrosis, HF development [45]. Initially Gal-3 was studied as a cardiac injury biomarker, though its role as a kidney injury biomarker was evaluated in several latest studies [46, 47]. Plasma Gal-3 levels after cardiac surgeries were analyzed for AKI prediction among 1,498 patients — the highest Gal-3 tertile was associated with severe AKI (odds ratio (OR) 2.95; p<0.001) [48].

In the long-term study of 1,320 patients with type 2 diabetes mellitus and eGFR ≥30 mL/min/1.73 m^2, Tan et al. (2018) demonstrated that Gal-3 was independently associated with 2-fold serum creatinine levels (RR 1.19, CI 95 % [1.14; 1.24], p<0.001) even after adjusting for baseline eGFR and albuminuria status [49]. Some data show that plasma Gal-3 levels on admission of patients with various CVD to the intensive care unit was robustly associated with AKI regardless of other known AKI predictors (OR 1.12, CI 95 % [1.04, 1.2]). Elevated plasma Gal-3 levels correlated with AKI severity: 16.6 (12.7–34.2) ng/mL without AKI, from 23.6 (18.2–34.2) ng/mL for AKI Stage 1 to 38 (24.5–57.1) ng/mL for Stage 3 [50]. These studies presume potential plasma and urine Gal-3 use as a biomarker of AKI severity in the heterogenous population, regardless of renal dysfunction origin. Besides, it has been reported that Gal-3 plays a key role in the renal interstitial fibrosis and CKD progression [51]. Gal-3 is a robust biomarker of unfavorable cardiovacular prognosis in AKI patients [52]. These results underline the role of Gal-3 in the cardiorenal syndrome. Some non-clinical studies have started to identify Gal-3 as a significant prognostic factor in Type 3 cardiorenal syndrome (acute renocardial syndrome) [53].

Endothelial dysfunction biomarkers

An interaction between matrix metalloproteinase 2 (MMP-2) and subclinical atherosclerosis was summarized in CKD patients in a meta-analysis (2016) including 16 studies [54]. MMP-2 and tissue metalloproteinase 1 inhibitor were most commonly analyzed in those studies, as well as their interaction with the subclinical atherosclerosis parameter (carotid intima media thickess (IMT)). Only MMP-2 demonstrated stable positive association with IMT. Authors concluded that MMP-2 imbalance was involved in the pathogenesis of atherosclerosis, its clinical signs, and cardiovascular prognosis in CKD patients [54]. Some data indicate that increased MMP-2 and MMP-9 activity in kidney tubules may lead to structural changes in the basal tubular membrane, which triggers the epithelial-mesenchymal transition, which leads to decreased cellular adhesion, while epithelial cells gain the mesenchymal phenotype, expressing and producing α-smooth cell actin and extracellular matrix protein [55]. All these mechanisms subsequently trigger tubular atrophy and renal fibrosis. MMP-2 and MMP-9 can release the latent transforming growth factor beta, which mediates crossover interactions between endothelial cells and vascular smooth muscle cells [55]. MMP imbalance and changes in endothelial cells are factors for the abnormal expansion of extracellular matrix, vascular calcification, atherogenesis; they also promote high pulse pressure, which leads to CVD and CKD progression [55]. The literature data report limited use of endothelial dysfunction biomarkers, including MMP-7 and MMP-9, in clinical conditions [1]. Zhang J. (2022) defines the following limitations: endothelial CVD biomarkers in humans are usually non-specific and have limited sensitivity; small sample sizes in clinical trials may be a serious obstacle for the development of robust biomarkers [1]. Thus, multicenter large-scale clinical trials are important for MMP evaluation. One should account for the fact that biomarkers of endothelial origin are usually related to other biomarkers, and without corresponding interactions the isolated use of endothelial biomarkers limits their application.

Microribonucleic acids

Microribonucleic acids (microRNA) are endogenous small non-coding RNA consisting of 21–24 nucleotides which control the post-transcription gene expression, inducing microRNA target destabilization or inhibiting protein translation [16].

Being the main pathogenetic CVD process, atherosclerosis is regulated with several microRNA molecules. Several molecules have been identified that participate in endothelial dysfunction (microRNA-31, 126) [56], development of atherosclerotic plaques (21, 155, 221), cholesterol homeostasis (122, 33a/b), neoangiogenesis (155, 210, 221, 222), and even plaque instability and rupture (100, 127, 145) [57].

A large number of microRNA was tested as potential diagnostic and prognostic biomarkers of various cardiovascular diseases. Changes in expression have been reported in patients with LVH, CAD, chronic heart failure, peripheral artery disease, and stroke [58, 59].

A small number of studies analyzed the microRNA-133a association with the development of CVE in the CKD patient population, as well as its association with CVD risk factors and other complications in CKD [58, 60]. Plasma microRNA-133a levels were analyzed using the PCR method in 30 patients with terminal renal failure

on hemodialysis [60]. Significant decrease in microRNA-133a levels was confirmed in the group of patients on hemodialysis with LVH versus patients without LVH and the control group. Elmadbouly A.A. et al. (2017) concluded that plasma microRNA-133a levels may be used as a new biomarker for LVH and left ventricular dysfunction prediction in CKD on hemodialysis [60].

Wang Y. et al. (2020) studied cicrulating microRNA-21 levels as a diagnostic biomarker in older patients with Type 2 cardiorenal syndrome (i.e. chronic renal dysfunction developed due to chronic cardiac pathology) [16]. Authors demonstrate that in the population of older patients circulating microRNA-21 has a small diagnostic value in Type 2 cardiorenal syndrome (sensitivity 55.9 %, specificity 84.9 %), unlike the combination of microRNA-21 and Cystatin C (sensitivity 88.1 %, specificity 83.6 %) [16].

Hypoxia biomarkers

It is well-known that anemia prevalence increases with CKD and chronic HF progression. Pharmacological mechanisms of anemia, such as decreased endogenous erythropoietin (EPO) and oxygen transport, lead to tissue hypoxia [61]. Thus, hypoxia biomarkers (hypoxia-induced factor 1α (HIF-1α) and EPO) are considered potentially useful in patients with chronic HF and CKD. Efremova E.V. et al. (2022) [34] analyzed various biomarkers in patients with chronic HF and CKD and reported EPO superiority over other markers. Based on the author's opinion, this defines the leading role of hypoxia and not only myocardial stress or inflammation in the prognosis of these patients. Low EPO levels define the favorable prognosis within a 1-year long follow-up of elderly patients in chronic cardiorenal syndrome [34]. The same study did not detect the association between HIF-1α and eGFR ($r = -0.05$, $p = 0.64$), and EPR ($r = 0.16$, $p = 0.15$) [34]. Thus, accounting for the high prognostic potential of these biomarkers and ambiguity of the results obtained, their studies should be continued.

Further potential studies of CVD biomarkers in renal diseases (CKD, AKI)

MicroRNA use for CVD prediction is promising, though currently it has not been sufficiently tested for routine use among CKD patients, which requires its further analysis, especially determining threshold values in specific clinical conditions.

Gal-3 studies as a diagnostic biomarker in CVD patients with CKD and as a prognostic biomarker in this patient cohort are also quite promising.

Despite the fact that MMP demonstrates high potential as subclinical atherosclerosis and CAD biomarkers, they are not sufficiently studied in CKD. Larger studies are required for several MMP with more uniform approaches for CVD detection in CKD.

Determining reference values for various biomarkers in CKD is an important clinical task. Reference values are determined only for troponin and natriuretic peptides that are less analyzed in the CKD population than for CVD in the general population. Threshold values are not sufficiently analyzed for all other biomarkers. Besides, it is well-known that the biomarker level may change as the GFR decreases, which requires the analysis of change range depending on the CKD stage for the possibility of use in the clinical practice as a diagnostic or prognostic biomarker.

EPO and HIF-1α demonstrate a high prognostic potential in the cardiorenal syndrome, however they have not been sufficiently studied in large-scale studies, and their threshold values for various CKD stages have not been determined.

Conclusion

Despite multiple achievements in cardionephrology, CKD patient mortality from CVD remains high, which requires constant searches of newer and robust biomarkers and predictors of cardiovascular morbidity and mortality in CKD patients. Currently the majority of analyzed cardiovascular outcome predictors in CKD patients can evaluate the prognosis in significant clinical signs [7, 38]. Besides, one should not just detect biomarkers, but also determine their threshold values in patients with various CKD stages.

Biomarker studies have an important value specifically in early CKD stages (in patients with creatinine clearance ≥60 mL/min/1.73 m^2), when the prophylactic and therapeutic measures are the most efficient. Many molecules participating in oxidative stress, inflammation, AKI, and other pathological studies are currently actively studied as CVD biomarkers in CKD patients, including in early stages.

Thus, new studies are required for the biomarkers that can timely and efficiently prevent cardiovascular diseases in CKD patients, improving their survival.

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Камышникова Л.А. (ORCID ID: https://orcid.org/0000-0002-6129-0625): формирование идеи и концепции рукописи, анализ и систематизация данных литературы, поиск литературных источников, написание статьи, окончательное утверждение рукописи для публикации, ответственность за все аспекты рукописи

Горбачевская К.С. (ORCID ID: https://orcid.org/0000-0003-2650-1738): поиск литературных источников
Ефремова О.А. (ORCID ID: https://orcid.org/0000-0002-6395-1626): редактирование рукописи, утверждение окончательного варианта статьи
Оболонкова Н.И. (ORCID ID: https://orcid.org/0000-0002-5308-8072): научное консультирование и поиск литературных источников
Болховитина О.А. (ORCID ID: https://orcid.org/0000-0001-7961-4352): научное консультирование и поиск литературных источников

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication
Kamyshnikova L.A. (ORCID ID: https://orcid.org/0000-0002-6129-0625): formation of the idea and concept of the manuscript, analysis and systematization of literature data, search for literary sources, writing an article, final approval of the manuscript for publication, responsibility for all aspects of the manuscript
Gorbachevskaya K.S. (ORCID ID: https://orcid.org/0000-0003-2650-1738): search for literary sources
Efremova O.A. (ORCID ID: https://orcid.org/0000-0002-6395-1626): editing the manuscript, approval of the final version of the article
Obolonkova N.I. (ORCID ID: https://orcid.org/0000-0003-1595-3501): scientific advice and search for literary sources
Bolkhovitina O.A. (ORCID ID: https://orcid.org/0000-0001-7961-4352): scientific advice and search for literary sources

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В.Н. Ларина*[1], Е.А. Стоделова[1], Ж.М. Салмаси[2], А.Н. Казимирский[2], Г.В. Порядин[2]

[1] — ФГАОУ ВО РНИМУ им. Н.И. Пирогова Минздрава России, кафедра поликлинической терапии лечебного факультета, Москва, Россия
[2] — ФГАОУ ВО РНИМУ им. Н.И. Пирогова Минздрава России, кафедра патофизиологии и клинической патофизиологии лечебного факультета, Москва, Россия

РОЛЬ ЭКСТРАКЛЕТОЧНЫХ НЕЙТРОФИЛЬНЫХ ЛОВУШЕК В РАЗВИТИИ ПОСТКОВИДНОГО СИНДРОМА И ЕГО ОСЛОЖНЕНИЙ

V.N. Larina*[1], E.A. Stodelova[1], Zh.M. Salmasi[2], A.N. Kazimirskij[2], G.V. Porjadin[2]

[1] — Pirogov Russian National Research Medical University, Department of Outpatient Therapy, Faculty of General Medicine Moscow, Russia
[2] — Pirogov Russian National Research Medical University, Department of Pathophysiology and Clinical Pathophysiology, Faculty of General Medicine Moscow, Russia

The Role of the Innate Immune System in the Development of Postcovid Syndrome and its Complications

Резюме

На сегодняшний день в мире актуальна проблема сохранения симптомов после выздоровления от новой коронавирусной инфекции. Клиническая картинка постковидного периода имеет множественные проявления: общие, респираторные, сердечно-сосудистые, желудочно-кишечные, кожные и другие симптомы. На данный момент не определены четкие лабораторные критерии, позволяющие установить диагноз данного состояния, но показана роль нейтрофилов в развитии как острого заболевания, так и постковидного синдрома. Образование нейтрофильных экстраклеточных ловушек (нетоз) является одним из патофизиологических механизмов течения новой коронавирусной инфекции. Кроме того, доказано влияние процесса нетоза на развитие осложнений в постковидном периоде. В статье обсуждается история термина, разнообразные клинические проявления постковидного периода, а также — роль механизмов врожденного иммунитета на всех этапах течения новой коронавирусной инфекции.

Ключевые слова: *коронавирусная инфекция, COVID-19, постковидный синдром, экстраклеточные нейтрофильные ловушки, нетоз, НЭЛ*

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Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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*Контакты: Вера Николаевна Ларина, e-mail: larinav@mail.ru
*Contacts: Vera N. Larina, e-mail: larinav@mail.ru
ORCID ID: https://orcid.org/0000-0001-7825-5597

Abstract

To date, the problem of preserving symptoms after recovery from a new coronavirus infection is urgent in the world. This condition is called postcovid syndrome. The clinical picture of postcovid syndrome has multiple manifestations: general, respiratory, cardiovascular, gastrointestinal, skin and other symptoms. At the moment, there are no laboratory criteria for the diagnosis of this condition, but the great role of neutrophils in the development of both acute disease and postcovid syndrome has been proven. The formation of neutrophil extracellular traps (not toz) is one of the pathophysiological mechanisms of the course of a new coronavirus infection. In addition, the effect of the ketosis process on the development of complications in the postcovid period has been proven. The article discusses the history of the term, various clinical manifestations of the postcovid period, as well as the role of innate immunity mechanisms at all stages of the course of a new coronavirus infection.

Key words: *coronavirus infection, COVID-19, postcovid syndrome, extracellular neutrophil traps, netosis, NETs*

Conflict of interests

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Relevance

The epidemics of the novel coronavirus infection (COVID-19) started in the People's Republic of China in March 2019 and, according to the Johns Hopkins University, as of today, 217 countries have experience with this disease. The novel coronavirus infection is an acute respiratory viral disease caused by SARS-CoV-2 virus which affects primarily upper respiratory tract. The clinical forms of the disease are acute respiratory viral infection, atypical pneumonia without respiratory insufficiency, acute respiratory distress syndrome (pneumonia with acute respiratory failure), sepsis, septic shock, DIC, thrombosis, thrombembolia.

According to the official website Стопкоронавирус.рф for January 2023, approximately 21 million people are COVID survivors. Some patients still have symptoms of COVID-19 after clinical recovery. This condition is called post-COVID-19 syndrome; in foreign sources, it is called long COVID. The International Classification of Diseases, 10th Edition, now has several codes characterising the course of the post-COVID period in humans: U08.9, U09.9, U12.9.

The objective of this article is to present information on the post-COVID syndrome and its symptoms to healthcare practitioners. The article discusses the role of the inborn immunity and neutrophil extracellular traps in development of post-COVID syndrome and its complications. The review is based on full-text scientific publications from open sources (eLibrary, PubMed, Web of Science). The search depth was 4 years, starting from 2019. Analysis of available information makes it possible to conclude that post-COVID observation is essential for prevention of various complications.

Definition and Clinical Characteristics of Post-COVID Syndrome

The term "long COVID" was introduced by social network users to describe their own general state after the novel coronavirus infection. These data drew mass media's attention and after that the studies of such symptoms in patients were conducted [1].

One of the first studies was conducted in Italy with participation of patients who were followed up in outpatient settings after recovery from COVID-19. The study enrolled 143 patients with the mean age of 56.5 years old. The patients' condition was assessed on the average in 60.3 days after recovery. It was demonstrated that only 12.6 % of patients did not have any COVID-19-associated symptoms, while 32 % of patients had 1 or 2 symptoms, 55 % of patients suffered from 3 and more symptoms [2].

Following a literature review by Shin Jie Yong, various descriptions of post-COVID syndrome were identified (Table 1) [3].

According to the World Health Organisation, post-COVID syndrome is a condition in persons with potential or confirmed novel coronavirus infection, usually in 3 months after COVID-19 initiation, accompanied by symptoms which last at least for 2 months and cannot be attributed to an alternative diagnosis. Symptoms can be experienced for the first time, after recovery from COVID-19, or can persist after the previous disease. Also, symptoms can change or repeat over time [4].

According to the US Centers for Disease Control and Prevention, post-COVID condition is a wide range of emerging, persisting or current health problems which can be experienced in four and more weeks after

Table 1. *Definition and characteristics of postcovid syndrome*

Definition	Characteristic
Postcovid syndrome	Long-term COVID-19 disease, which is cyclical, progressive and multiphase Persistence of symptoms for more than 2 months The persistence of symptoms for more than 3 months from the moment of the first symptoms
Lingering covid	Multi-organ symptoms that persist for several months after acute COVID-19 The persistence of symptoms, for more than 100 days The persistence of symptoms for more than 4 weeks after the initial infection or diagnosis
Chronic postcovid syndrome	Multi-organ symptoms that persist for several months after acute COVID-19
Covid with residual phenomena	The persistence of symptoms, for more than 100 days
Late effects of SARS-CoV-2 infection	The persistence of symptoms for more than 4 weeks after the initial infection or diagnosis
COVID-19 Postactive syndrome	The persistence of symptoms for more than 4 weeks after the appearance of the first symptom
Acute postcovid symptoms	Persistence of symptoms for 5-12 weeks
Long-term postcovid symptoms	Persistence of symptoms for 12-24 weeks
Persistent postcovid symptoms	Persistence of symptoms for more than 24 weeks
Subacute COVID-19 Ongoing symptomatic COVID-19	Persistence of symptoms for 1-3 months from the moment of the first symptoms
Chronic COVID-19 syndrome	The persistence of symptoms for more than 3 months from the moment of the first symptoms
Long-term COVID syndrome	Persistence of symptoms for more than 3 months from the moment of the first symptoms

infection with COVID-19. It has been noted that even persons who previously had no COVID-19 symptoms during several days or weeks after infection, can have post-COVID conditions. Also, researchers classify post-COVID conditions into new symptoms or long-term symptoms, multisystemic consequences, including multisystem inflammatory syndrome and sequellae of hospitalisation, including post-ICU syndrome [5].

Specialists of the Moscow City Therapeutic Scientific Society identify the following processes during COVID-19 infection: asymptomatic process; acute process with various symptoms; long-lasting process associated with symptoms of acute infection and post-COVID syndrome, where new disease symptoms appear or regressed symptoms re-appear several months after recovery [6].

Clinical manifestations of post-COVID syndrome vary: respiratory symptoms (dyspnoea and cough), cardiovascular symptoms (chest tightness, headache, palpitations), general symptoms (fatigue, fever), neurological symptoms (cognitive disorders, headache, sleep disorders, dizziness), gastrointestinal symptoms (nausea, diarrhoea, abdominal pain, loss of appetite), skeletal muscle symptoms (joint and muscle pain), psychiatric symptoms (depression, anxiety), ENT disorders (ear pain, sore throat, anosmia), and skin rash [6-7].

According to Huang C et al. [8], 76 % of patients who participated in a large cohort study had at least one complaint during follow-up after dismissal from hospital (mean follow-up time after onset of symptoms was 186 days), and female patients had the highest number of complaints. The most common post-COVID symptoms were fatigue and muscle weakness (63 %), sleep disorders (26 %), anxiety or depression (23 %). It was found out that these symptoms had persisted for over 6 months after recovery.

The study by Niedziela JT et al. [9] enrolled 200 patients who had COVID-19 and did not have any severe comorbidities. Patients were divided into two groups depending on treatment regimen: at home (114 patients) and inpatient settings (86 patients). The rate of symptoms on the average in 105–107 days after the acute phase of the disease was similar in both groups and made 30.7 % in non-hospitalised patients and 38.4 % in hospitalised patients. The most common symptoms were anosmia, loss of taste, palpitations, fatigue and cough. The study groups did not have any differences in post-COVID symptoms.

The diagnosis of post-COVID syndrome is made only on the basis of an assessment of persistent or new symptoms after the infection, overall poor condition. There are no laboratory diagnostic criteria for this diagnosis. Also, the information on post-COVID syndrome duration and factors impacting its development are insufficient.

Role of Neutrophils in the Pathogenesis of Post-COVID Syndrome

One of the mechanisms of COVID-19 development is attraction and activation of neutrophils in the site of infection. Neutrophils are a type of leukocytes, blood granulocytes, that take an active part in inflammatory reactions. Varying composition of chemical granules of neutrophils allows them selecting numerous antibacterial strategies in sites of infection:

- Phagocytosis
- Degranulation
- Ability to form neutrophil extracellular traps (NETosis) [10].

Development of the novel coronavirus infection is associated with an increase in neutrophil/lymphocyte ratio, impacting the severity of the disease and clinical prognosis. Therefore, neutrophils and their effector mechanisms are becoming important mediators in COVID-19 immunopathogenesis [11].

At the beginning of the 21st century, V. Brinkmann et al. described a new strategy of the antibacterial effect of neutrophils — formation of net-like structures in extracellular space (neutrophil extracellular traps, NETs).

NETs are extracellular structures, similar to chromatin fibre networks, lined with highly active proteases and nuclear, cytoplasmic and granular proteins. Release of extracellular neutrophil traps during controlled neutrophil cell death (NETosis) can be caused by various inducers: microorganisms, bacterial components, activated platelets, complementary peptides, autoantibodies, interleukins (IL) IL-8, etc. [12].

There are several morphological forms of neutrophil extracellular traps; two of them are of most interest: network-like which is highly efficient in trapping pathogens and characterises an inflammation with favourable outcome; and thread-like which is observed in aseptic inflammation and can be a secondary alteration factor after enzymatic hydrolysis. In post-COVID period, a NET looks like an non-organised cluster of thin threads [13].

Extracellular traps were found in patients both in the acute period of the novel coronavirus infection and after recovery (refer to Table 2).

Table 2. *Results of studies related to the determination of the number of extracellular neutrophil traps or their products in patients with coronavirus infection*

Авторы/ Authors	**Период определения нейтрофильных экстраклеточных ловушек или их продуктов у пациентов/ Period of determination of neutrophil extracellular traps or their products in patients**	**Обнаруженные результаты/ Found results**
Fernández S. et al.	48-72 hours after hospitalization	Extracellular neutrophil traps
Zuo Y. et al.	1-25 day of hospitalization	Serum markers of extracellular neutrophil traps
Panda R. et al.	1st and 7th day of the disease	Serum markers of extracellular neutrophil traps
Eleonora Petito et al.	2-5 day of the disease	Serum markers of extracellular neutrophil traps
Masso-Silva JA et al.	1, 3, 5, 7, 9, 11 days of illness	Serum markers of extracellular neutrophil traps
Guéant JL et al.	4-14 day of the disease	Extracellular neutrophil traps
Kinnare N et al.	1-3 days of hospitalization	Serum markers of extracellular neutrophil traps
Кассина Д.В., и соавт	Day of hospitalization and up to 12 days after hospitalization	Extracellular neutrophil traps
Ng, H. et al.*	1-7 day of hospitalization, 4 months from the onset of the disease	Serum markers of extracellular neutrophil traps

Note. * The study of Ng, H. et al. [14] included 106 patients with moderate and severe COVID-19. When examining blood serum: levels of citrullinated histone H3, cell-free DNA, neutrophil elastase were elevated in patients with COVID-19 compared with healthy people. Subsequently, 55 patients were followed up for 4 months (median 122 [109-132] days) after acute illness. During this period, blood plasma was taken with the determination of serum markers of NEL, the content of which decreased to the level of healthy people after 4 months, while the work did not take into account the patient's well-being after recovery and the preservation or appearance of complaints

The paper by A. N. Kazimirskiy et al. [15] dedicated to comparison of clinical and laboratory characteristics of patients with post-COVID syndrome included 21 inpatient patients aged 18–59 years (36 [27÷50]) 1–3 months after the disease. 11 patients had mild disease, 7 patients had moderate disease and 3 patients had severe disease. A group of healthy controls comprised 20 patients aged 18–59 years (38.5 [29÷51.5]) without a history of coronavirus infection. The following parameters were elevated in blood biochemistry of patients with post-COVID syndrome: ALT (1.7 times), GGT (2.1 times) and alkaline phosphatase (3.7 times); the number of extracellular purine bases was elevated as well. Patients with a history of moderate coronavirus infection had a higher level of NETs vs. patients with mild disease; and patients who had severe disease did not have any traps [$p < 0.05$]. All patients in post-COVID period had one form of NETs: thin single threads, pointing out to active aseptic inflammation.

Role of NETosis in Development of Pathologic Disorders in Post-COVID Period

An active NETosis process results in unfavourable blood-clotting disorders and immunothrombosis. Excessive formation of extracellular neutrophil traps triggers a cascade of pathophysiological disorders in patients with a history of the novel coronavirus infection.

NETosis is activated by several mechanisms in the presence of SARS-CoV-2 virus. On the one hand, virus-infiltrated neutrophils directly induce NETosis and release NETs. On the other hand, exposure of neutrophils to SARS-CoV-2 boosts production of pro-inflammatory mediators (IL-8, IL-1β) by epithelial cells and macrophages, activating NETosis. Another path of NET production activation is virus-induced platelet activation which can enhance this process by interaction with neutrophils.

It was confirmed that, in septic conditions, formation of NETs and NETosis by-products act as direct inflammation enhancers: NETosis stimulates release of free DNA and by-products (e.g. elastases and histones). As a result, macrophages and endothelial cells express excessive amount of pro-inflammatory cytokines, which boost NETs production, thus forming a vicious circle of hyperinflammation in COVID-19. Hyperinflammation (also known as cytokine storm) is typical of COVID-19; it develops together with immunothrombosis and facilitates development of acute respiratory distress syndrome and extensive organ failure [16].

NET formation is a link between the processes of inflammation and clotting. Antimicrobial agents released during NET formation also activate platelets. Reaction of activated platelets and immune cells stimulates the clotting system and causes a related process which connects thrombotic and inflammatory paths [16]. Morphological blood clot substrate is neutrophil-generated cells which consist of decondensed thread-like chromatin. This is how the blood clot frame is formed and platelets and clotting are activated [17].

Statistically significant relations between system inflammation in COVID-19 and dramatic increase in the number of NET markers have been identified; assumptions have been made about their key role in the severity of acute respiratory distress syndrome, cardiovascular, renal and inflammatory manifestations on later stages of the disease. The study by Guéant JL et al. [18] enrolled 155 patients aged 25–86 years with confirmed novel coronavirus infection. Controls were 35 persons with a negative COVID-19 test. NET markers (neutrophilic elastase, myeloperoxidase DNA, histone DNA and double-stranded DNA) in the blood of outpatient and hospitalised COVID-19 patients were significantly higher vs. controls. There was an association between NET components and clinical manifestations and biomarkers of a severe disease.

Currently, global literature sources describe a few cases of confirmed relations between neutrophil extracellular traps and the course of post-COVID period. The main mechanisms of post-COVID syndrome development are as follows: virus persistence, persistent hyperinflammation, autoantibody production, changes in the homeostasis system with abnormal clotting. According to the authors, NETosis is a process ensuring the relation between the inborn immunity system, persistent inflammation, endothelial dysfunction, hemostasis and blood clotting [19].

The relationship between the processes of NET activation is confirmed by the study conducted by Pisareva E. [20], where 42 post-COVID-19 patients were followed up. Each of them had at least one symptom of post-COVID syndrome 6 months after discharge from ICU. Blood plasma tests demonstrated that serum marker levels of neutrophil extracellular traps in these patients were higher vs. healthy volunteers. It makes the author think that uncontrolled NET activation due to COVID-19 can be maintained by a feedback path resulting from release of system NETosis by-products.

According to Płazak W et al. [21], NET formation is one of the pathogenic mechanisms of clotting stimulation and enhanced atherosclerosis progression in patients after COVID-19, together with such

mechanisms as endothelial dysfunction, presence of aPL antibodies, complement system activation.

For patients in post-COVID period, several hypotheses were made regarding persistent blood thickening, affected by a number of pathophysiological factors: persistent inflammation, autoantibody production, virus-activated leukocytes and platelets, causing persistent inmmatory reaction. In post-COVID period, the following is observed: persistent blood clotting sustained by persistent activation of endothelial cells and platelets and enhanced fibrinous clot formation [22]. Thus, this process results in emergence of a group of patients who have symptoms after recovery from COVID-19 and develop cardiovascular complications. Thus, for instance, the total rate of blood clotting (including arterial and venous complications) on day 30 after discharge was 2.5 % (95 % confidence interval 0.8–7.6) [23]. Large cohort studies also conform this hypothesis: during 12 months after COVID-19, the patients had an increased risk of such cardiovascular complications as acute cerebrovascular event, heart rhythm disorders, myocarditis and pericarditis, complications of coronary heart disease [24].

Scharf RE et al. [25] noted that the mechanisms of post-COVID syndrome development include virus persistence and impaired adaptive immunity, NET formation, hyperinflammation and homeostasis activation. The immunological disbalance in post-COVID period is also discussed by Islam MS et al. [26]; they note that SARS-CoV-2 proteins directly react with immune mediators, resulting in impaired production of type 1 interferon and enhanced neutrophil activation. They introduced the term "NETinjury" to denote a cascade of immunological reactions including NETosis and bleeding disorder which cause organ microclotting.

Appearance of such symptoms as fatigue, muscle pain and cognitive disorders after recovery from COVID-19 can also be associated with excessive NETosis. Possible mechanisms of a cerebrovascular event are related to blood clotting and include inhibitors of angiotensin converting enzyme 2 (inhibitor of ACE2) — mediated endothelial damage, reduction in ACE2 inhibitor levels, acute inflammation and bleeding disorder associated with an infection, formation of NETs and aPL antibodies, hyperglycemia and acute stress [27].

Schematic presentation of pathological disorders in post-COVID period and their association with NETosis is as follows (refer to Figure 1).

A lot of experts note the significance of neutrophils in pathogenesis of arterial hypertension [28] and their higher level during the entire period of hospitalisation in patients with COVID-19 and arterial hypertension [29].

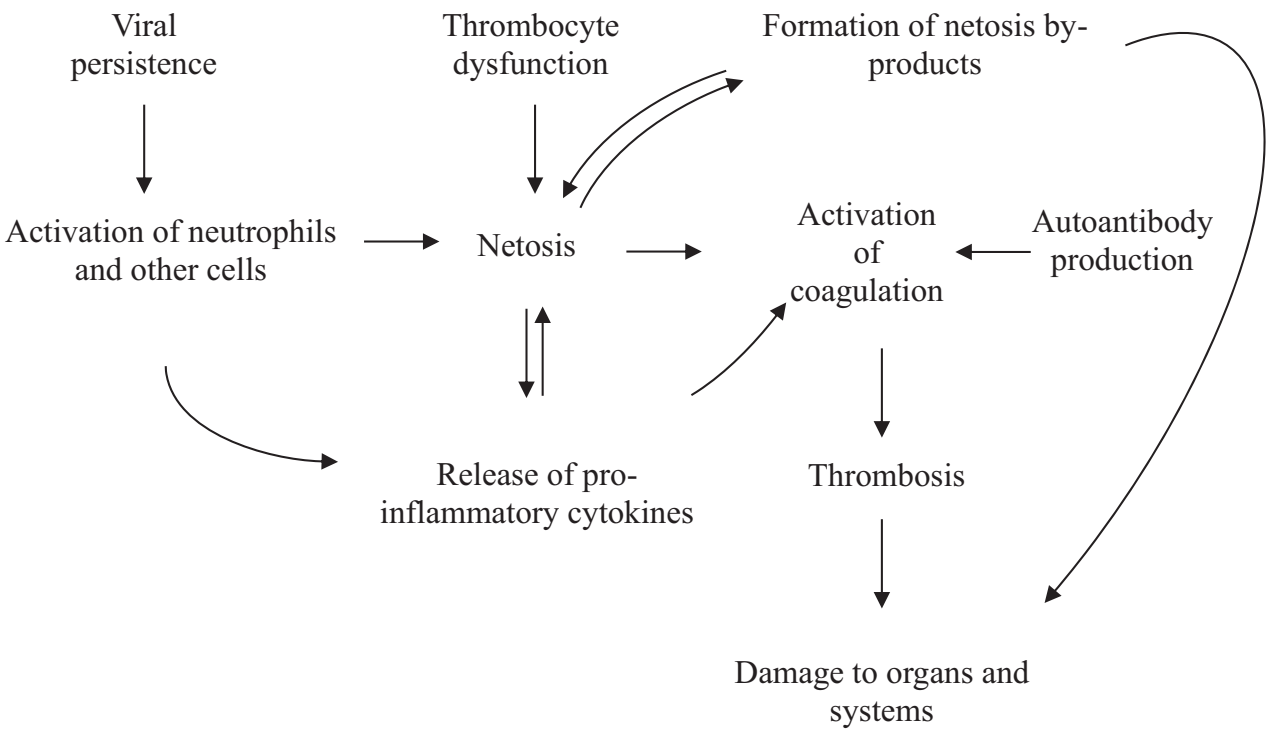

Figure 1. *The relationship of pathological disorders in the postcovid period*

NETosis directly affects chronic diseases; NETs are known to contribute as pro-hypertensive mediators in arterial hypertension. Besides, ACE2 inhibitor is a common receptor for the cardiovascular system and COVID-19 infection pathophysiology, as renin-angiotensin system inhibitors are first-line antihypertensive agents, and SARS-CoV-2 uses ACE2 inhibitors as a receptor for body penetration. When a patient with arterial hypertension is infected with COVID-19, reduced ACE2 inhibitor levels can cause inadequate immune response, including delayed pro-inflammatory cytokine storm, leading to neutrophil and macrophage infiltration and tissue damage. Once in the site of infection, neutrophils identify viral particles, and NET production is triggered, which is presumably a new mechanism of cardiovascular system damage after an infection [30].

Besides, a higher level of NETosis products is observed in patients with obesity and diabetes mellitus, and these conditions are thought to be pro-NETonic and can be associated with thrombotic complications [31].

A common feature of all post-COVID complications is involvement of organs which are closely related to the vascular and hemic system. The cardiovascular and respiratory systems are involved first of all. However, vessel wall inflammation and impaired clotting processes create conditions for tromboembolic episodes, involvement of other organs and systems, such as nervous system, GIT, liver and kidneys [32].

Conclusion

The real clinical practice and international scientific society confirm that a number of patients have persistent symptoms of the past novel coronavirus infection over a long period of time after clinical recovery. The pathogenesis of the post-COVID syndrome is based on a number of mechanisms, including a long-term inflammation resulting from formation of neutrophil extracellular traps — NETosis, a form of programmed cell death. The inflammatory status of a patient in post-COVID period can be evaluated on the basis of NETs blood count, requiring deeper studies in order to develop a therapy to mitigate negative consequences of NETosis.

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Ларина В.Н. (ORCID ID: https://orcid.org/0000-0001-7825-5597): разработка концепции и дизайна, сбор, анализ и интерпретации данных, проверка критически важного интеллектуального содержания, окончательное утверждение рукописи для публикации, ответственная за все аспекты работы

Стоделова Е.А. (ORCID ID: https://orcid.org/0000-0001-9002-749): сбор, анализ и интерпретации данных, подготовка рукописи, ответственная за все аспекты работы

Салмаси Ж.М. (ORCID ID: https://orcid.org/0000-001-8524-0019): разработка концепции и дизайна, анализ и интерпретации данных, проверка критически важного интеллектуального содержания

Казимирский А.Н. (ORCID ID: https://orcid.org/0000-0002-3079-4089): разработка концепции и дизайна, анализ и интерпретации данных, проверка критически важного интеллектуального содержания

Порядин Г.В. (ORCID ID: https://orcid.org/0000-0003-2010-3296): разработка концепции и дизайна, анализ и интерпретации данных, проверка критически важного интеллектуального содержания

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Larina V.N. (ORCID ID: https://orcid.org/0000-0001-7825-5597): concept and design development, collection, analysis and interpretation of data, validation of important intellectual content, final approval of the manuscript for publication, responsible for all aspects of the work

Stodelova E.A. (ORCID ID: https://orcid.org/0000-0001-9002-749): collection, analysis and interpretation of data, preparation of the manuscript, responsible for all aspects of the work

Salmasi Zh.M. (ORCID ID: https://orcid.org/0000-001-8524-0019): concept and design development, data analysis and interpretation, review of critical intellectual content.

Kazimirskij A.N. (ORCID ID: https://orcid.org/0000-0002-3079-4089): concept and design development, data analysis and interpretation, review of critical intellectual content.

Porjadin G.V. (ORCID ID: https://orcid.org/0000-0003-2010-3296): concept and design development, data analysis and interpretation, review of critical intellectual content.

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Н.С. Чипигина*[1], Н.Ю. Карпова[1], А.С. Винокуров[1,2,3], Е.Е. Аринина[4], Ю.А. Иванова[1], А.А. Гаспарян[1], П.А. Кашковская[1], А.Г. Макаев[1], М.С. Сапко[1]

[1] — ФГАОУ ВО «Российский национальный исследовательский медицинский университет им. Н.И. Пирогова» Минздрава России, Москва, Россия
[2] — ГБУЗ «Городская клиническая больница им. В.П. Демихова Департамента здравоохранения города Москвы», Москва, Россия
[3] — ГБУЗ «Московский многопрофильный клинический центр «Коммунарка» Департамента здравоохранения города Москвы», Москва, Россия
[4] — ФГБУ «Федеральный центр мозга и нейротехнологий» ФМБА России, Москва, Россия

СЕПТИЧЕСКАЯ ЭМБОЛОГЕННАЯ ПНЕВМОНИЯ — ОСОБЕННОСТИ КЛИНИКИ И ДИАГНОСТИКИ (ОБЗОР ЛИТЕРАТУРЫ И СОБСТВЕННЫЕ НАБЛЮДЕНИЯ)

N.S. Chipigina *[1], N.Yu. Karpova [1], A.S. Vinokurov [1,2,3], E.E. Arinina[4], Yu.A. Ivanova [1], A.A. Gasparyan[1], P.A. Kashkovskaya[1], A.G. Makaev[1], M.S. Sapko[1]

[1] — Pirogov National Research Medical University, Ministry of Health of Russia, Moscow, Russia
[2] — V.P. Demikhov City Hospital of Moscow City Health Department, Moscow, Russia
[3] — Moscow Multidisciplinary Clinical Center «Kommunarka», Moscow, Russia
[4] — «Federal Center for Brain and Neurotechnologies» of the Russian Federal Medical and Biological Agency, Moscow, Russia

Septic Embologenic Pneumonia — Clinical and Diagnostical Features (Review and Own Observations)

Резюме

В отличие от простой пневмонической инфильтрации, диагноз септической эмбологенной пневмонии ставит перед врачом принципиальную задачу поиска первичного септического эмбологенного очага, в том числе инфекционного эндокардита правых отделов сердца, и соответствующего изменения тактики ведения пациента. Сходство основных общих клинических и респираторных симптомов септической эмбологенной пневмонии с проявлениями других воспалительных процессов в легких делают их дифференциальную диагностику затруднительной без привлечения дополнительных лучевых методов исследования. В обзоре описаны особенности этиологии и патогенеза, а также клиника, осложнения и принципы диагностики септической эмбологенной пневмонии.

Ключевые слова: *септическая эмболия легких, пневмония, инфекционный эндокардит, наркомания, S. aureus*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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*Контакты: Наталия Семеновна Чипигина, e-mail: chipigina-natalia56@yandex.ru
*Contacts: Natalia S. Chipigina, e-mail: chipigina-natalia56@yandex.rufcv
ORCID ID: https://orcid.org/0000-0002-2083-0437

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Abstract

In contrast to trivial bacterial pneumonia, the diagnosis of septic pulmonary embolism poses a fundamental task for the doctor to search for primary sources of emboli, including right side infective endocarditis, and to change the tactics of managing the patient accordingly. The similarity of the main clinical common and respiratory symptoms of septic pulmonary embolism with symptoms of other inflammatory processes in the lung makes their differential diagnosis difficult without the involvement of additional radiologic investigation methods. The review describes the special features of etiology and pathogenesis, as well as the clinic, complications and principles of diagnosis of septic embolic pneumonia.

Key words: *septic pulmonary embolism, pneumonia, infectious endocarditis, drug use, S. aureus*

Conflict of interests

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IE — infective endocarditis, CCT — chest computed tomography, SEP — septic embologenic pneumonia, EchoCG — echocardiography

Septic embologenic pneumonia (SEP) is a specific clinical syndrome developing as a result of infected emboli (usually septic thrombi) entering the pulmonary vasculature (predominantly small arteries), with their subsequent mechanical obstruction, invasion of microbial pathogens into the vascular wall and secondary infection, inflammation, impaired blood flow in the corresponding regions of the lung parenchyma with necrosis, suppuration, and destruction cavities [1–4]. The sources of such embolism (usually multiple one) include various primary extrapulmonary infectious pathological processes accompanied by the formation of septic thrombi — they can be classified into cardiogenic, peripheral endogenous, and exogenous embologenic foci [3, 5].

The sources used in the literature review were searched in PubMed and eLIBRARY.RU using the following key words: septic embologenic pneumonia, septic pulmonary embolism, right-sided infective endocarditis, Lemierre's syndrome, septic thrombophlebitis within the period of 1990–2023.

Extrapulmonary SEP sources

Typical SEP sources (traditional triad of active extrapulmonary SEP sources) include right-sided infective endocarditis (IE), acute thrombosis of the internal jugular vein with confirmed bacteremia (Lemierre's syndrome) in purulent inflammatory diseases of the head and neck, and septic thrombophlebitis of pelvic veins (including the postpartum one) [6–8]. SEP risk groups also include patients with a wide spectrum of acute or chronic purulent/septic processes — abscesses or cellulitis of soft tissues [7], abscesses of internal organs [9, 10], osteomyelitis [11], especially against the background of diabetes mellitus, hemodialysis, malignancies, and other diseases accompanied by immunodeficiency, increased risks of bacteremia and thromboses [1, 7, 12–14]. SEP morbidity has been increasing as a result of IE and septic thrombophlebitis in intravenous drug users [2, 7, 15], as well as in cases associated with the infection of central venous catheters, intracardiac devices, or medical interventions [2, 16–19].

The systematic literature review by Ye et al. (1978–2012) [2], which includes 76 articles with data about 168 patients with SEP, demonstrated that 26 % patients with SEP were intravenous drug users, 12.5 % had permanent intravascular catheters, and 3 % had permanent pacemakers. Most common diagnosis among patients with SEP included right-sided IE (12 %), hepatic abscess (9 %), skin and soft tissue infections, septic thrombophlebitis, Lemierre's syndrome, odontogenic infectious diseases (5–6 % each). In separate cases sources of infected emboli included pharyngeal abscess, purulent myositis, renal abscess and urinary tract infection, prostatic abscess, post-abortion purulent endometritis, osteomyelitis, septic arthritis. In 10 SEP cases (6 %) the primary infection focus was not verified [2]. Jing Jiang et al. [1] retrospectively analyzed 98 SEP cases hospitalized into the pulmonology department or the intensive care unit; the following SEP sources were the most significant: purulent skin and soft tissue infections (30.6 %), right-sided IE (20.4 %), hepatic abscess (14.3 %), catheter associated intravascular infections (9.2 %). In single cases SEP sources were represented by the urinary tract infection, perianal abscess, cholecystitis and cholangitis, infectious endophthalmitis, abdominal cavity abscess, periodontal abscess, meningitis; in 3 % of patients the SEP source

could not be diagnosed [1]. According to Goswami U et al. [18], 88 % of all SEP cases were associated with skin and soft tissue infections (44 %), right-sided IE (27 %), or septic deep vein thrombophlebitis (17 %).

SEP in right-sided IE

In right-sided IE the incidence of SEP diagnosis is 49.1–100 %; the lesions are usually bilateral and relapsing [20–26]. Based on our prior observations (data not published), SEP was diagnosed in 99 of 109 patients with right-sided IE (90.8 %); 85 % of those were referred to the inpatient department with the preliminary diagnosis of community-acquired pneumonia, 28.4 % were hospitalized into the intensive care unit as they required mechanical ventilation due to widespread pulmonary lesions, septic shock; the SEP diagnosis was morphologically confirmed in all 17 deceased patients with right-sided IE (15.6 %). Based on the Utsunomiya H et al. data, "new" embolic pulmonary lesions after the right-sided IE diagnosis and the onset of antibacterial treatment develop in 46.2 % of patients with the IE of the tricuspid valve [27]. IE affecting the tricuspid valve [9], especially with the maximum vegetation size of over 15 mm [27, 28] is an independent risk factor for "new" embologenic pulmonary lesions.

The modern right-sided IE in adults is most often associated with the drug abuse or intracardiac electronic devices, permanent vascular catheters in patients on hemodialysis; in rare cases it may be related to uncorrected congenital heart diseases [29, 30]. The increasing drug abuse trend observed in the latest decades in many countries has led to the enhanced significance of drug abuse IE as a SEP source [31–34]. IE in drug users is right-sided in 59–88.9 % cases [33, 35, 36] and complicates with SEP in 30.6–98.9 % [33, 35–37]. According to Moss R. and Munt B. data, echocardiographic signs of IE are detected in intravenous drug users with fever in 13 % cases; if bacteremia is also found in drug users with fever, the incidence of IE diagnosis reaches 41 % [38]. SEP is included into the minor IE signs of modified Duke diagnostic criteria; thus, when SEP is diagnosed in all cases (especially in drug users, patients with intracardiac devices, or congenital heart diseases), IE should always be considered, with echocardiography and blood cultures ordered within 24 hours [39, 40].

SEP: Causative agents

Causative agents of SEP correspond to the etiology of the primary embologenic infection focus [7]. Microorganisms isolated in the sputum culture correspond to the causative agents isolated from blood and the local septic focus.

The systematic literature review of Ye et al. [2] has shown that the blood cultures were positive in 90.7 % patients with SEP, and generally the most common causative agent was S. aureus (methicillin-sensitive (MSSA) in 28.6 % of patients with SEP and methicillin-resistant (MRSA) in 16 % of cases). Besides, this study underlines that bacteremia caused by Fusobacteria necrophorum (anaerobic flora of the oral cavity) was typically observed in Lemierre's syndrome or oropharyngeal infections, while Klebsiella pneumonia blood cultures were mostly positive in hepatic abscess cases. This coincides with other literature data regarding the SEP etiology in hepatic abscesses and descriptions of invasive Klebsiella pneumonia syndrome [10, 41, 42], while Candida growth was observed predominantly in SEP associated with infected permanent catheters [2]. At the same time, based on Doran HM et al. observations, 90 % of all SEP cases in patients with leukemias or lymphoproliferative diseases are caused by the fungal infection (Candida or Aspergillus) [43]. The majority of SEP cases in right-sided IE (60–90 %) are caused by S. aureus (MSSA or MRSA); more uncommon causative agents of right-sided IE with SEP include Staphylococcus lugdunensis, Streptococcus pneumonia, Pseudomonas aeruginosa and other Gram-negative bacteria, fungi (polymicrobial infection is possible) [44, 45]. Apart from impaired venous blood flow due to inflammatory edema, the pathogenesis of septic thrombophlebitis as a SEP source possibly presumes the capability of separate microorganisms (especially those, such as Fusobacterium necrophorum or S. aureus) to cause endothelial dysfunction and thrombosis due to inflammatory mechanisms and direct production of thrombogenic toxins [7, 46].

SEP: Clinical signs and diagnosis

SEP symptoms depend on the size of emboli, volume of pulmonary lesions, and presence of complications. At the disease onset they may vary from moderate respiratory symptoms — cough (dry or with purulent sputum; 14–100 % of patients), pleuritic pain (22–80 %), hemoptysis (4–80 %), dyspnea (19–91 %) combined with fever and chills (85–100 %) — to life-threatening conditions in the form of severe respiratory failure and septic shock (19 % of patients) [18, 20, 47, 48]. Crackles may be auscultated in lungs of 75 % patients [48]. These respiratory clinical SEP signs are non-specific and cannot be differentiated from the symptoms of other pneumonias. Chest X-rays are more significant for SEP diagnosis if the following signs are detected: bilateral lesions; multiple larger obscure round or irregular foci and shadows with a tendency to cavitate (in 50 % of patients), quick changes reflecting repeated embolic episodes, and slow

regression with preserved cystic thin-walled cavities (in 81 % of patients) [49, 50]. Such X-ray features in a patient with fever, bacteremia, and symptoms confirming the primary purulent-septic infectious focus or the SEP risk group (e.g., intravenous drug use) combined with hemoptysis episodes reflecting the formation of lung abscesses or infarctions can help to diagnose SEP. However, the sensitivity of X-rays in SEP diagnosis is currently insufficient [18, 47, 51], while signs of primary embologenic process at the onset of SEP are evident only in 24 % of patients [18]. In particular, 50–80 % of IE patients with tricuspid valve lesions develop the tricuspid regurgitation murmur later than signs of pulmonary lesions [52]. In any case, when SEP is suspected, chest computed tomography (CCT) is required for further evaluation and intepretation of pulmonary lesions. Its availability has significantly facilitated SEP diagnosis [18].

Chest CT: Modern standard of SEP diagnosis

CCT is the modern "golden standard" of SEP diagnosis which helps to detect typical diagnostic signs (Fig. 1) early: simultaneous presence of several (>2 in 93 % of patients) foci (80–100 %); dense infiltrates (75 %) without the air bronchogram symptom, including dense regions with the halo or inverse halo sign; cavities (57.9–71 %) of various sizes with chaotic peripheral locations (nearly 100 %); "nutrient vessel" sign (90 %), reflecting the hematogenous origin of lesions; quick (within several days) changes in abscesses, thin-walled cavities, and new foci in both lungs (80 %) [1, 4, 18, 42, 51, 53–55]. With that, the differential diagnosis should include other types of pulmonary lesions with focal cavitations — destructive metastases, lung abscesses of other origin, pulmonary tuberculosis, sterile lung infarction without infections,

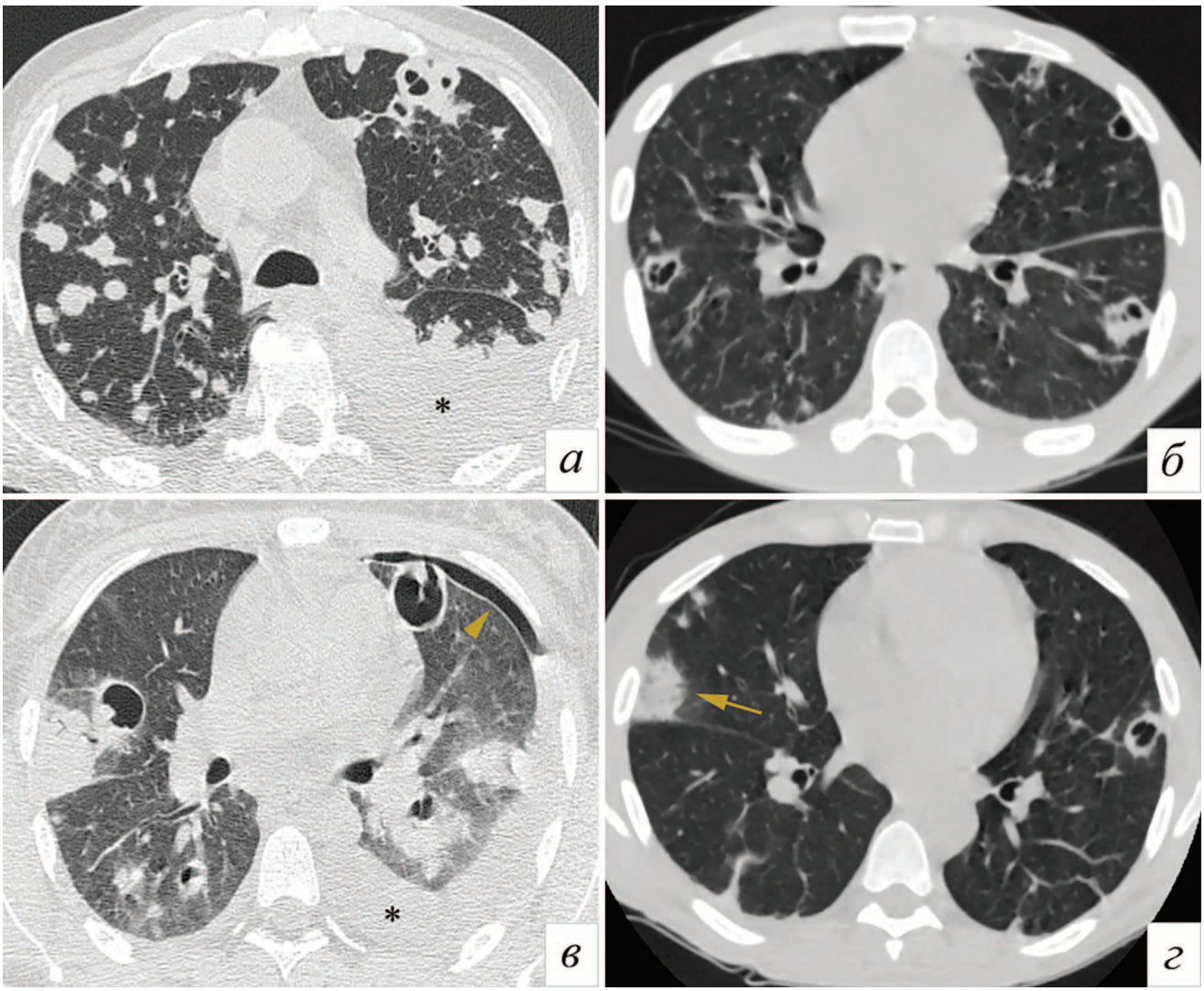

Figure 1. *Transversal chest CT images of different patients with septic pulmonary embolism (SPE). In cases of SPE in various combinations chaotic nodules (а), thin-walled cavities in subpleural location (б-г), as well as opacities- consolidations (в) and a "reverse halo" sign (arrow) are observed. SEP can be complicated by effusion into the pleural cavity (*) and even pneumothorax (arrow head)*

aspergillosis and other fungal infections, granulomatosis with polyangiitis [4, 56–58].

The diagnosis of SEP is still difficult; moreover, the term SEP is not included into the International Classification of Diseases 10 — this pneumonia is usually defined as "pneumonia in diseases classified in other sections". Without unified diagnostic criteria, the SEP syndrome may be diagnosed with the presence of all following four signs:

1) clinical symptoms of the inflammatory lung disease (fever, chills, cough, pleuritic pain, dyspnea, hemoptysis);

2) detection of multiple peripheral foci with cavitations, allowing to suspect the embologenic origin of the pulmonary disease, on imaging;

3) diagnosis of the extrapulmonary embologenic infectious focus;

4) exclusion of other causes of pulmonary changes [1, 7].

It is evident that SEP has specific etiological, pathogenetic, and diagnostic signs; in clinical practice the detection of SEP may become the "key" to the diagnosis of primary embologenic infectious focus, in particular right-sided IE [4, 50], which is demonstrated in the case below.

The male patient S., 46 years old, was hospitalized on April 21, 2020 to the inpatient department for COVID-19 patients with complaints of fever up to 38.0 °C, chills, dry cough, feeling of chest tightness, dyspnea at rest. The patient got sick a week before, when he developed fever up to 38.0 °C, myalgia, followed by the dry cough and worsening weakness. On April 20, 2020 he called an ambulance due to severe dyspnea; an outpatient lung CT was ordered — "multiple foci of pulmonary tissue consolidation of various sizes, with the most massive ones in the left lower lobe, together with ground glass opacities with preserved bronchial lumina; several consolidation areas with signs of cavitation (bronchiectasis?)" described in both lungs. The patient was urgently transferred to the inpatient department with suspected viral pneumonia. Within the prior 14 days the patient did not contact persons with laboratory-confirmed COVID-19 or under observation regarding the nSARS-CoV-2 infection. The patient was not occupied. Earlier he used intravenous drugs; he denied using the drugs in the months prior, though multiple traces of intravenous injections were detected on the skin. On admission to the emergency department, the patient's condition was severe. The patient's consciousness was clear. He was oriented in place and time. Body temperature 38.8 °C. Peripheral lymph nodes were not palpated. The nasal breathing was free. RR 26–28/min. Oxygen saturation on room air 88 %. BP 105/70 mm Hg. The pulse was regular. HR 124/min. The abdomen was soft and nontender on palpation. The liver was not enlarged. The spleen was not palpable. The heart and lungs were not auscultated. The following lab results were derived on admission: white blood cells 15×10^9/L, band neutrophils 18 %, hemoglobin 119 g/L, platelets 80×10^9/L; creatinine 198 μmol/L, AST 144 U/L, ALT 78 U/L, albumin 28 g/L, CRP 488 mg/L, sharply increased procalcitonin level. The patient was hospitalized into the intensive care unit with the preliminary diagnosis "Unspecified coronavirus infection, community-acquired bilateral polysegmental severe pneumonia, CT stage 2, Grade 2 respiratory failure". Treatment for coronavirus pneumonia was started, with oxygen insufflation via nasal cannula with the rate of 10 L/min. Repeated chest MSCT (April 21, 2020; 2.40 a.m.) revealed the following: bilateral asymmetric decrease of pulmonary tissue pneumatization due to the presence of more than 3 "ground glass" opacity areas, predominantly in peripheral and subpleural regions, with irregular shape, unclear contours, dense rims and the "inverse halo" pattern, sized approximately up to 30 mm. Multiple foci with irregular contours and uneven cavitation in the largest structures are detected in all segments of both lungs (predominantly in peripheral and subpleural regions in a peribronchovascular pattern). The following conclusion was made: "The probability of viral etiology is average; detected changes may correspond to the polysegmental bilateral inflammatory process related to septic embolism. Differential diagnosis is primarily required with granulomatosis with polyangiitis" (Fig. 2). Based on the history (drug abuse) and CT signs of SEP, right-sided IE was suspected. The negative PCR coronavirus test returned on April 21, 2020; blood cultures were collected, and transthoracic EchoCG was ordered, which revealed signs of tricuspid IE lesions (marginal coarse small vegetations, Grade 2–3 tricuspid regurgitation).

The following diagnosis was established: "Primary acute infectious endocarditis with tricuspid valve lesions. Grade 2–3 tricuspid regurgitation. Septic embologenic bilateral pneumonia with abscesses. Secondary thrombocytopenia. Secondary anemia. Background condition: Intravenous drug abuse. Complications: Septic shock. Grade 2 respiratory failure. Acute kidney injury syndrome". Based on the highest probability of staphylococcal IE etiology, vancomycin treatment (10 mg/kg of body weight) was started. The patient's condition was unstable against the background of therapy administered; O_2 saturation up to 85 % at the oxygen flow of 15 L/min. The patient underwent orotracheal intubation, and mechanical ventilation was started in the SIMV-PC-PS mode. The fever persisted. The repeated EchoCG (April 23, 2020) revealed the following: "Tricuspid valve leaflets had increased echogenicity,

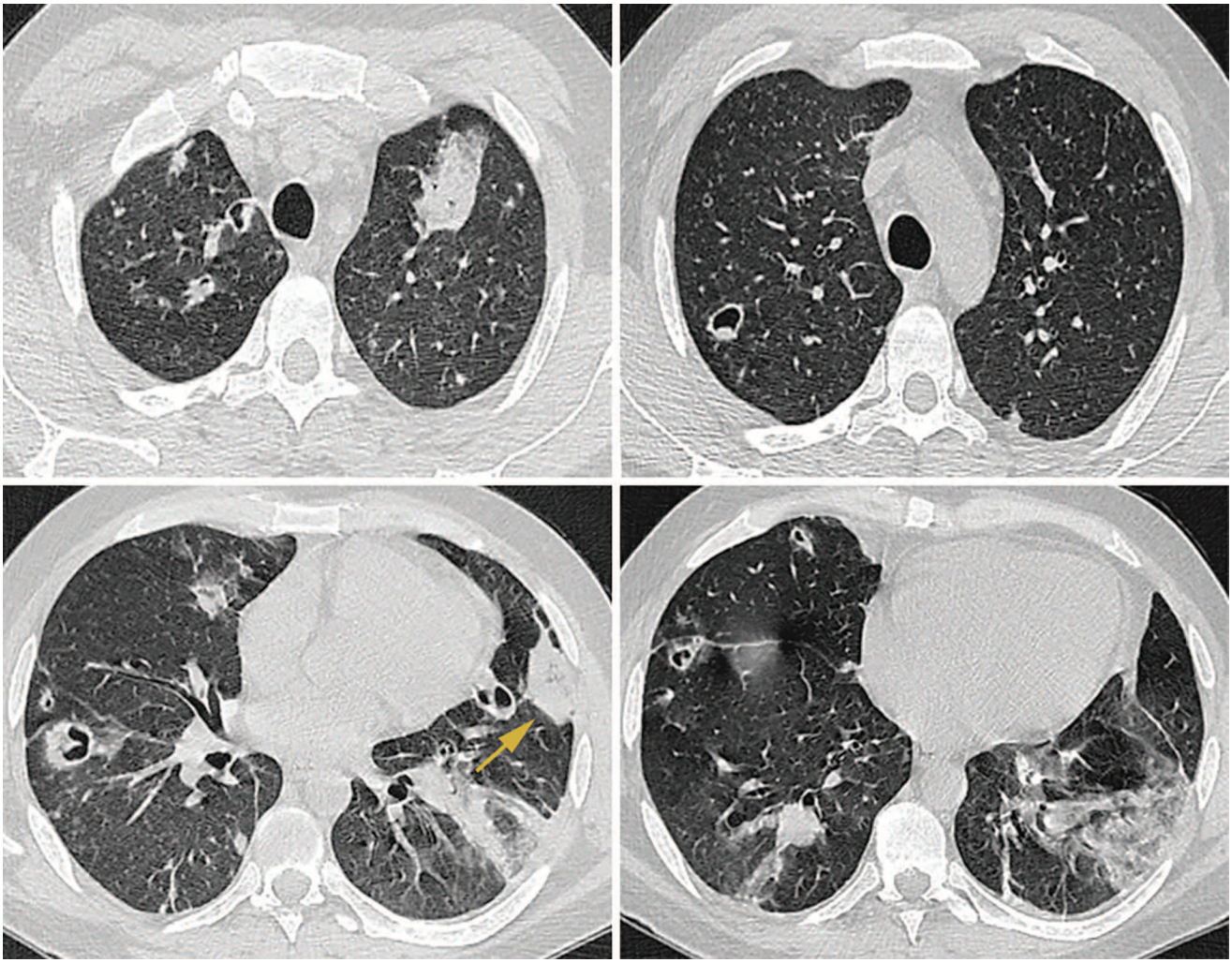

Figure 2. *Transversal chest CT images of patient C. from 21.04.2020 г. In both lungs there are chaotic nodules and opacities of the lung tissue, multiple thin–walled cavities*

with marginal indurations, but were not thickened. The round-ovoid pedunculated lesion with moderately increased echogenicity sized 12×6 mm was detected on the valvular leaflet, partially entering the right ventricle. Moderate to significant valvular regurgitation. Estimated systolic pressure in the pulmonary artery was approximately 55 mm Hg" (Fig. 3).

The patient's condition progressively worsened; on April 23, 2020 (Day 3 of treatment) the patient dies after worsening respiratory failure. The autopsy confirmed the diagnosis of acute IE with the tricuspid valve lesion, complicated with bilateral septic polysegmental embologenic pneumonia with abscesses, acute focal tubulo-interstitial nephritis with the acute kidney injury syndrome. No signs of diffuse pulmonary lesions were detected. The antemortem blood cultures confirmed that the most probable IE causative agent was S. aureus sensitive to oxacillin, vancomycin, linezolid, cefoxitin, ciprofloxacin (the growth was obtained in three blood cultures dated April 21, 2020).

During the first months of COVID-19 epidemics, due to maximum awareness of physicians regarding the viral pneumonia combined with insufficient diagnostic experience with the pathology described, patients with respiratory symptoms and fever of various etiology often were hospitalized erroneously to COVID-19 inpatient departments. The decision on hospitalization was often made based just on CT changes in lungs, which could be interpreted incorrectly. Unlike SEP, typical CT signs of viral pneumonia include "ground glass" opacities, while focal lesions and cavities are quite rare, which should be accounted for in the differential diagnosis of these conditions [4, 59, 60]. In the case presented, the diagnosis of tricuspid valve IE was timely established due to the correct evaluation of SEP signs detected in the repeated CCT. Unfortunately, the condition severity (mechanical ventilation required) and intensive care in the patient with the right-sided IE was initially associated with the unfavorable outcome [61].

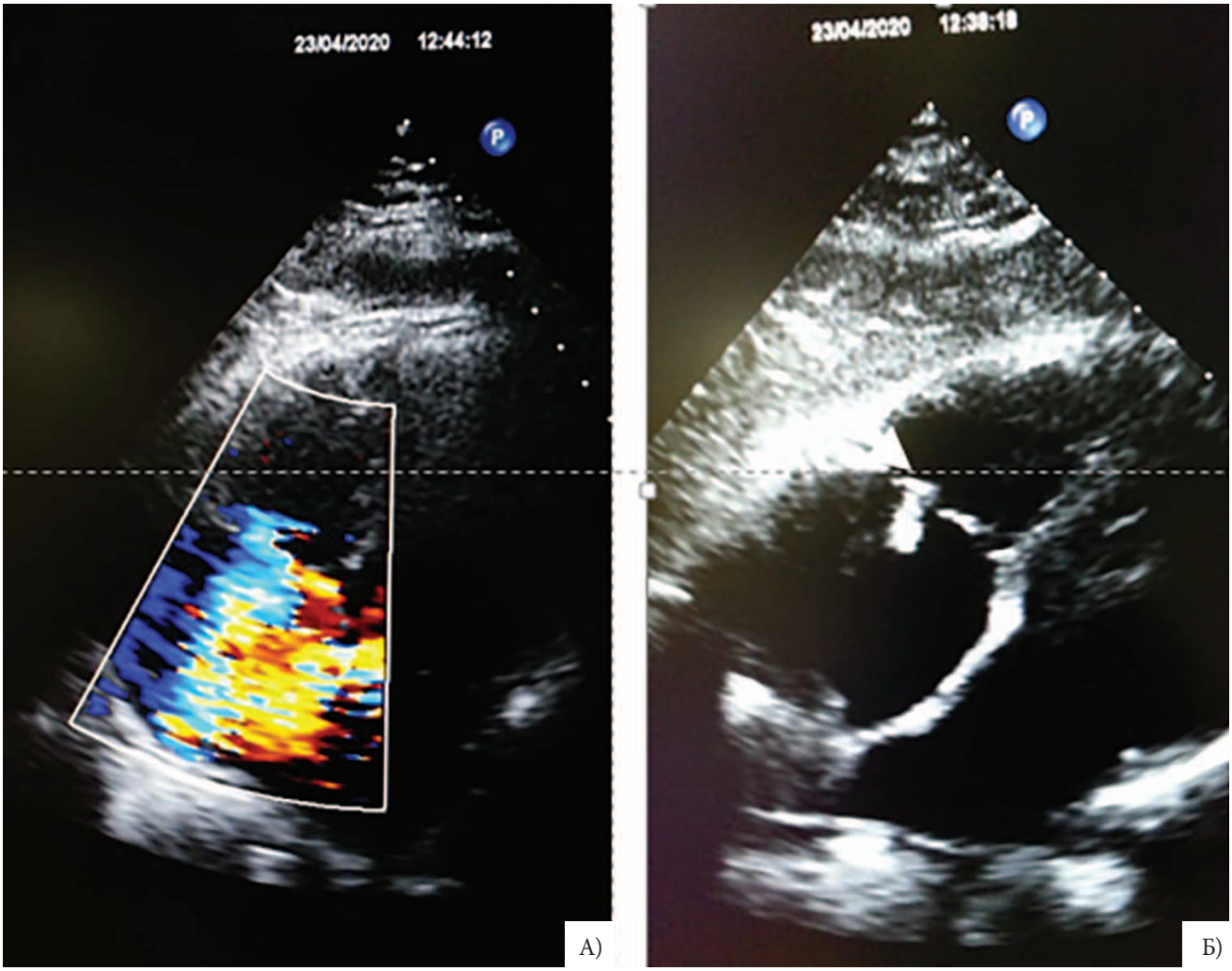

Figure 3. *Echocardiographic images of patient C.*
A) tricuspid valve regurgitation of 2-3 degrees
Б) large vegetation on the tricuspid valve

SEP: Complications and outcomes

In 23.8–65 % cases SEP is complicated with pleural effusion, pleural empyema (8.3 %) [2, 18, 19, 42], pneumothorax (3.5 %) [14, 62–65], pulmonary hemorrhage in single cases, including due to the rupture of infectious pulmonary artery aneurysm; bronchopleural fistulae have been described as well [7, 66]. SEP often leads to quick worsening of the patient's condition with the development of respiratory failure, respiratory distress syndrome, septic shock, disseminated intravascular coagulation syndrome, impaired consciousness — thus, 25.5–63 % of patients require treatment in the intensive care unit [1, 18, 19, 42].

SEP treatment with antibiotics is administered based on the sensitivity of the causative agent which is isolated or most probable in the clinical situation; primary antibacterial treatment should usually be broad-spectrum [7, 42, 67, 68]. Managing the patient with SEP may require mechanical ventilation, surgical interventions in empyema, pneumothorax, pulmonary hemorrhage. If necessary, purulent-septic primary processes, including right-sided IE, are treated surgically, intracardiac or intravenous devices are removed. Thus, persistence of a large vegetation on a tricuspid valve or the pulmonic valve, especially its enlargement, despite recurrent embologenic episodes in lungs against the background of antibacterial treatment, is a sign of ineffective infection control, being one of the indications to surgical IE treatment [39, 40]. In cases of septic thrombi complicated with SEP, anticoagulant therapy is often added; however, due to the high risk of pulmonary hemorrhages, the issue of anticoagulant therapy safety and duration in SEP is still debatable [2, 7]; in right-sided IE such therapy is not indicated due to high bleeding risk and lack of safety evaluation in controlled trials [39, 40, 48].

Mortality in SEP reaches 10–30 %, it depends both on efficient control of primary embologenic infectious focus

and severity of SEP signs [1, 2, 10, 18, 19, 42]. Mortality risk factors include low oxygen saturation and impaired consciousness in patients with SEP [19], fungal infections or causative agents multiresistant to antibiotics, inefficacy or late onset of empiric antibacterial treatment, refractory septic shock with multiorgan failure, severe coagulation disorders, pulmonary hemorrhage [1, 2, 18, 42]. The multidisciplinary approach is required in the majority of cases for successful SEP treatment, including the participation of intensive care specialists, general practitioners, pulmonologists, cardiologists, surgeons, ENT physicians, neurologists, and other medical specialists.

Conclusion

SEP is a special life-threatening pulmonary pathology which is difficult to diagnose, develops secondarily as a complication of several purulent-septic processes, including right-sided IE and septic thromboses associated with purulent inflammatory diseases of soft tissues, internal organs, osteomyelitis. Accurate SEP diagnosis presumes the way to understanding the risk of corresponding complications and often the key to the diagnosis of primary sources of septic embolism in the pulmonary artery system. The detection of typical CCT signs is currently the most important step in the SEP diagnosis. Timely diagnosis and adequate treatment of SEP requires awareness and knowledge about this rare pathology among general practitioners, pulmonologists, intensive care specialists, cardiologists, ENT physicians, dentists, surgeons, and other specialists.

Вклад авторов:

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Чипигина Н.С. (ORCID ID: https://orcid.org/0000-0002-2083-0437): концепция работы, сбор и обработка материала, написание текста, редактирование

Карпова Н.Ю. (ORCID ID: https://orcid.org/0000-0002-7546-4841): концепция работы, редактирование и утверждение окончательного варианта статьи

Винокуров А.С. (ORCID ID: https://orcid.org/0000-0002-0745-3438): концепция работы, написание текста статьи, редактирование, подготовка лучевых изображений

Аринина Е.Е. (ORCID ID: https://orcid.org/0000-0002-6431-037X): наблюдение и описание случая, представленного в статье

Иванова Ю.А. (ORCID ID: https://orcid.org/0009-0005-1446-7722): подбор и анализ литературы

Гаспарян А.А. (ORCID ID: https://orcid.org/0000-0003-1699-7717): подбор и анализ литературы

Кашковская П.А. (ORCID ID: https://orcid.org/0009-0001-0856-9503): подбор и анализ литературы

Макаев А.Г. (ORCID ID: https://orcid.org/0000-0003-2628-2440): подбор и анализ литературы

Сапко М.С. (ORCID ID: https://orcid.org/0009-0009-8151-8023): подбор и анализ литературы

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Chipigina N.S. (ORCID ID: https://orcid.org/0000-0002-2083-0437): the concept of work; data mining, analysis and interpretation; preparation of a draft of the manuscript, editing

Karpova N.Yu. (ORCID ID: https://orcid.org/0000-0002-7546-4841): the concept of work; final editing

Vinokurov A.S. (ORCID ID: https://orcid.org/0000-0002-0745-3438): the concept of work; preparation of a draft of the manuscript, editing; ray images preparation

Arinina E.E. (ORCID ID: https://orcid.org/0000-0002-6431-037X): observation and description of the case presented in the article

Ivanova Yu.A. (ORCID ID: https://orcid.org/0009-0005-1446-7722): selection and analysis of literature

Gasparyan A.A. (ORCID ID: https://orcid.org/0000-0003-1699-7717): selection and analysis of literature

Kashkovskaya P.A. (ORCID ID: https://orcid.org/0009-0001-0856-9503): selection and analysis of literature

Makaev A.G. (ORCID ID: https://orcid.org/0000-0003-2628-2440): selection and analysis of literature

Sapko M.S. (ORCID ID: https://orcid.org/0009-0009-8151-8023): selection and analysis of literature

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Г.А. Игнатенко, Г.Г. Тарадин*, Т.Е. Куглер

ФГБОУ ВО Донецкий государственный медицинский университет
им. М. Горького Минздрава России, Донецк, Россия

ОСОБЕННОСТИ ГИПЕРТРОФИИ ЛЕВОГО ЖЕЛУДОЧКА И ХАРАКТЕРИСТИКА ФЕНОТИПИЧЕСКИХ ВАРИАНТОВ У БОЛЬНЫХ ГИПЕРТРОФИЧЕСКОЙ КАРДИОМИОПАТИЕЙ

G.A. Ignatenko, G.G. Taradin*, T.E. Kugler

The Federal State-Funded Educational Institution of Higher Education
Donetsk State Medical University named after M. Gorky, Donetsk, Russia

Specifics of Left Ventricular Hypertrophy and Characteristic of Phenotypic Variants in Patients with Hypertrophic Cardiomyopathy

Резюме

Гипертрофическая кардиомиопатия характеризуется генетической и фенотипической гетерогенностью, что проявляется в различных вариантах локализации и протяженности гипертрофии миокарда. **Цель**. На основании данных эхокардиографии оценить особенности гипертрофии левого желудочка, распространенность и клинико-инструментальные показатели фенотипических вариантов гипертрофической кардиомиопатии. **Материалы и методы**. Обследовано 295 больных с гипертрофической кардиомиопатией в возрасте от 18 до 88 лет (60,3±13,4 лет), мужчин 183 (62 %), женщин 112 (38 %). Диагноз устанавливался на основании двухмерной эхокардиографии. Оценивались выраженность, локализация и протяженность гипертрофии миокарда, максимальная толщина гипертрофированного сегмента, масса миокарда, индекс массы миокарда левого желудочка, наличие и выраженность среднежелудочковой обструкции и обструкции выносящего тракта левого желудочка. В зависимости от преимущественной локализации и протяженности гипертрофии больные были распределены в 8 групп согласно рекомендациям по гипертрофической кардиомиопатии МЗ РФ. Проведен анализ и сравнение полученных результатов в зависимости от фенотипа кардиомиопатии. **Результаты**. Средняя продолжительность заболевания — 10,5±7,52 лет. Средние значения индекса массы тела у всех пациентов составили 28,2±2,82 кг/м^2. Наиболее часто отмечался фенотип с базальной гипертрофией межжелудочковой перегородки (n=130, 44,1 %), 1 группа. У 47 (15,9 %) больных выявлена гипертрофия межжелудочковой перегородки «обратной кривизны» (3 гр.), у 41 (13,9 %) — «нейтральная межжелудочковая перегородка» (2 гр.), у 36 (12,2 %) — симметричная гипертрофия левого желудочка (8 гр.), по 11 (3,7 %) пациентов имели комбинированную гипертрофию межжелудочковой перегородки и других отделов левого или правого желудочка (4 гр.) и свободной стенки ЛЖ (7 гр.), у 10 (3,4 %) — среднежелудочковая гипертрофия левого желудочка (6 гр.) и у 9 (3,1 %) — апикальная гипертрофия (5 гр.). Наибольшее значение максимальной толщины миокарда отмечено у больных 6 группы 19,3 (19-20,4 мм). Среднежелудочковая обструкция выявлена в 6 группе (90,0 %), обструкция выносящего тракта левого желудочка чаще регистрировалась в 4 и 8 группах (81,8 % и 77,8 %), а реже — в группе 5 (22,2 %) (p <0,01). У больных 7 группы не было выявлено случаев с обструкцией выносящего тракта левого желудочка в базальном состоянии. Максимальные значения показателей массы миокарда и индекса массы миокарда левого желудочка отмечены в группе 8 — 402 (356-439) г и 195 (173-218) г/м^2, соответственно (p <0,01). **Заключение**. Эхокардиография представляет информативный метод оценки наличия, выраженности гипертрофии миокарда и определения фенотипического варианта гипертрофической кардиомиопатии. Наиболее часто регистрируются варианты гипертрофии межжелудочковой перегородки, среди которых самым распространенным является фенотип гипертрофии базальной её части. Каждый фенотип гипертрофической экспрессии характеризуется особенностями эхокардиографических параметров.

Ключевые слова: *гипертрофическая кардиомиопатия, гипертрофия миокарда, фенотип, эхокардиография, обструкция*

*Контакты: Геннадий Геннадьевич Тарадин, e-mail: taradin@inbox.ru
*Contacts: Gennady G. Taradin, e-mail: taradin@inbox.ru
ORCID ID: https://orcid.org/0000-0003-3984-8482

Конфликт интересов
Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract
Hypertrophic cardiomyopathy is characterized by genetic and phenotypic heterogeneity which manifests in different variants of localization and extent of myocardial hypertrophy. **Aim**: to evaluate specifics of left ventricular hypertrophy, the prevalence and characteristics of clinical and instrumental features of phenotypic variants of hypertrophic cardiomyopathy. **Materials and methods**. The study includes 295 patients with hypertrophic cardiomyopathy aged 18 to 88 years (60.3±13.4 years), 183 men (62 %), and women 112 (38 %). The diagnosis of which was established by 2D echocardiography. The severity, localization and extent of myocardial hypertrophy, the maximum thickness of the hypertrophied segment, left ventricular myocardial mass, left ventricular myocardial mass index, the presence and severity of mid-ventricular and left ventricular outflow tract obstruction were evaluated. Depending on the predominant localization and extent of hypertrophy, patients were divided into 8 groups according to the recommendations for hypertrophic cardiomyopathy of the Ministry of Health of the Russian Federation. The analysis and comparison of the obtained results are carried out. **Results.** The average duration of the disease is 10.5±7.52 years. The mean values of the body mass index in patients — 28.2±2.82 kg/m^2. The phenotype with basal hypertrophy of the septum (n=130, 44.1 %), group 1 was most often noted. In 47 (15.9 %) patients, hypertrophy of the septum of "reverse curve" (2 group) was detected, in 41 (13.9 %) — "neutral septum" (3 group), in 36 (12.2 %) — symmetrical hypertrophy of the left ventricle (8 group), 11 (3.7 %) of patients had combined hypertrophy of the septum and other parts of the left or right ventricle (4 group) and the free left ventricular wall (7 group), in 10 (3.4 %) — middle ventricular hypertrophy of the left ventricle (6 group) and in 9 (3.1 %) — apical hypertrophy (5 group). The highest value of the maximum thickness of the myocardium was noted in patients of the 6th group 19.3 (19-20.4 mm). Mid-ventricular obstruction was detected in group 6 (90 %), left ventricular outflow tract obstruction was more often registered in groups 4 and 8 (81.8 % and 77.8 %), and less often in group 5 (22.2 %) (p <0.01). In group 7, there were no cases of rest obstruction of left ventricular outflow tract. The maximum values of myocardial mass and left ventricular myocardial mass index were noted in group 8 — 402 (356-439) g and 195 (173-218) g/m^2, respectively (p <0.01). **Conclusion**. Echocardiography is an informative tool for assessing the presence, severity myocardial hypertrophy and determination of the phenotypic variant of hypertrophic cardiomyopathy. Variants of septal hypertrophy are most commonly registered one, among which the most frequent is the phenotype of basal septal hypertrophy. Each phenotype of hypertrophic expression is characterized by its echocardiographic parameters.

Key words: *hypertrophic cardiomyopathy, myocardial hypertrophy, phenotype, echocardiography, obstruction*

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OT — outflow tract, HCM — hypertrophic cardiomyopathy, LVH — left ventricular hypertrophy, LVMMI — left ventricular myocardium mass index, EDD — end-diastolic dimension, LV — left ventricle, MV — mitral valve, LVMM — left ventricular myocardium mass, BSA — body surface area, RV — right ventricle, PWTd — LV posterior wall thickness, diastolic, IVSTd — interventricular septum thickness, diastolic, echoCG — echocardiography

Introduction

Hypertrophic cardiomyopathy (HCM) is a genetic myocardial disease defined by left and/or right ventricular (RV) myocardium hypertrophy, usually asymmetric due to a thick interventricular septum (IVS), which cannot be attributed solely to a higher pressure-induced load, and observed in the absence of any other cardiac or system disease, metabolic or multisystemic syndrome associated with left ventricular (LV) hypertrophy [1–3].

LV myocardium hypertrophy is a primary pathomorphological and diagnostic sign of HCM, which defines a cascade of subsequent pathophysiological events: LV outflow tract (OT) obstruction, diastolic dysfunction, microcirculation involvement, and various cardiac rhythm and conduction disorders [4].

HCM is diagnosed on the basis of unexplained and usually symmetric LV hypertrophy (LVH) using imaging methods, the use of which makes it possible to assess the presence, intensity, primary localisation, and extension

of hypertrophic myocardium. Besides, visualisation methods, especially echocardiography (echoCG), are capable of assessing the presence and intensity of LVOT obstruction and cardiac valve condition (especially that of the mitral valve, MV), subvalvular structures, systolic and diastolic function of LV [5].

When echoCG was introduced in clinical practice in 1970s, it was then possible to identify the array of forms of myocardium hypertrophy in HCM [6–8]. According to the HCM Clinical Guidelines approved by the Ministry of Health of Russia in 2020, cardiomyopathy can be symmetric and asymmetric, and the latter form includes seven variants of LVH [3]. Understanding the various forms of HCM improves disease diagnosis, which is not limited only to detection of basal IVS hypertrophy, and makes it possible to study pathogenesis taking into genotype/phenotype correlation as well as to select a most optimal therapy. However, to date there is insufficient information on the rate of proposed phenotypes, only a general idea that HCM is a disease, the primary sign of which is asymmetric hypertrophy with IVS involvement [5, 9, 10].

Objective

Using a 2D echoCG, to assess the features of LVH, morbidity and the characteristics of clinical and instrumental parameters of various HCM phenotypes.

Materials and Methods

A cross-sectional study was conducted. Analysis covered all diagnosed HCM cases found in the database of a multiprofile inpatient clinic during a period from 2000 to 2022 and medical records of 295 patients (183 males (62 %) and 112 females (38 %)) 18 to 88 years of age (mean age: 60.3 ± 13.4 years) with HCM.

The disease was diagnosed on the basis of 2D echoCG results where one or several LV segments was ≥ 15 mm thick and any other pathological process which could cause hypertrophy was absent [1-3].

Exclusion criteria for the study were: patients with inadequate echo window; stage 2–3 arterial hypertension (systolic blood pressure: > 160 mm Hg, diastolic blood pressure: > 100 mm Hg), stage II–III hypertensive disease; aortic valve stenosis; marked aortic regurgitation, congenital heart disorders; history of active sporting activities within the previous year, clinical, laboratory, morphological data or a history of Anderson Fabry disease Anderson, Danon disease, Friedreich's ataxia, isolated cardiac glycogenosis, cardiac amyloidosis and other infiltrative, endocrine and metabolic diseases which can cause myocardium thickening or hypertrophy.

All patients underwent echoCG using Vivid-3 Pro apparatus (General Electric, USA) with a 3 MHz phase sensor, with the patient lying on the left side, breathing quietly and with the exhalation recommended for transthoracic echoCG by the American Society of Echocardiography (2019) [11].

The thickness of LV segments was measured during diastole, with the sensor oriented perpendicularly to the parasternal long axis (IVS, posterior wall of LV), parasternal short axis (IVS septum, anterior, side and posterior wall of LV), apical axis (2- and 4-chamber position) in order to measure the thickness of myocardium in the LV apex.

The left ventricular myocardium mass (LVMM) was calculated in accordance with the recommendations of the American Society of Echocardiography [12] using the following formula: LVMM = 0.8 x [1.04 x (EDD + PWTd + IVSTd)^3 — EDD^3)] + 0.6 g, where EDD is end-diastolic dimension, PWTd is LV posterior wall thickness, diastolic, and IVSTd is interventricular septum thickness, diastolic.

Left ventricular myocardium mass index (LVMMI) was calculated as follows: LVMMI = LVMM/BSA (g/m^2), where LVMM is body surface area, m^2.

LVOT gradient was calculated using the modified Bernoulli distribution: gradient = 4V^2, where V is the LVOT blood flow velocity (m/s). The blood flow velocity was measured using a constant wave Doppler mode, with the control volume positioned at the LVOT level.

Obstruction at rest was at gradient ≥ 30 mm Hg; obstruction with stimulation was at the normal resting value (< 30 mm Hg) and ≥ 30 mm Hg after physical exercises; no obstruction was observed at a normal value (< 30 mm Hg) both at rest and after physical exercises.

If the thickness of any segment of LV was ≥ 15 mm, hypertrophy localisation and extension were identified. Then patients were divided into 8 groups depending on phenotypic expression of hypertrophy in accordance with the morphological HCM classification [3]: hypertrophy of the basal segment of IVS (group 1), hypertrophy of entire IVS, or neutral IVS (2), reverse curvature hypertrophy of IVS (3), combined hypertrophy of IVS and other segments of LV or RV (4), apical hypertrophy with or without involvement of other LV segments (5), mid-ventricular hypertrophy of IVS with hypertrophic free wall of LV (6), hypertrophy of free wall of LV (7), and symmetric (or concentric) LV hypertrophy (8).

8 phenotypic variants of LVH were compared in groups depending on gender. Mean values of the maximum thickness the hypertrophic myocardium segment,

LVMM, LVMMI, pressure gradient in LVOT were assessed in each of the 8 phenotypic groups of HCM patients; also, the rate of LVOT obstruction was analysed.

Statistical processing and result presentation were performed using licensed Jamovi 2.3.21.0. The values were assessed for correspondence with the normal distribution, and Shapiro-Wilk test was used. The data are presented as a mean arithmetic and standard deviation (M±SD) for values with normal distribution, and as a median with interquartile range (Me (IQR)) for parameters with non-normal distribution. Categorical variables are presented as absolute values and per cents. For intergroup comparison for quality, chi-square (χ^2) was used, while for quantitative comparison, single-factor analysis of variance or Kruskal-Wallis test were used. Results with $p < 0.05$ were statistically significant.

Results

Males prevailed in all phenotypic variants of HCM, except for apical LVH; however, the differences were not statistically significant ($p > 0.05$). Mean disease duration from the first complaint to HCM diagnosis was 10.5±7.52 years. Mean body mass index (BMI) in all patients was 28.2±2.82 mg/m^2.

EchoCG revealed that the most common phenotypic variant is hypertrophy of the basal segment of IVS, which was recorded in 130 (44.1 %) cases (group 1). 47 (15.9 %) patients had reverse curvature hypertrophy of IVS (group 3); 41 (13.9 %) patients — neutral IVS (group 2); 36 (12.2 %) patients — symmetric LVH (group 8); 11 (3.7 %) patients had combined hypertrophy of IVS and other segments of LV or RV (group 4) and hypertrophy of free wall of LV (group 7); 10 (3.4 %) patients — "sand glass" LVH (group 6); and 9 (3.1 %) patients — apical LVH (group 5). Clinical characteristics of patients with HCM divided into phenotypic groups are presented in Figure 1 and Table 1.

Most common complaints were weakness, fatigue in 221 (74.9 %) patients, chest pain and shortness of breath in 202 (68.5 %) patients. Also, patients complained of palpitations, arrhythmias — 133 (45.1 %) patients and dizziness — 118 (40 %) patients. Presyncope and syncope were observed in 27 (9.15 %) patients.

Comorbidities included arterial hypertension in 48 (16.3 %) patients, coronary heart disease (CHD) in 22 (7.46 %) patients, type 2 diabetes mellitus in 61 (20.68 %) patients, cerebrovascular diseases in 67 (22.77 %) patients, thyroid diseases in 38 (12.8 %) patients, and cancer in 6 (2.03 %) patients.

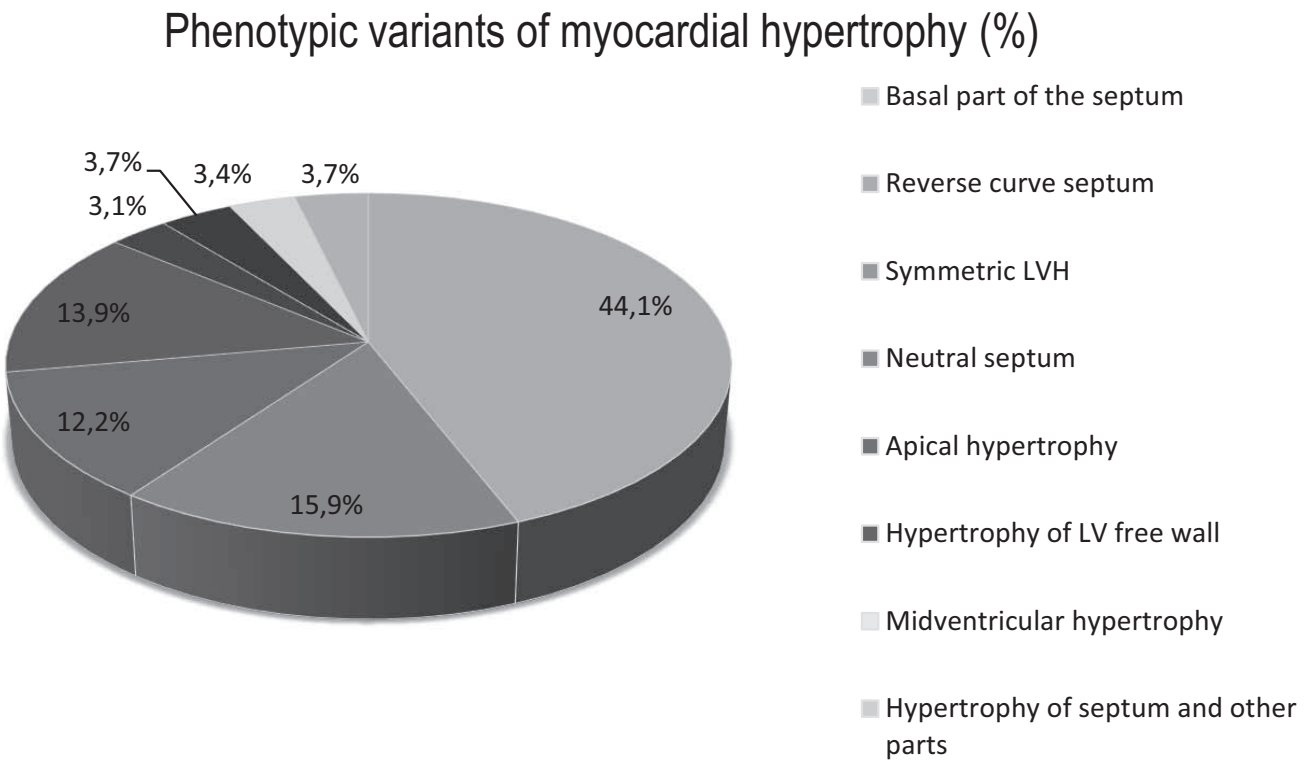

Figure 1. *Prevalence of phenotypic variants of myocardial hypertrophy in patients with hypertrophic cardiomyopathy*
Notes: LV — left ventricle; LVH — LV hypertrophy

Table 1. General characteristic of patients with hypertrophic cardiomyopathy

Parameters	Total (n=295)
Sex, male (%)	183 (62 %)
Age, years, mean±MD	60,3±13,4
Duration of the disease, years §	10,5±7,52
BMI, kg/m², mean±MD	28,2±2,82
Complaints, n (%):	
• Chest pain	202 (68,47 %)
• Dyspnoe	202 (68,47 %)
• Weakness, fatigue	221 (74,91 %)
• Palpitation, heart rate irregularity	133 (45,08 %)
• Dizziness	118 (40,0 %)
• Pre-, syncope	27 (9,15 %)
Concomitant diseases, n (%):	
• Arterial hypertension	48 (16,27 %)
• Coronary artery disease	22 (7,46 %)
• Diabetes mellitus	61 (20,68 %)
• Cardiovascular disease	67 (22,77 %)
• Thyroid disease	38 (12,8 %)
• Malignant disease	6 (2,03 %)
Heart failure	168 (56,95 %)

Note: § — the duration of the disease is considered to be the time from the diagnosis of hypertrophic cardiomyopathy or the presence of severe left ventricular hypertrophy (≥ 15 mm) in the absence of obvious causes that can cause hypertrophy of such severity, and signs of another systemic, metabolic or infiltrative disease

Table 2. Results of electrocardiographic and echocardiographic investigations in patients with hypertrophic cardiomyopathy

Parameters	Total, n (%)	Variant 1	Variant 2	Variant 3	Variant 4	Variant 5	Variant 6	Variant 7	Variant 8
	295 (100)	130 (44,1)	41 (13,9)	47 (15,9)	11 (3,7)	9 (3,1)	10 (3,4)	11 (3,7)	36 (12,2)
Electrocardiography									
Sinus rhythm, n	204 (69,15)	87 (42,64)	24 (11,76)	36 (17,65)	8 (3,92)	5 (2,45)	6 (2,94)	10 (4,90)	27 (13,24)
	in % to group	87 (66,92)	24 (58,54)	36 (76,60)	8 (72,73)	5 (55,56)	6 (60,0)	10 (90,91)	27 (75,0)
Atrial fibrillation, n	91 (30,84)	43 (47,25)	17 (18,68)	11 (12,08)	3 (3,29)	4 (4,39)	4 (4,39)	1 (1,09)	9 (9,89)
	in % to group	43 (33,08)	17 (41,46)	11 (23,40)	3 (27,27)	4 (44,44)	4 (40,0)	1 (9,09)	9 (25,0)
AV-blocks, n	31 (10,5)	14 (45,16)	5 (16,13)	5 (16,13)	2 (6,45)	0	0	2 (6,45)	3 (9,68)
	in % to group	14 (10,77)	5 (12,20)	5 (10,64)	2 (18,18)	0	0	2 (18,18)	3 (8,33)
Intraventricular conduction blocks, n	122 (41,36)	55 (45,08)	15 (12,30)	21 (17,21)	2 (1,64)	5 (4,10)	8 (6,56)	3 (2,46)	13 (10,66)
	in % to group	55 (42,31)	15 (36,59)	21 (44,68)	2 (18,18)	5 (55,56)	8 (80,0)	3 (27,27)	13 (36,11)
Pseudo-infarction Q, n	59 (20)	30 (50,85)	10 (16,95)	5 (8,47)	3 (5,08)	1 (1,69)	3 (5,08)	3 (5,08)	4 (6,78)
	in % to group	30 (23,08)	10 (24,39)	5 (10,64)	3 (27,27)	1 (11,11)	3 (30,0)	3 (27,27)	4 (11,11)
QRS fragmentation, n	18 (6,1)	8 (44,44)	0	4 (22,22)	2 (11,11)	0	1 (5,56)	0	3 (16,67)
	in % to group	8 (6,15)	0	4 (8,51)	2 (18,18)	0	1 (10,0)	0	3 (8,33)
T inversion in precordial leads, n	236 (80)	100 (42,37)	36 (15,25)	41 (17,37)	7 (2,97)	7 (2,97)	9 (3,81)	8 (3,39)	28 (11,86)
	in % to group	100 (76,92)	36 (87,80)	41 (87,23)	7 (63,64)	7 (77,78)	9 (90,0)	8 (72,73)	28 (77,78)
Prolonged QTc, n	14 (4,75)	5 (35,71)	2 (14,29)	1 (7,14)	2 (14,29)	0	1 (7,14)	1 (7,14)	2 (14,29)
	in % to group	5 (3,85)	2 (4,88)	1 (2,13)	2 (18,18)	0	1 (10,0)	1 (9,10)	2 (5,56)
Amplitude signs of LV hypertrophy, n§	213 (72,2)	93 (43,66)	27 (12,68)	33 (15,49)	7 (3,29)	7 (3,29)	8 (3,76)	9 (4,23)	29 (13,61)
	in % to group	93 (71,54)	27 (65,85)	33 (70,21)	7 (63,64)	7 (77,78)	8 (80,0)	9 (81,82)	29 (80,56)

Table 2. (The end)

Parameters	Total, n (%)	Variant 1	Variant 2	Variant 3	Variant 4	Variant 5	Variant 6	Variant 7	Variant 8
	295 (100)	130 (44,1)	41 (13,9)	47 (15,9)	11 (3,7)	9 (3,1)	10 (3,4)	11 (3,7)	36 (12,2)
Echocardiography									
Mitral valve insufficiency, n	85 (28,81)	30 (35,29)	16 (18,82)	14 (16,47)	3 (3,53)	4 (4,71)	4 (4,71)	2 (2,35)	12 (14,12)
	in % to group	30 (23,08)	16 (39,02)	14 (29,79)	3 (27,27)	4 (44,44)	4 (40,0)	2 (18,18)	12 (33,33)
Diastolic dysfunction, n	235 (79,66)	106 (45,11)	32 (13,62)	37 (15,74)	7 (2,98)	7 (2,98)	7 (2,98)	10 (4,26)	29 (12,34)
	in % to group	106 (81,54)	32 (78,05)	37 (78,72)	7 (63,64)	7 (77,78)	7 (70,0)	10 (90,91)	29 (80,56)
Pulmonary artery pressure, mm Hg	25 (20,5-31)	24 (22-30)	25 (22-38)	24 (20-31,5)	25 (19,5-29,5)	25 (24-30)	23,5 (22,3-25)	21 (18-27)	24,5 (19-35)
EDV, ml	149 (116-184)	145 (115-175)	162 (109-189)	168 (132-201)	113 (97,5-178)	148 (143-168)	186 (146-222)	163 (126-186)	148 (124-177)
ESV, ml	56 (40-71,0)	55 (38,5-65)	58,5 (46-76)	63,1 (44-76,5)	43 (28,5-73)	65 (56-71)	47,5 (39,5-62,5)	58 (34,5-63)	54 (43,8-66,8)
Stroke volume, ml	91,2 (73,5-114)	90,5 (69-110)	87 (68-109)	94,6 (83,5-127)	75 (67,1-104)	94,6 (86-98)	108 (101-133)	113 (79,5-125)	90 (81,3-112)
Ejection fraction, %	64 (56,5-69,6)	64 (55-70)	61 (50,8-67,9)	64 (57,1-69)	68 (61,5-73,5)	60,1 (55-64)	69,6 (68,4-73,3)	67 (65-68,6)	62,5 (57-72,3)
Mean maximal thickness of hypertrophied myocardium, mm (Me (IQR))	17,8 (16,4-19,0)	16,9 (16-18,2)	18,0 (16,4-19,3)	18,0 (16,6-19,3)	18,7 (18,2-19,3)	19,1 (18,0-20,1)	19,3 (19,0-20,4)*	18,6 (16,4-19,5)	18,0 (16,9-19,0)
Obstruction of left ventricular outflow tract, n	183 (62,03)	83 (45,36)	27 (14,75)	25 (13,66)	9 (4,92)	2 (1,09)	9 (4,92)	0	28 (15,30)
	in % to group	83 (63,84)	27 (65,85)	25 (53,19)	9 (81,81)	2 (22,22)*	9 (90,0)	0	28 (77,78)
Rest gradient, mm Hg (Me (IQR))	20,0 (8,50-36,0)	20,8 (8,50-35,0)	17,0 (9,0-32,0)	15,0 (5,0-35,0)	23,0 (16,3-44,0)	6,50 (3,50-15,5)*	39,5 (35,6-42,8)	11,0 (6,0-11,5)	25,8 (13,9-38,0)
MMLV, g (Me (IQR))	345 (284-411)	349 (284-400)	363 (297-421)	338 (270-390)	290 (273-336)	280 (234-288)	342 (282-376)	317 (257-369)	402 (356-439)*
MMLVI, g/m2 (Me (IQR))	168 (143-202)	169 (141-200)	187 (150-204)	164 (133-200)	146 (142-152)	138 (127-152)	163 (138-197)	151 (129-164)	195 (173-218)*
Left atrium, mm	4,52 (4,17-4,97)	4,50 (4,10-4,98)	4,60 (4,10-5,10)	4,40 (4,07-4,81)	4,58 (4,30-5,0)	4,78 (4,39-5,11)	4,58 (4,46-4,70)	4,33 (4,10-4,65)	4,63 (4,30-4,91)

Notes: AV — atrioventricular; LV — left ventricle; EDV — end-diastolic volume; ESV — end-systolic volume; MMLV — LV myocardial mass; MMLVI — MMLV index. Variant 1 — hypertrophy of the basal part of the septum; 2 — hypertrophy of the entire septum ("neutral" septum); 3 — hypertrophy of the septum "reverse curve"; 4 — combined hypertrophy of the septum and other parts of the left (LV) or right ventricle; 5 — apical hypertrophy of the LV; 6 — mid-ventricular hypertrophy of the LV with hypertrophy of the free LV wall; 7 — hypertrophy of the free LV wall; 8 — symmetrical (or concentric) LV hypertrophy. Values are mean ± standard deviation, n (%) or median (interquartile range). * p <0.05 in comparison with intergroup values; § — amplitude signs of LV hypertrophy were determined by Cornell and/or Sokolow-Lyon voltage criteria

EchoCG results were used to analyse the correlation of the most marked LV myocardium hypertrophy depending on the phenotypic variant (Table 2). The most marked hypertrophy (mean values) demonstrated statistically significant differences (p = 0.003) depending on the phenotypic variant: patients with mid-ventricular hypertrophy of IVS with hypertrophic free wall of LV (group 6) — 19.3 (IQR: 19.0-20.4) mm, 19.1 (IQR: 18.0-20.1) mm (group 5), 18.7 (IQR: 18.2–19.3) mm (group 4), 18.6 (IQR: 16.4–19.5) mm (group 7), 18.0 (IQR: 16.6–19.3) mm (group 3), 18.0 (IQR: 16.9–19.0) mm (group 8), 18.0 (IQR: 16.4–19.3) mm (group 2), 16.9 (IQR: 16.0–18.2) mm (group 1) (Figure 2).

The correlation between the presence and type of obstruction in the middle section of LV and LVOT (both at rest and after stimulation) and a certain morphological phenotype of myocardial hypertrophy was studied. The most common was mid-ventricle obstruction (MVO) in group 6 — 9 (90.0 %) patients; LVOT obstructions were observed more often in group 4 — 9 (81.8 %) patients and group 8 — 28 (77.8 %) patients; more rarely in group 5 — 2 (22.2 %) patients; the difference was statistically significant at p < 0.01. Patients in group 7 (hypertrophy of free wall of LV) did not have basal LVOT obstructions.

Comparison of gradients at rest also revealed differences, depending on the LVH phenotype: the highest values were observed in group 6 — 39.5 (IQR: 35.6–42.8) mm Hg, while the lowest values were recorded in group 5 — 6.50 (IQR: 3.50–15.5) mm Hg (p < 0.01). The gradient distribution is presented in Figure 3.

LVMM values had their own peculiarities: the lowest values were recorded in group 5 — 280 (IQR: 234–288) g, while the highest values were recorded in group 8 — 402 (IQR: 356–439), the difference was statistically significant at p < 0.01.

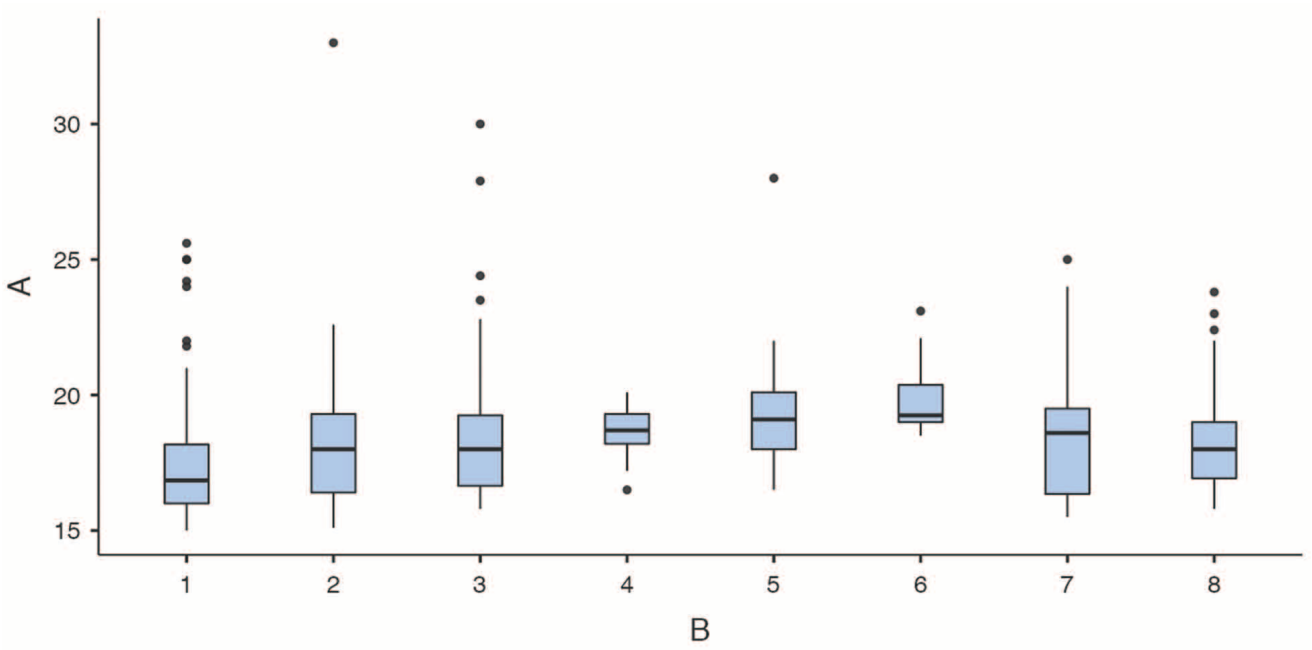

Figure 2. *Medians and quartiles of maximum thickness of hypertrophied myocardium in different phenotypic variants of left ventricular hypertrophy. A — myocardial thickness, mm. B — phenotypic variant, group number (p=0.003)*

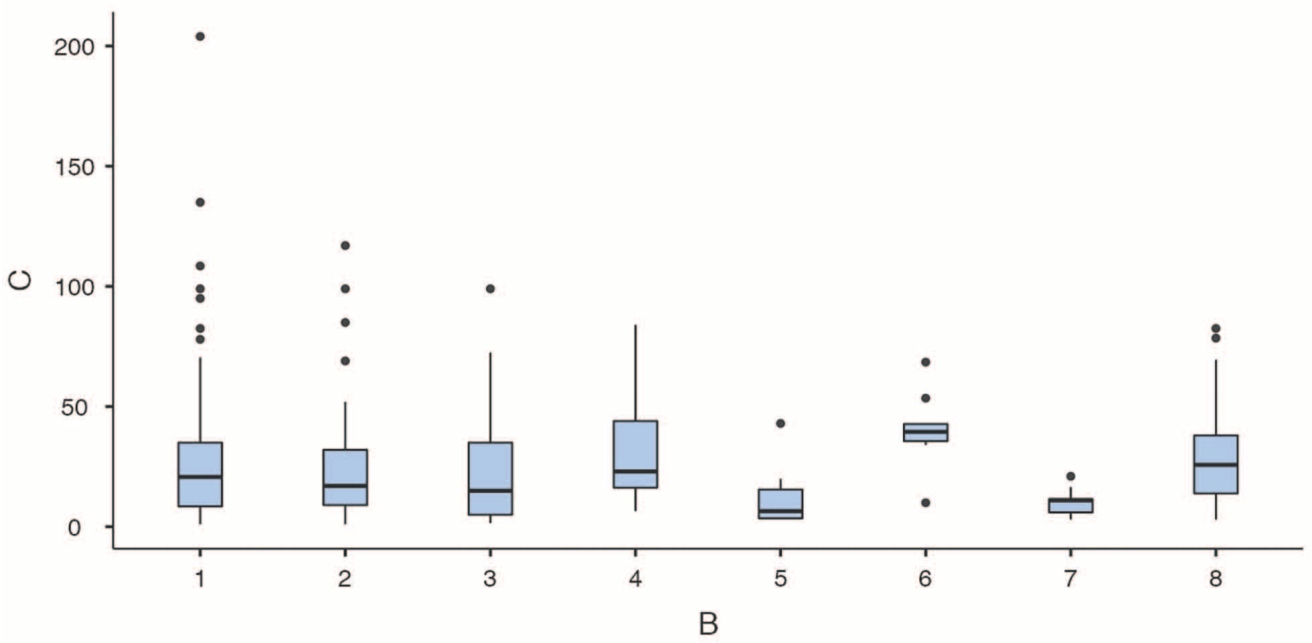

Figure 3. *Medians and quartiles of rest gradient values in different phenotypic variants of left ventricular hypertrophy. C — gradient, mm Hg, B — phenotypic variant, group number (p <0.01)*

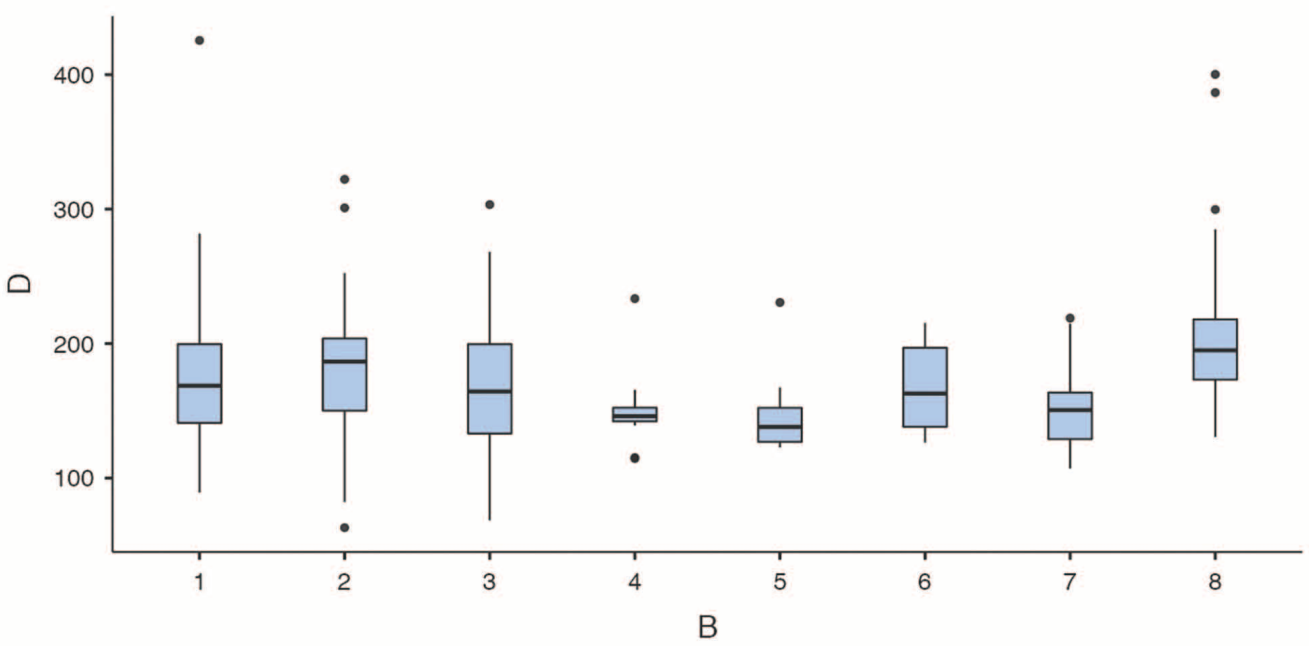

Figure 4. *Medians and quartiles of left ventricular myocardium mass index in different phenotypic variants of left ventricular hypertrophy. D — left ventricular myocardial mass index, g/m², B — phenotypic variant, group number (p <0.01)*

Like LVMM, the highest LVMMI values were observed in group 8 — 195 (IQR: 173–218) g/m², and the result was statistically more significant vs. other LVH phenotypes (p < 0.01) (Figure 4).

Discussion

After the introduction of 2D echoCG and, later, of heart MRI for HCM diagnosis, various phenotypes of myocardial hypertrophy can now be distinguished. In 1981, B.J. Maron et al. proposed four LVH patterns in this pathology: LVH limited to the anterior section of IVS (type 1); hypertrophy of anterior and posterior section of IVS (type 2); combined IVS hypertrophy and free wall of LV (type 3), and variants of anterior wall of IVS and other LV walls (type 4) [13]. Later H.G. Klues et al. [7] separated concentric and apical LVH, however, the share in the total number of patients was low. The authors identified 12 LVH patterns in 600 patients with HCM. Besides, they found out that in a majority of cases (71.7 %) hypertrophy involves two and more segments of myocardium; 34 % of patients had ≥ 3 segments affected, thus confirming that the pathological process is mostly diffuse [7]. I.S. Syed et al. [6] analysed IVS hypertrophy variants and identified its sub-types: reverse curvature, neutral and sigmoid.

With the understanding of the genetic and clinical heterogeneity of HCM and with the advent of highly informative imaging methods, the knowledge of a variety of myocardial hypertrophy phenotypes extended. MRI, a diagnostic method with high space resolution, ensures complete reconstruction of LV chamber and makes it possible to more precisely identify the presence, intensity and extent of myocardial hypertrophy. M.S. Maron et al. [14] used MRI results to present an abundance of morphological variants of HCM in 333 patients. The authors mentioned that myocardial hypertrophy in this condition is usually segmental. Generally, one or several LV segments are thicker than other, with a marked difference in the point where the thickness changes. Some patients present with fragmented patterns of segmental hypertrophy and LV wall involvement. According to the authors, none of the morphological forms of HCM is a classic or typical one; however, all researchers agree that IVS hypertrophy is prevailing [7].

Literature sources do not provide any common classification of HCM phenotypes. Researchers are of the opinion that any classification fails to highlight the diversity of the forms of hypertrophy in this disease. The ease of classification use in clinical practice by functional healthcare providers and cardiologists should be taken into account as well. On the other hand, it would be advantageous

to study the phenotypical variety with an assessment of constitutional, anamnestic data and the relation to other clinical and laboratory parameters. According to the Recommendations for HCM [3] developed by experts of the Ministry of Health of Russia, there are eight morphological types of cardiomyopathies which we use in our study; they are based on echoCG results of 295 patients. Russian experts thoroughly studied the information on HCM phenotypes and prepared their recommendations taking into account the abundance of hypertrophy patterns. The proposed classification covers asymmetric and symmetric forms of the disease. Diagnosing symmetric or concentric LVH is often challenging as regards result interpretation, provided that this hypertrophy variant is typical of secondary hypertrophy and for various HCM phenocopies [15, 16].

Despite the various available classifications of HCM phenotypes, their prevalence in patients has not been established yet. The published echoCG study results [6, 7, 17, 18, 43] for the prevalence of phenotypes in this cardiomyopathy are based on the classification taking into account morphological variants of IVS and describe 4–5 patterns. With the introduction of heart MRI, it is now possible to find areas of local myocardial hypertrophy due to better space imaging as compared to echoCG [14, 15, 19–21]. In recent years, extended classifications of phenotypes in HCM have been proposed, which include basal IVS hypertrophy, diffuse IVS hypertrophy (neutral type), concentric HCM, mid-ventricle hypertrophy, apical HCM, hypertrophy of free LV wall [3, 20, 21]. However, there are limited data on the rate of these phenotypes in HCM. Thus, our study presents information related to the prevalence and morphological features of various phenotypic variants in HCM using 2D echoCG in a relatively large group of patients.

When patients were divided into groups depending on prevalence of a hypertrophic expression phenotype, it was found out that 130 (44.1 %) patients had basal IVS hypertrophy. Reverse curvature IVS hypertrophy was observed in 47 (15.9 %) patients, neutral IVS hypertrophy and concentric hypertrophy was recorded in 41 (13.9 %) and 36 (12.2 %) patients, respectively. Phenotypes with IVS hypertrophy combined with other sections of LV and RV and hypertrophy of free LV wall — 11 (3.7 %) patients, hypertrophy of middle section of IVS and free LV wall — 10 (3.4 %) patients and apical LV hypertrophy — 9 (3.1 %) patients — were rare (Figure 1). Therefore, most often hypertrophy was limited to IVS (218 cases, 73.9 %), and the most common phenotype was basal IVS hypertrophy.

Analysis of results of previous studies of prevalence of HCM phenotypes demonstrated that the most common pattern is anterior septal hypertrophy and hypertrophy of entire IVS (neutral type) [2, 6–8, 22]. Probably, rare observation of hypertrophy of anterior, anteriolateral LV wall (group 7) in our study is due to the limited capabilities of 2D echoCG in the location of these walls and space imaging of all myocardial segments [23].

Out of 295 patients with HCM in our study, 183 (62 %) patients were males, like in the majority of studies, where male subjects prevail [1, 24]. According to a number of scientists, a higher share of male subjects is a result of a lower level of diagnosis in women, for whom correct diagnosis is less frequent, than gender predisposition of men to HCM [25].

Mean patient BMI was 28.2±2.82 kg/m^2. In other words, the patients were overweight. The papers on the impact of BMI on the course and clinical manifestations of HCM note that overweight is associated with a higher phenotypical expression of cardiomyopathy [26]. Researchers believe that BMI in HCM has a U-shape correlation with hospital mortality: underweight patients and patients with stage III obesity had significantly higher mortality rates. At the same time, patients with stage I and II overweight (preobesity) demonstrated lower mortality compared to patients with normal BMI [17]. According to our information, there were no significant differences in BMI in phenotypic groups.

Patients with HCM may have no complaints, thus complicating timely diagnosis [27]. The main symptoms of this disease are caused by the four major pathophysiological disorders: diastolic dysfunction, LVOT obstruction, imbalance between oxygen supply and demand by myocardium, and arrhythmias [4]. Usually, patients with HCM complain of shortness of breath during physical activities, chest pain, dizziness, presyncope and syncope, and palpitations/arrhythmias [3, 21]. In our study, most often patients complained of chest pain and shortness of breath (202 patients, 68.8 %), weakness, fatigue (n = 221, 74.9 %), palpitations/arrhythmias (n = 133, 45.1 %), and dizziness (n = 118, 40 %). Presyncope and syncope were recorded in 27 patients (9.15 %).

In our study, the maximum thickness of hypertrophic myocardium was statistically higher in group 6 (mid-ventricular hypertrophy of IVS with hypertrophic free wall of LV): 19.3 (IQR: 19.0–20.4) mm, while the minimum myocardium thickness was observed in group 1: 16.9 (IQR: 16.0–18.2) mm. These values correlate with mean values observed in other studies (20–21 mm) [9, 28, 29]. It is assumed that higher hypertrophy intensity can be associated with a more unfavourable prognosis [15]. Besides, assessment of the thickness and changes in phenotype are of clinical and scientific interest [9].

In our study, prevalence of mid-ventricle hypertrophy ("sand glass" type) was low and was recorded in 10 (3.4 %) patients. Patient examination showed that mid-ventricle obstruction was found in 9 out of 10 cases (90 %) in group 6 (mid-ventricular hypertrophy of IVS with hypertrophic free wall of LV), demonstrating that practically all patients with mid-ventricular IVS hypertrophy have MVO. According to literature sources, MVO is observed nearly in 10 % of patients with HCM [30]. It is assumed that patients with MVO have a higher risk of progressive cardiac failure and sudden cardiac death [1, 30]. Approximately 25 % of cases are accompanied by formation of apical LV aneurysms which are associated with a higher rate of cardiovascular mortality [30]. In our study, none of patients had an apical aneurysm.

In general, the results of our work confirm the idea of HCM as a disease which is mostly obstructive: MVO and LVOT obstruction was observed in 182 (62 %) patients. LVOT obstruction was most common in group 4 (n = 9, 81.8 %) and group 8 (n = 28, 77.8 %). Most often LVOT obstruction was observed in patients with various phenotypes of isolated LV hypertrophy (groups 1–3), and in group 5 (n = 2, 22.2 %) and group 7 (n = 0) it was quite rare.

LVOT obstruction is recorded approximately in 2/3 of patients with HCM [1–4]. It is assumed that it is caused by the two main mechanisms: IVS hypertrophy with narrowed LVOT, creating conditions for abnormal blood flow, and anatomical changes in MV and subvalvular structures, including cusp elongation, anterior displacement of papillary muscles, making MV more susceptible to pathologically oriented vectors of systolic blood flow [2].

When assessing LVMM and LVMMI values, it is essential to take into account that usually HCM is associated with asymmetric LVH. LVMM and LVMMI are calculated with the help of thickness of IVS, posterior LV wall (diastolic) and end-diastolic dimension [12]. That is why the values of parameters in symmetric (or concentric) LVH is quite relative when assessing hypertrophy intensity. For instance, in apical HCM these values can be within a normal range, while limited basal IVS hypertrophy can present with higher LVMM and LVMMI values. According to the results of our study, LVMM and LVMMI values for all patients and within groups were normal. The lowest values were recorded in group 5 and the highest values were observed in group 8 (concentric hypertrophy) (Table 2). Taking into account the low significance of traditionally calculated LVMM and LVMMI values in HCM, special systems for assessment of LVH intensity were proposed which are based on determination of the number of hypertrophic segments and myocardium thickness [31].

Study Limitations

Study limitations are a result of a mostly retrospective nature of our study. The results are based on 2D echoCG, which is readily available and informative, but cannot visualise all sections of myocardium. In some patients, examination is obstructed by constitutional characteristics, chest shape and pulmonary diseases. Compared to MRI, echoCG is incapable of comprehensive assessment of free LV wall, anterior and lateral LV wall as well as apical area. Besides, a major disadvantage is reduced accuracy in wall thickness measurement due to inadequate distinction of endocardial surface and cardiac cavity and occasional oblique sections which distort measurement results.

We are unable to study the presence and characteristics of genetic mutations of sarcomere proteins and to compare results with phenotypical manifestations. Genetic testing is an additional method of examination of patients with HCM, the results of which allow diagnosing disease where myocardial hypertrophy is below the diagnostic level (13–14 mm) and is an important stage in differential diagnosis of HCM and its phenocopies.

Conclusion

This study conducted in a representative cohort using 2D echoCG allowed assessing prevalence and characteristics of phenotypes of hypertrophic expression in HCM. EchoCG makes it possible to assess the myocardial thickness, presence and localisation of hypertrophy, to identify the main phenotypic variants of the disease. The most common is isolated IVS hypertrophy, with prevailing basal IVS hypertrophy. Very common are phenotypes of IVS hypertrophy with reverse curvature, hypertrophy of entire IVS and concentric LV hypertrophy.

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Игнатенко Г.А. (ORCID ID: https://orcid.org/0000-0003-3611-1186): интеграция авторского коллектива, разработка концепции, дизайна исследования, окончательное редактирование и утверждение рукописи

Тарадин Г.Г. (ORCID ID: https://orcid.org/0000-0003-3984-8482): выполнение исследования, анализ и интерпретация данных, обзор литературных данных; согласие автора быть ответственным за все аспекты работы

Куглер Т.Е. (ORCID ID: https://orcid.org/0000-0001-5547-6741): выполнение исследования, сбор, анализ и интерпретация данных, представление результатов исследования, статистический анализ данных, оформление рукописи

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Ignatenko G.A. (https://orcid.org/0000-0003-3611-1186): alignment of author team, development of the concept, study design, the final editing and approval of the manuscript

Taradin G.G. (https://orcid.org/0000-0003-3984-8482): performing of the study, analysis and interpretation of data, review of literature sources; agreement of author to be responsible for all aspect of the work

Kugler T.E. (https://orcid.org/0000-0001-5547-6741): performing of the study, data collection, analysis and interpretation of data, presentation of study results, statistical analysis of data; execution of the manuscript

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Д.А. Вишняк*[1,2], А.Х. Каримова[2], Ю.А. Кулай[2], М.В. Чернобай[1], В.Р. Кофеева[2], Г.М. Хайруллина[2], Э.Т. Муллаярова[2], А.Г. Исаева[2]

[1] — БУ ВО образования Ханты-Мансийского автономного округа-Югры «Сургутский государственный университет», кафедра внутренних болезней, Сургут, Россия
[2] — БУ Ханты-Мансийского автономного округа-Югры «Сургутская окружная клиническая больница», нефрологическое отделение, клинико-диагностическая поликлиника, Сургут, Россия

УСПЕШНОЕ ВЫНАШИВАНИЕ БЕРЕМЕННОСТИ ПРИ ТЕРМИНАЛЬНОЙ ПОЧЕЧНОЙ НЕДОСТАТОЧНОСТИ: МИФ ИЛИ РЕАЛЬНОСТЬ (НА ПРИМЕРЕ КЛИНИЧЕСКОГО НАБЛЮДЕНИЯ)

D.A. Vishnyak*[1,2], A.H. Karimova [2], Yu.A. Kulai [2], M.V. Chernobai [1], V.R. Kofeeva [2], G.M. Khairullina [2], E.T. Mullayarova [2], A.G. Isaeva [2]

[1] — Surgut State University, Surgut, Russia
[2] — Surgut District Hospital, Surgut, Russia

Successful Pregnancy with Terminal Renal Failure: Fiction or Reality (on the Example of Clinical Observation)

Резюме

195 миллионов женщин на Земле страдают от хронической болезни почек, что не препятствует им планировать материнство. Даже у абсолютно здоровых женщин беременность сопряжена с рисками. Эти риски увеличиваются, когда речь заходит о патологии почек. Известно, что беременность у женщин с заболеваниями почек даже при сохранной почечной функции сопровождается серьезными проблемами как для матери, так и для плода. Нами представлено клиническое наблюдение успешно выношенной беременности пациентки 23-х лет, имеющей терминальную почечную недостаточность. Коморбидность пациентки (хроническая болезнь почек, язвенный колит, анемия и др.) требовало комплексной терапии и междисциплинарного подхода, что было реализовано с первых дней наблюдения женщины. Высокопрофессиональная работа команды специалистов (нефрологи, реаниматологи, акушеры-гинекологи, гастроэнтерологи, инфекционисты, врачи функциональной диагностики, урологи и др.) определила успешный исход настоящего наблюдения. В статье расставлены акценты на факторах, отягощающих течение данного наблюдения, а также имеющих благоприятное влияние на исход.

Ключевые слова: *хроническая болезнь почек, беременность, гемодиализ, заместительная почечная терапия*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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*Контакты: Диана Анатольевна Вишняк, e-mail: Diana100187@yandex.ru
*Contacts: Diana A. Vishnyak, e-mail: Diana100187@yandex.ru
ORCID ID: https://orcid.org/0000-0002-8473-5930

ния города Москвы «Городская клиническая больница имени А.К. Ерамишанцева Департамента здравоохранения города Москвы» в лице профессора, д.м.н. Козловской Натальи Львовны, Бюджетному учреждению Ханты-Мансийского округа-Югры «Окружная клиническая больница» в лице к.м.н., главного внештатного нефролога ХМАО-Югры Пьянкиной Оксаны Владимировны за сотрудничество и оказанную помощь на всех этапах ведения пациентки, а также к.м.н., главному врачу Сургутской окружной клинической больницы Шестаковой Галине Никандровне, заведующему Центром диализа Сургутской окружной клинической больницы Малашенко Сергею Михайловичу и всем специалистам Центра диализа, где пациентка получала и продолжает получать помощь, главному акушер-гинекологу Сургутской окружной клинической больницы Денисовой Ольге Леонидовне и специалистам Бюджетного учреждения Ханты-Мансийского автономного округа-Югры «Сургутский окружной клинический центр охраны материнства и детства», а также всем докторам, консультирующим и наблюдающим пациентку, мультидисциплинарная высококомпетентная помощь которых определила успешный исход настоящего наблюдения.

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Abstract

195 million women on Earth suffer from chronic kidney disease — some of them are planning to become mothers. Even in absolutely healthy women, pregnancy is fraught with risks. These risks increase when it comes to kidney pathology. It is known that pregnancy in women with kidney diseases, even with preserved renal function, is accompanied by serious problems for both the mother and the fetus. We present a clinical observation of a 23-year-old patient with terminal renal insufficiency who successfully carried out the pregnancy. The patient's polymorbid condition (chronic kidney disease, ulcerative colitis, anemia, etc.) required complex therapy and an interdisciplinary approach, which was implemented from the first days of the woman's observation. The highly professional work of a team of specialists (nephrologists, resuscitators, obstetricians-gynecologists, gastroenterologists, infectious disease specialists, functional diagnostics doctors, urologists, etc.) determined the successful outcome of this observation. The article focuses on the factors aggravating this observation, as well as determining, on the contrary, a favorable outcome.

Key words: *chronic kidney disease, pregnancy, hemodialysis, renal replacement therapy*

Conflict of interests

The authors declare no conflict of interests

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CKD-EPI — Chronic Kidney Desease Epidemiology Collaboration, Hb — hemoglobin, Fe — serum iron, AV — arteriovenous fistula, IBD — inflammatory bowel disease, RRT — replacement renal therapy, BMI — body mass index, LK — left kidney, MBD — mineral and bone disorders, NCVI — novel coronavirus infection Sars-CoV2, LMH — low molecular heparin, NMRC — National Medical Research Center, TSI — transferrin saturation with iron, RK — right kidney, TIBC — total iron-binding capacity, PTH — parathyroid hormone, PU — proteinuria, eGFR — estimated glomerular filtration rate, PT — parenchyma thickness, ESRD — end stage renal disease, US — ultrasonic examination, CKD — chronic renal disease, UC — ulcerative colitis

Introduction

195 million of women all over the earth suffer from chronic kidney disease (CKD); however, it does not prevent them from planning pregnancy. The incidence of stage 1, 2 and 3 CKD in women of childbearing age is at least 3 %, while the incidence of stage 3–5 CKD is approx. 0.6–0.7 % [1, 2].

For the first time, a successful pregnancy in a hemodialysis female patient was described by P. Confortini et al. (1971). The authors described a 35-year-old woman who carried pregnancy to term and gave birth to a 1950 g infant, the woman was undergoing hemodialysis for 24 hours weekly [3].

While earlier a pregnancy in kidney insufficiency patients was no less than a miracle and a rare event, now this scenario is possible; there are more and more foreign and Russian authors describing epidemiology, outcomes and management of pregnancies in CKD

patients, as well as in patients with end stage renal disease (ESRD) who undergo replacement renal therapy (RRT) [4, 5, 11, 19, 21]. The rate of success of such pregnancies increased from 25 % in 1980s to over 80–90 % at the present time [3]. In the Australia and New Zealand Dialysis and Transplant Registry, the rate of pregnancies in such patients was 3.3 per 1000 patient/year in 1996–2008 vs. 0.54 and 0.67 in 1976–1985 and 1986–1995, respectively [6, 7].

In 2022, the search for "pregnancy with chronic kidney disease" in the PubMed returned 2755 publications. In 1955–2022, the number of manuscripts on this topic grew, with the majority of articles, reviews, case studies falling on the recent decade. In Russia, there are still very few publications describing such cases, with a majority of publications (both in Russia and abroad) being dedicated to pregnancies in pre-dialysis CKD patients. Publications about the features of pregnancies in women undergoing RRT can be counted on one hand.

It is obvious that introduction of dialysis was revolutionary for the management of patients with end stage renal disease; however, this method does not allow to fully recover and restore a number of normal physiologic processes, including reproductive function. Despite numerous advances, pregnancies in women undergoing dialysis are rare and are high risk. Currently, it is acknowledged that all forms of early CKD are associated with a higher risk of unfavourable pregnancy outcomes, and it is true even for such basic conditions as a history of stone disease, underlying acute kidney injury or stage 1 CKD [8, 9].

According to the 2011 systematic review, the rate of unfavourable maternal outcomes in CKD patients was 11.5 %, i. e., more than 5 times higher than in healthy women (2 %) [1, 2]. The real incidence of pregnancy complications in pregnant women with CKD can be significantly underestimated [1]. The rate of complications grows with the renal function deterioration. In 1950, perinatal mortality in a group of patients with serum creatinine of 132.5–265 μmol/L was 58 %, while with creatinine of > 265 μmol/L the mortality was 100 %, by 1980, the rates decreased to 10 % and 53 %, correspondingly. According to the 1985–2007 data, perinatal mortality in women with serum creatinine of 125–180 μmol/L was 5 %, with persistent postpartum loss of renal function of over 25 % vs. the baseline value (20 %), the incidence of ESRD one year after delivery was 2 %. With an increase in plasma creatinine to > 180 μmol/L, these values increased to 10 %, 50 % and 35 %, respectively [10].

Therefore, pregnancy management of patients undergoing the replacement therapy with long-term hemodialysis is a current problem of the modern healthcare, the nephrological point of view of which is described in the case study below.

Clinical Case Report

Patient M., 23 years of age. Born in Tajikistan. G1.

Upon admission to the Nephrology Unit of the Budgetary Institution of the Khanty-Mansiysk Autonomous Region — Yugra Surgut Regional Clinical Hospital in November 2021, the pregnant patient complained of marked fatigue.

The medical record shows that in June 2018 the patient had loose stool up to 10 times a day with otherwise satisfactory condition, accompanied by non-specific mild extended abdominal pains. She consulted a GP at the place of her residence. An examination revealed abnormal laboratory findings: mild anemia (Hb 98–103 g/L), hyperazotemia (urea 13.7–14 mmol/L, createnine 297–308 μmol/L), reduced Chronic Kidney Desease Epidemiology Collaboration (CKD-EPI) estimated glomerular filtration rate (eGFR) up to 15.9 mL/min, GFR (Rehberg Test) — 12 mL/min, hyperuricemia (384 μmol/L), spot urine proteinuria (PU) 300 mg/L, microscopic hematuria, sclerotic kidney (right kidney — 70*37 mm, parenchyma thickness — 11 mm, left kidney — 69*41 mm, parenchyma thickness — 11 mm), renal cysts, evidencing a chronic kidney pathology and criteria for CKD diagnosis. During examination, differential diagnosis included primary and secondary glomerulopathy, abnormal urinary system development. Sclerotic kidney was a contraindication for renal biopsy [11] and hindered verification of the true cause of ESRD in this case study.

Taking into account that the patient was complaining mostly of GIT problems, she was treated in the Gastroenterology Unit. An endoscopic examination revealed pathognomonic signs of inflammatory bowel disease (IBD). Biopsy material morphology confirmed ulcerative colitis. Baseline therapy with mesalamine was initiated. During the inpatient treatment and examination in the Nephrology Unit, consistent results were obtained. After discharge, the patient was dynamically followed up by the Centre for IBD and CKD Office of the Surgut Regional Clinical Hospital. Of note, medical records for this period are not complete.

This pregnancy started in August 2021 without any sound pre-conceptional preparation. First visit to the maternity welfare clinic was on time.

Upon physical examination the following findings were obtained: height — 153 cm, weight — 35 kg, body mass index (BMI) — 14.9 kg/m^2; skin of lower limbs with areas of hyperkeratinization (fish-skin disease); according to the patient, diuresis is normal (1500–2500 mL/day). During the follow-up period, blood pressure was normal and did not require management with medicines.

Upon examination during hospitalisation into a specialised unit because of a first pregnancy and concomitant somatic pathology (IBD) in September–October 2021 on

week 4–8 of gestation, the negative laboratory parameters were evidencing condition severity: Hb — 80–100 g/L; serum iron (Fe) — 5.3 μmol/L; total iron-binding capacity (TIBC) — 46 μmol/L; transferrin saturation with iron (TSI) — 11.5 %; creatinine — 305–415 μmol/L; urea — 13–17 μmol/L; GFR (Rehberg Test) — 12 mL/min; vitamin D — 13 ng/mL; parathyroid hormone (PTH) — 608 ng/mL; albumin-adjusted Ca — 1.18 mmol/L; phosphorus — 1.47–1.93 mmol/L. Anemia was treated in accordance with clinical guidelines for anemia in chronic kidney disease patients, taking into account iron exchange parameters and blood count. The patient received ferric carboxymaltose to correct iron deficit. Once iron levels were normal, alpha-1-erythropoietin (erythropoiesis-stimulating agent) was added to the therapy. The obstetrician-gynaecologist recommended acetylsalicylic acid and magnesium hydroxide starting from week 12 of pregnancy.

It is obvious that the severe decompensated somatic pathology and comorbidities were associated with a high risk of complications both for the mother and the foetus, and pursuant to Order No. 736 of the Ministry of Health and Social Development of Russia dated December 3, 2007, On Approval of the List of Medical Indications for Induced Abortion, these findings were an absolute indication and a reason for termination of this pregnancy. The Order envisages that chronic renal insufficiency of any origin, with pre-conception createnine levels of over 200 μmol/L or a progressive increase in creatinine levels at any period of gestation, is a direct indication for pregnancy termination; and this conclusion was approved by the interdisciplinary medical team meeting. Besides, the patient was remotely consulted by specialists from the Federal State Budgetary Institution Academician V. I. Kulakov National Medical Research Center for Obstetrics, Gynaecology and Perinatal Medicine. They recommended to terminate the pregnancy and initiate RRT. If the patient refuses to terminate the pregnancy, RRT of at least 20 h/week should be initiated. The method of choice is long-term hemodialysis. However, the situation was complicated not only because the patient refused to terminate her pregnancy, but she also refused to initiate RRT, leading to clinical condition deterioration. On November 6, 2021, the patient refused to terminate her pregnancy, to initiate RRT, and to stay for any further inpatient treatment.

Next time she was hospitalised to the Nephrology Unit one month later, when she was 12 weeks pregnant, for additional examination, determination of the management strategy, and identification of the possibility to prolong this pregnancy, as well as for deciding on RRT initiation. The examination showed progressive system complications of end stage renal disease: anemia (Hb — 98–77 g/L), hyperazotemia (creatinine — 380–449 μmol/L; urea — 18–24 mmol/L), metabolic acidosis (blood pH — 7.2); hyperparathyroidism (PTH — 193 ng/mL); GFR (Rehberg Test) — 11.3 mL/min, proteinuria (PU 1.95 g/s). Another multidisciplinary medical team meeting was held; a remote consultation was sought from leading specialists and institutions specialising in expert assistance to this group of patients (V. I. Kulakov National Medical Research Center for Obstetrics, Gynaecology and Perinatal Medicine, Center for Pregnant Women with Kidney and Urinary Tract Pathologies at the State Budgetary Healthcare Institution of the City of Moscow A. K. Eramishantsev City Clinical Hospital of the Moscow Healthcare Department (Prof. N. L. Kozlovskaya, Dr. Med. Sci.), Budgetary Institution of the Khanty-Mansiysk Autonomous Region — Yugra Regional Clinical Hospital O. V. Pyankina, Cand. Med. Sci.). Taking into account the refusal to terminate the pregnancy and consent to RRT, long-term hemodialysis was initiated on December 15, 2021, at ween 19 of pregnancy, using a permanent dialysis catheter inserted in the internal jugular. Bicarbonate dialysis with ultrafiltration to 0.05–0.1–0.2 L (Elisio 13M dialysis unit) was performed 6 times weekly for 2–3 h; interdialytic weight gain was 0.04–0.12–0.6 kg. Dry weight was adjusted weekly taking into account blood pressure, oedema, weeks of pregnancy, foetus weight, and amniotic fluid volume. When the target blood urea levels were achieved, hemodialysis duration was reduced to 2—3 hours daily. On December 28, 2021, an arteriovenous (AV) fistula was formed in the lower third of left forearm. In December 2021, when the patient was 17–19 weeks pregnant, she had mild novel coronavirus infection Sars-CoV2 (NCVI), no antivirals were prescribed (Fig. 1). The entire pregnancy was associated with constant hospital admissions, examinations and treatment in the Nephrology Unit of the multidisciplinary inpatient clinic.

On May 12, 2022, the patient underwent term Stark C-section at 37 weeks and 3 days of pregnancy at the Budgetary Institution of the Khanty-Mansiysk Autonomous Region — Yugra Surgut Regional Clinical Centre for Mother and Child Protection. The newborn weighted 2980 g, Apgar scale — 8–9 points. After 10 months of dynamic follow-up, the baby boy's development corresponds to the age and gender standards.

After the operative delivery, the patient stayed in the Nephrology Unit, where she had hemodialysis for 2–4 hours 3 days a week. The woman was added to the kidney transplant waiting list.

Clinical diagnosis:

Primary diagnosis: unspecified nephropathy evolving to C5D A2 CKD. Long-term hemodialysis from December 15, 2021. Vascular access: AV fistula in the lower third of left forearm from December 28, 2021.

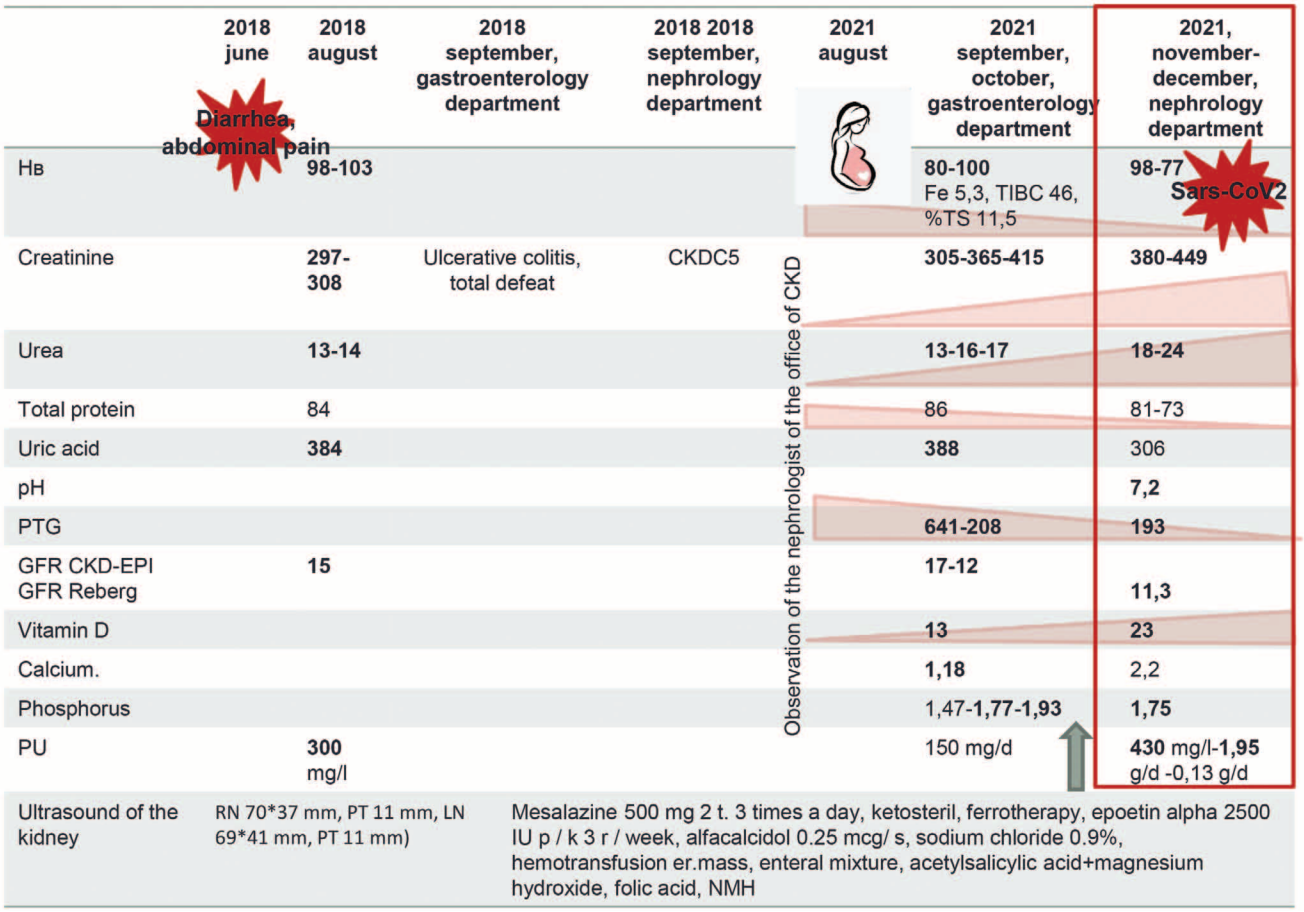

Figure 1. *Anamnesis of patient M., 23 years old*

Primary disease complications: Mineral and bone disorders (MBD) CKD: hyperphosphatasia, secondary hyperparathyroidism, vitamin D deficit. Secondary hyperuricemia. Mixed origin anemia (iron-deficient anemia and anemia of chronic diseases), moderate. Metabolic acidosis.

Secondary diagnosis: Ulcerative colitis (total), partial clinical remission. Helicobacter pylori-associated duodenal ulcer, clinical remission. Weight deficit. Mild protein-energy malnutrition. Acquired fish-skin disease, remission. Renal cysts. Mild coronavirus infection with identified virus (PCR, positive result dated December 17, 2021), survivor. Asymptomatic bacteriuria. Secondary functional ureterohydronephrosis.

First-time term operative delivery at 37 weeks and 3 days of pregnancy. Joel-Cohen incision. Stark C-section on May 12, 2022.

Discussion

Modern literature sources describe just a few cases of pregnancy during RRT. The study by I. G. Nikolskiy et al. (2011–2017) presents data on pregnancy complications and outcomes in 311 women with various CKD stages. However, only 7 and 6 patients in this large population had stage 4 and 5 CKD, respectively (4 %). In a similar study by Chinese authors who analysed the course and outcome of pregnancy in 293 patients with CKD, stage 4 was diagnosed only in 5 patients [12]. It is worth mentioning that healthcare providers in Surgut had not have any experience in managing such patients; therefore, this clinical observation was of utmost interest for various specialists in the region.

It is obvious that RRT in this case was strictly necessary. Hemodialysis was an optimal RRT method. However, selection of an RRT method for pregnant women is polemical. There are both pros and contras of hemodialysis and peritoneal dialysis (Table 1). All publications dedicated to this matter state that it is imperative to initiate RRT before or in the first trimester of pregnancy as soon as possible [13, 14]. Hemodialysis intensification improves pregnancy outcomes (better results for the foetus are achieved with 24–28 hours of hemodialysis per week [15] of 24–36 hours of hemodialysis per week) [16]. Alternative strategies are also possible (introduction of intermittent hemodialysis to peritoneal dialysis [17] and transition from peritoneal dialysis to hemodialysis in the second trimester [18]). However, even with

Table 1. *Hemodialysis and peritoneal dialysis pros and cons during pregnancy [2, 3, 6, 7]*

Hemodialysis	
Pros	*Cons*
• Less dietary restrictions • Less water restriction • Less overload using the technique	• Worse metabolic control (intermittent dialysis) • Higher risk of hemodynamic instability • Need for hypocoagulation • Lower autonomy
Peritoneal dialysis	
Pros	*Cons*
• Better metabolic control (continuous dialysis) • Lower risk of hemodynamic instability • Higher degree of autonomy • No need for anticoagulation • Preserving residual kidney function	• Higher risk of infectious complications ¥ • Higher risk of non-infectious complications ¤ • More difficulty managing volume • Higher % of intrauterine growth restriction • Increase in the frequency of exchanges ŧ

Примечания: ¥ — peritonitis/peritoneal dialysis catheter tunnel infection/outlet orifice infection; **¤** — peritoneal dialysis catheter dysfunction caused by obstruction/shifting or associated pain; **ŧ** — volume increase is not tolerated, especially in the last trimester

positive results from hemodialysis or peritoneal dialysis, an ideal RRT strategy during pregnancy may be never identified [19].

In this case study, it should be emphasised that hemodialysis was introduced on the early stages of pregnancy, principles of hemodialysis intensification were followed, the patient was compliant and felt good during the entire pregnancy. The total weight gain was 10 kg, haemodynamics was stable during the entire period of dynamic follow-up, there were no signs of foetus suffering, anemia and mineral and bone disorders were adequately corrected, the patient was under active obstetrical observation. Comorbidities were in remission due to maintenance baseline therapy.

At the same time, lack of adequate pre-conceptional preparation, presence of functional ureterohydronephrosis on week 26–27 of pregnancy (calix extension to 15–17 mm, pelvis extension to 18à24 × 27 mm, extension of upper third of ureter up to 6 mm) (no drainage was performed), COVID infection on week 15–16 of pregnancy, repeated asymptomatic bacteriuria during pregnancy treated with antibacterials after bacteriological urine tests for antibiotic susceptibility (amoxicillin and clavulanic acid, fosfomicin, ceftriaxone), comorbidities (ulcerative colitis, gastric ulcer, fish-skin disease), underlying cachexy, in addition to decompensated extragenital pathology (ESKD) could undoubtedly lead to poor pregnancy outcome both for the mother and the newborn.

Pregnancies in CKD patients are known to be associated with a high risk of perinatal complications; however, recently outcomes of such pregnancies have been quite promising. Favourable pregnancy outcome is possible with a comprehensive risk assessment, pregnancy planning, thorough individualised observation with a dynamic assessment of key blood parameters, prevention and management of complications [20-22]. This is the well-coordinated, highly-professional work of a multidisciplinary team (nephrologists, Ob/Gyn, critical care physicians, gastroenterologists, infection disease doctors, urologists, function test specialists) who followed up the patient during her pregnancy that made the favourable outcome come true.

In order to improve prognosis and prevent fast CKD progression, it is recommended to closely monitor renal disorder patients after delivery [20-22].

Conclusions

Severe comorbidity in this patient necessitated a comprehensive therapy and a multidisciplinary approach, which were implemented from the very first days of observation. Highly professional teamwork of healthcare providers (nephrologists, critical care physicians, Ob/Gyn, gastroenterologists, infection disease doctors, function test specialists, urologists, etc.) resulted in favourable outcome in this case study. Obviously, in case of pregnant women with CKD, basic functional parameters both of the mother and the foetus are regularly followed up. Relatively timely RRT initiation made adequate hyperazotemia correction possible, thus reducing endogenous intoxication and, together with strategies aimed at pregnancy prolongation and maintenance, ensured stable pregnancy and favourable outcome. Currently, we can claim that successful pregnancy and delivery in women with end-stage renal insufficiency are not a myth.

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Вишняк Д.А. (ORCID ID: https://orcid.org/0000-0002-8473-5930): формирование идеи и концепции рукописи, анализ и систематизация данных литературы, написание статьи, создание графического

материала, окончательное утверждение рукописи для публикации, ответственность за все аспекты рукописи

Каримова А.Х.: формирование идеи и концепции рукописи, анализ и систематизация данных, окончательное утверждение рукописи для публикации

Кулай Ю.А.: формирование идеи и концепции рукописи, анализ и систематизация данных, окончательное утверждение рукописи для публикации

Чернобай М.В.: формирование идеи и концепции рукописи, анализ и систематизация данных литературы, написание статьи, создание графического материала, окончательное утверждение рукописи для публикации

Кофеева В.Р.: формирование идеи и концепции рукописи, анализ и систематизация данных, окончательное утверждение рукописи для публикации

Хайруллина Г.М.: формирование идеи и концепции рукописи, анализ и систематизация данных, окончательное утверждение рукописи для публикации

Муллаярова Э.Т.: формирование идеи и концепции рукописи, анализ и систематизация данных, окончательное утверждение рукописи для публикации

Исаева А.Г.: формирование идеи и концепции рукописи, анализ и систематизация данных, окончательное утверждение рукописи для публикации

Authors' contribution:

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Vishnyak D.A. (ORCID ID: https://orcid.org/0000-0002-8473-5930): formation of the idea and concept of the manuscript, analysis and systematization of literature data, writing an article, creating graphic material, final approval of the manuscript for publication, responsibility for all aspects of the manuscript

Karimova A.H.: formation of the idea and concept of the manuscript, analysis and systematization of data, final approval of the manuscript for publication

Kulai Yu.A.: formation of the idea and concept of the manuscript, analysis and systematization of data, final approval of the manuscript for publication

Chernobai M.V.: formation of the idea and concept of the manuscript, analysis and systematization of literature data, writing an article, creating graphic material, final approval of the manuscript for publication

Kofeeva V.R.: formation of the idea and concept of the manuscript, analysis and systematization of data, final approval of the manuscript for publication

Khairullina G.M.: formation of the idea and concept of the manuscript, analysis and systematization of data, final approval of the manuscript for publication

E.T. Mullayarova: formation of the idea and concept of the manuscript, analysis and systematization of data, final approval of the manuscript for publication

Isaeva A.G.: formation of the idea and concept of the manuscript, analysis and systematization of data, final approval of the manuscript for publication

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М.М. Ребровская*[1], А.А. Климовская[2], Е.В. Ефремова[1], Н.С. Шаповал[1], О.Н. Сигитова[3]

[1] — ФГБОУ ВО «Ульяновский государственный университет», Институт медицины, экологии и физической культуры, Ульяновск, Россия
[2] — ГУЗ городская поликлиника № 1 имени С.М. Кирова, Ульяновск, Россия
[3] — ФГБОУ ВО Казанский ГМУ Минздрава России, Казань, Россия

ФЕНОМЕН ЛОЖНОЙ ТРОМБОЦИТОПЕНИИ. АЛГОРИТМ РЕШЕНИЯ ДИАГНОСТИЧЕСКОЙ ПРОБЛЕМЫ И ОПИСАНИЕ КЛИНИЧЕСКОГО СЛУЧАЯ

M.M. Rebrovskaya*[1], A.A. Klimovskaya[2], E.V. Efremova[1], N.S. Shapoval[1], O.N. Sigitova[3]

[1] — Ulyanovsk State University, Institute of Medicine, Ecology and Physical Culture, Ulyanovsk, Russia
[2] — City polyclinic № 1 named after S.M. Kirov, Ulyanovsk, Russia
[3] — Kazan State Medical University, Kazan, Russia

False Thrombocytopenia Phenomenon. Algorithm for Diagnostic Problem Solution and Description of Clinical Case

Резюме

Лабораторные методы исследования активно применяются клиницистами для уточнения и установления диагноза, но часто возникают случаи, которые сбивают с толку практикующих врачей и заставляют проводить широкий дифференциально диагностический поиск. Выявление тромбоцитопении в общем анализе крови требует тщательного обследования пациента, соотношения результатов анализа с клинико-анамнестическими данными и критического отношения к лабораторным показателям. Одним из ложных диагностических феноменов, затрудняющих правильную интерпретацию снижения числа тромбоцитов, является псевдотромбоцитопения, ассоциированная с применением консерванта этилендиаминтетрауксусной кислоты. В данной статье представлен клинический случай пациентки с ЭДТА-ассоциированной псевдотромбоцитопенией, до выявления которой были проведены полный сбор жалоб и анамнеза, физикальный осмотр, дополнительные методы обследования, изучен обширный дифференциально-диагностический ряд.

Ключевые слова: *этилендиаминтетрауксусная кислота, ЭДТА, тромбоцитопения, псевдотромбоцитопения, ложная тромбоцитопения, лабораторный феномен, дифференциальная диагностика*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

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*Контакты: Мария Михайловна Ребровская, e-mail: rebrovskayamary@mail.ru
*Contacts: Mariya M. Rebrovskaya, e-mail: rebrovskayamary@mail.ru
ORCID ID: https://orcid.org/0009-0005-5166-758X

Abstract

Medical practitioners often face the problem of false diagnostic phenomena. Laboratory research methods are actively used by clinicians to clarify and establish a diagnosis. But there often occur some cases that are confusing and force to carry out a wide differential diagnostic search. The detection of thrombocytopenia in the complete blood count requires careful examination of the patient, the ratio of the analysis results with clinical and anamnestic data and a critical relation to laboratory indicators. One such phenomenon is pseudotrombocytopenia associated with using of the preservative ethylenediaminetetraacetic acid in a complete blood count. This article presents a clinical case of patient with EDTA-associated pseudotrombocytopenia, before the detection of which a complete collecting of complaints and history, physical examination, additional survey methods were carried out, an extensive differential diagnostic series was studied.

Key words: *ethylenediaminetetraacetic acid, EDTA, pseudotrombocytopenia, false thrombocytopenia, laboratory phenomenon, differential diagnosis*

Conflict of interests

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EDTA — ethylene diamine tetraacetic acid, PTP — pseudothrombocytopenia, CVD — cardiovascular diseases, NAFLD — non-alcoholic fatty liver disease

Relevance

EDTA-dependent or EDTA-associated pseudothrombocytopenia is a laboratory phenomenon which causes diagnostic errors mostly related to the detection of significant thrombocytopenia. The term "EDTA-induced pseudothrombocytopenia" is more commonly used in foreign scientific literature.

M.J. Mant (1975) and R. Manthorpe (1981) were the first to describe EDTA-associated pseudothrombocytopenia in their studies. At that time this event had the prevalence of approximately 1.2 % in the population; however, as new clinical cases emerged, the importance of this issue has increased. It has been demonstrated that EDTA-dependent PTP is more common among inpatients then outpatients [2]. In 1991, N. Berkman et al. have published the study of 18 inpatients with EDTA-associated pseudothrombocytopenia; they also analyzed 34 cases described in the literature at that time. Authors concluded that this phenomenon occurred in patients with autoimmune diseases, malignancies, liver pathology, and atherosclerosis [8]. Modern sources present different data about the EDTA-associated PTP. The study of K.A. Papayan et al. has demonstrated that this phenomenon is equally prevalent both in patients with chronic diseases and the healthy population. The condition prevalence is 1:1000, and it is not associated with hemorrhages and thromboses [1]. The data of A.S. Polyakov et al. demonstrate that the incidence of false EDTA-associated thrombocytopenia is 20 % among examined healthy persons and 50 % in patients with various pathologies [2], which confirms the high rate of PTP detection in the population. The widespread use of automatic hematological analyzers, where ethylene diamine tetraacetic acid is essential as a blood stabilizer, has led to the rare application of manual platelet count in the prepared blood smear and, consequently, to more frequent EDTA-PTP reporting [1].

The pathogenesis of EDTA-dependent PTP is poorly understood; however, specific antibodies exist that cause platelet aggregation in the EDTA blood tube. EDTA is a preservative widely used in laboratory diagnosis for venous blood stabilization. This substance can suppress platelet aggregation due to the formation of weakly dissociating complexes with calcium ions — this leads to the attenuation of calcium interaction with platelet membrane receptors and calcium shut-off from the blood coagulation process [1].

So, what is the role of EDTA in false thrombocytopenia? EDTA causes calcium ions to bind in the venous blood — this leads to the dissociation of two subunits of the glycoprotein IIb/IIIa receptor on the platelet membrane. Thus, the receptor conformation changes, and the previously closed epitope (area for specific antibody binding) is exposed. This leads to platelet activation and aggregation in the tube with EDTA [1]. Besides, such reactions have been described for other anticoagulant preservatives, e.g. heparin sodium, sodium citrate [5]. However, the studies of false thrombocytopenias available mostly concern the EDTA use. The mechanism of EDTA-dependent platelet aggregation may be presented as follows (Fig. 1).

Currently no unified clinical guidelines exist for the diagnosis of EDTA-dependent pseudothrombocytopenia. According to the literature data, specific criteria can be defined for the diagnosis of EDTA-dependent false thrombocytopenia (Table 1).

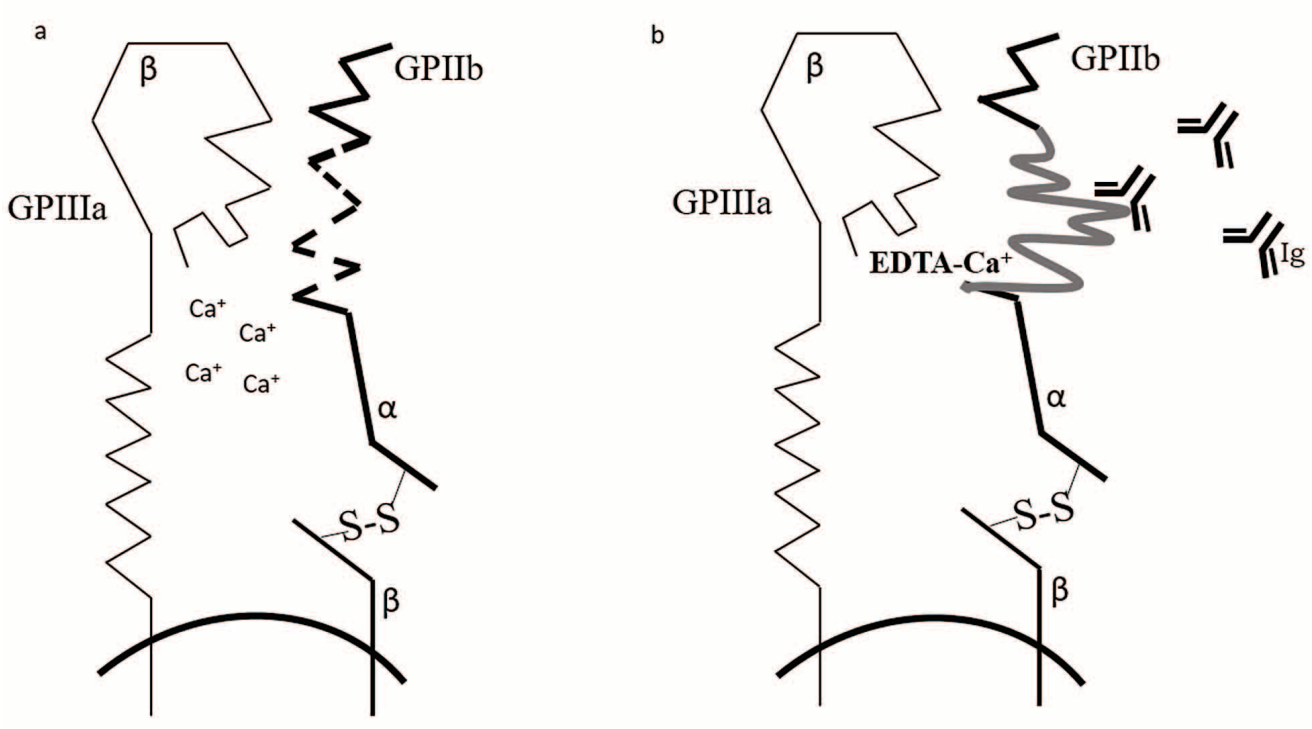

Figure 1. *The structure of the GP IIb/IIIa receptor on the platelet surface before reaction with EDTA (a) and the change in the conformation of the protein site by EDTA with the outcrop of a previously hidden epitope and specific antibodies bind with it (b). EDTA, ethylenediaminetetraacetic acid; Ca+, calcium ions*

Table 1. *Diagnostic criteria for EDTA-associated pseudotrombocytopenia. EDTA, ethylenediaminetetraacetic acid*

Diagnostic criteria for EDTA-associated pseudotrombocytopenia	
The number of platelets in the complete blood count	<100×10^9/L
In blood samples with using EDTA we find in repeated tests	Progressive platelet count reduction over time
When calculating the number of platelets in a blood smear according to Fonio	Normal platelet count
Manifestations of hemorrhagic syndrome	There are no any symptoms
Indicators of other formed blood elements, hematocrit level	In the normal range
The average volume of platelets	In the normal range

Our proper clinical observation is presented as a clinical case study.

Clinical case study

The female patient N., 62 years old, was invited by the general practitioner for standard laboratory and instrumental investigations (according to the Order of the Ministry of Health of the Russian Federation dated April 27, 2021 No. 404N, On approving the procedure for prophylactic medical examination and periodic screening examination of specific adult groups) to the polyclinics at place of residence. The complete venous blood count (February 1, 2023) demonstrated the platelet count of 41×10^9/L (reference range 180-400×10^9/L) with normal counts for other blood cells (red blood cells 4.2×10^{12}/L, white blood cells 8.4×10^9/L), as well as the normal hematocrit level — 44.0 %. The patient was

referred by the general practitioner to the hematologist. Before the hematologist counseling, the patient applied to the private laboratory individually for repeated blood collection: the venous blood count (February 3, 2023) demonstrated the platelet count of 17×10^9/L, with the laboratory comment of "confirmed by smear". Other blood cell counts and the hematocrit level were normal.

The patient asked for a second opinion in another hospital, where she was counseled by another general practitioner. The physical examination results were as follows: the general condition was satisfactory, without active complaints. The patient was overweight, but with normal constitution. Anthropometric data: height 164 cm, weight 75 kg, body mass index (BMI) 27.89 kg/m^2, waist circumference 86 cm. The skin color was physiological, and the skin was moderately humid. Visible mucous membranes were clear; no rash and signs of cutaneous hemorrhagic syndrome were detected. Cardiac borders were not enlarged. Pulmonary auscultation revealed vesicular breathing with no rales; the respiratory rate (RR) was 16/min. Cardiac auscultation revealed regular rhythm, clear cardiac tones, and no murmurs. Blood pressure (BP) was 125/80 mm Hg; the heart rate (HR) was 72/min; the pulse was symmetric, of satisfactory filling. The abdomen was soft and non-tender on palpation. The liver and spleen were not palpated; based on percussion results, no enlargement was noted. Bowel habits and urination were normal. Neurological examination revealed normal motor and sensory patterns. According to the patient, she did not have any epistaxis, gum bleeding or other evident hemorrhages. History: the patient underwent the surgery for the congenital heart disease — patent ductus arteriosus ligation via an open access at the age of 6. The patient had been suffering from essential hypertension since the age of 45; currently BP was controlled within the target values (130/80 mm Hg). The patient had been suffering from type 2 diabetes mellitus for 4 years; she took oral hypoglycemic therapy (metformin 1,500 mg). The patient was sick with the mild novel coronavirus infection twice (in November 2021 and September 2022). The family history was positive for cardiovascular diseases (CVD) (essential hypertension and two myocardial infarctions in a father; essential hypertension, acute cerebrovascular accidents, type 2 diabetes mellitus in a mother; early hypertension in a sister) and malignancies (high-grade gastric adenocarcinoma in a father). The patient was highly treatment-compliant, constantly taking hypotensive (enalapril, indapamide), oral hypoglycemic (metformin) and hypolipidemid (atorvastatin) drugs. The allergy history was negative. No new drugs or dose adjustments were introduced within a year; the latest vaccination was 6 months ago with a vector-based vaccine for the novel coronavirus (SARS-CoV-2) infection prophylaxis.

The venous blood was collected using a Vacutainer with the ethylene diamine tetraacetic acid (EDTA) preservative, and the capillary blood was collected from the finger with a dry glass capillary without preservatives in the laboratory of the second hospital. The capillary blood smears were prepared for Phonio platelet count. The venous blood was also collected for the D-dimer, coagulation panel, and biochemistry parameters. Urinalysis, fecal occult blood test, ultrasound of the abdominal cavity and kidneys were also monitored.

The following results were obtained (February 8, 2023): the platelet count in the venous blood collected with a Vacutainer with the EDTA preservative in the automatic analyzer was 11×10^9/L. A clear trend to successive platelet count decrease in the venous blood tests was observed (first test 41×10^9/L, second test 17×10^9/L, third test 11×10^9/L; the private laboratory confirmed the EDTA use as a preservative for the complete blood count), which is one of the criteria for EDTA-dependent pseudothrombocytopenia (Fig. 2).

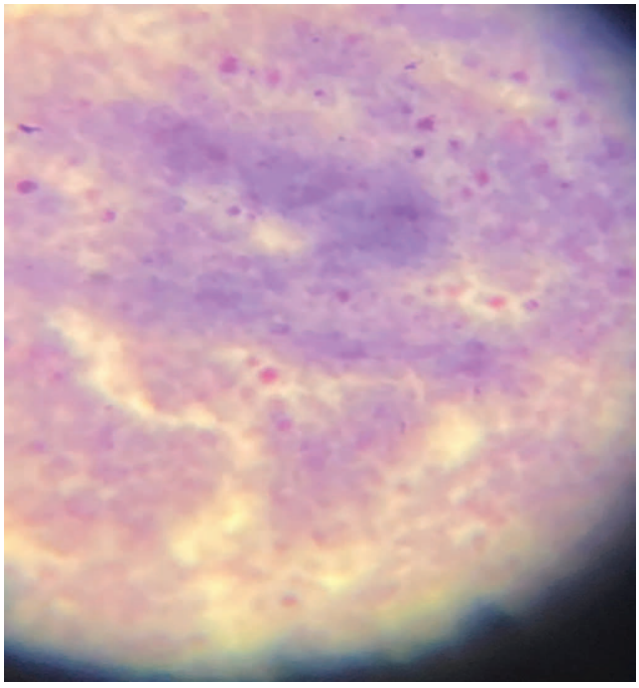

Figure 2. *Venous blood pattern in test tube (08.02.23) using EDTA of Patient N. Aggregated platelets reacted with preservative are visible as violet bands*

The platelet count in the capillary blood (Phonio method) was 372×10^9/L.

The coagulation panel parameters were normal: prothrombin time 9.9 seconds (9.0–14.0); prothrombin index 105.5 % (70.0–120.0); international normalized ratio (INR) 0.94 (0.80–1.20); activated partial thromboplastin time (APTT) 23.9 seconds (22.0–34.0); fibrinogen 3.9 g/L. The D-dimer level (February 8, 2023) was 74.4 ng/mL. The HbA1c level was 6.5 %. The serum creatinine level was 76 μmol/L; estimated glomerular filtration rate (GFR) based on the CKD-EPI equation (2021) was 72.4 mL/min/1.73 m^2. The urinalysis (February 8, 2023) was normal. The fecal occult blood test was negative.

Ultrasound of the abdominal cavity and kidneys (February 8, 2023) revealed fatty liver and diffuse parenchymal changes of the pancreas.

To confirm the diagnostic hypothesis, previous results of the patient tests were analyzed. In 2021, low platelet count was also detected in the complete blood count performed at the polyclinics at place of residence on November 15, 2021 (72×10^9/L), with a decreasing trend with the repeated count on December 3, 2021 (15×10^9/L). The private laboratory has detected the platelet count within the normal limits on December 14, 2021 (182×10^9/L). The preservative name used in the private laboratory at that time could not be established. After receiving the normal test result, the patient did not seek medical attention regarding this issue. All platelet count changes are presented using a time scale (Fig. 3).

Based on the data obtained, the following clinical diagnosis was established: Grade II essential hypertension. Controlled hypertension. Abdominal obesity. Complicated family history (CVD). Dyslipidemia. Left ventricular hypertrophy. Type 2 diabetes mellitus; target HbA1c level ≤7.0 %. Risk grade 3 (high). Target BP <130/<80 mm Hg. Non-alcoholic fatty liver disease (fibrosis stage to be defined). EDTA-associated pseudothrombocytopenia.

The diagnosis of EDTA-associated pseudothrombocytopenia was consequently confirmed by the hematologist.

The patient was recommended to monitor the complete blood count, with the platelet count to be determined using the Phonio method (without EDTA) 3 months later, and to test the coagulation panel / D-dimer 6 months later.

The patient gave written consent for data publication.

Discussion

The presented clinical case demonstrates the importance of detecting the EDTA-dependent pseudothrombocytopenia. The diagnostic search due to duplicate thrombocytopenia results with a decreasing trend coupled with the absence of hemorrhagic syndrome made us think about impaired platelet hemostasis with normal plasma factor levels, which could explain the absence of hemorrhages. The coagulation panel results were within

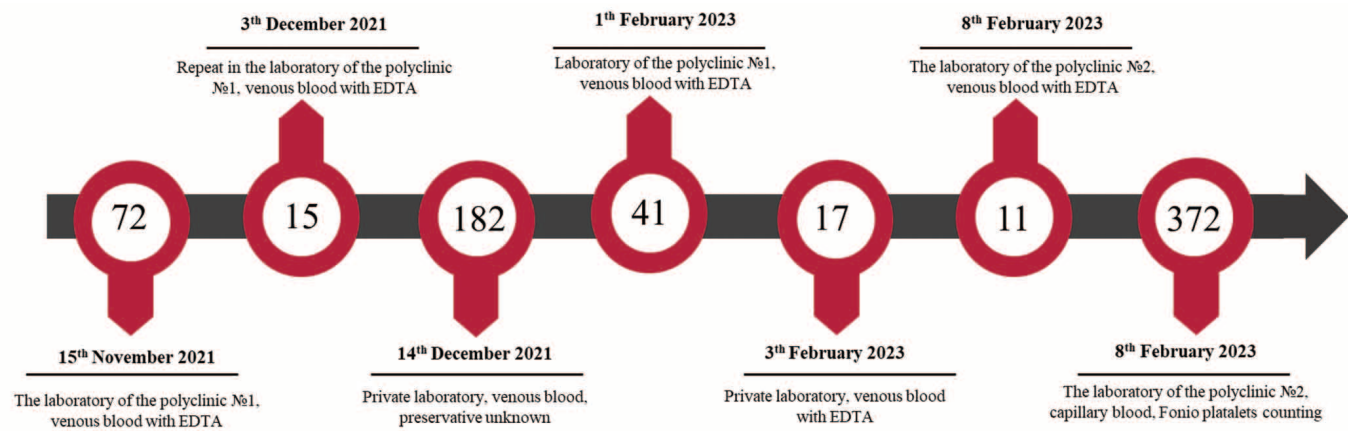

Figure 3. *The changes in the patient's blood platelet count over time, the number inside the circle corresponds to the number of platelets X $\times10^9$/L. EDTA, ethylenediaminetetraacetic acid; polyclinic № 1 — a medical institution at the place of residence; polyclinic № 2 — is a medical institution where patient N. went for a second opinion*

normal limits. The differential diagnosis was made with the following conditions: idiopathic thrombocytopenic purpura, drug- or vaccine-induced thrombocytopenia, severe liver pathology, malignancies [9]. The diagnostic search in thrombocytopenia is represented in the tabular form (Table 2).

However, the history, physical examination, laboratory and instrumental investigations did not confirm the hypothesis.

The examination of the comorbid patient (abdominal obesity, diabetes mellitus, essential hypertension) detected the signs of non-alcoholic fatty liver disease (NAFLD).

Table 2. *Differential diagnostics of various thrombocytopenia types*

The differential diagnostics of thrombocytopenia			
Group of disorders		**Disease/condition**	**Mechanism of development**
True pathology	Hereditary thrombocytopenia	Glantzman's thrombasthenia; the May-Hegglin anomaly; Wiskott-Aldrich syndrome; Bernard-Soulier syndrome; grey platelet syndrome; Fanconi anemia; congenital amegakaryocythemia	Mutations of platelet genes that change their morphology: micro- and macroformes (giant platelets), changes in platelet granules (gray cells due to decrease in a-granules), as well as leukocyte inclusions
	Acquired immune thrombocytopenia	Primary immune thrombocytopenia — idiopathic thrombocytopenic purpura (Verlhof's disease)	Production of autotrombocytic IgG antibodies against various complexes on the platelet surface, predominantly against glycoprotein IIb/IIIa. T-cell immune link imbalance
		Secondary immune — against the background of diseases: systemic lupus erythematosus, antiphospholipid syndrome, chronic viral hepatitis, HIV, rheumatoid arthritis, autoimmune thyroiditis, lymphoproliferative diseases, drug-induced TP, acute leukemia, myelodysplastic syndrome	Cross-pathogenetic reactions — heterogeneity of disorders in various immune units — immune dysregulation and autoaggression as a mechanism for the development of the underlying disease, followed by the formation of several clones of autoantibodies against platelets
	Acquired not immune thrombocytopenia	Consumption thrombocytopenia: DIC syndrome, thrombotic thrombocytopenic purpura (Moschkowitz's disease), hemolytic-uremic syndrome, thrombotic microangiopathies against the background of diseases with endothelial damage — heart defects, vascular atherosclerosis, diabetes mellitus	Intravascular thrombus formation, vascular occlusion, enhanced platelet destruction
		Platelet sequestration (Gaucher's disease, lymphomas, cirrhosis)	Increased platelet deposition in enlarged spleen with portal hypertension (splenomegaly)
		Hemodilution	In patients after massive blood loss and infusion therapy with platelet-free media
		Insufficient platelet production: aplastic anemia, acute and chronic myelo- and lymphoproliferative diseases, thrombocytopenia induced by chemo- and radiation therapy.	In aplastic anemia — due to fat infiltration in the bone marrow; in acute leukemia, chronic lympho- and myeloproliferative diseases, metastases to the bone marrow — due to suppression of the growth by the tumor substrate; in myelodysplastic syndrome — megakaryocytopoiesis disorder; in chemo- or radiation therapy, alcohol consumption — direct toxic effect on platelets
False pathology		EDTA-dependent pseudotrombocytopenia	Formation of platelet aggregates in a blood smear under the action of a preservative anticoagulant — EDTA

There are some data indicating the spontaneous or induced platelet aggregation in patients with NAFLD, concomitant hypertension and obesity, as well as in patients with isolated NAFLD. WIth that, patients demonstrate increased mean platelet volume with their decreased counts in the blood count due to aggregation [3]. One of the reasons for false platelet count decrease in such patients is the phenomenon of EDTA-associated or EDTA-dependent thrombocytopenia, which was confirmed in our patient. G. Trindade et al. (2021) described a clinical case of EDTA-induced pseudothrombocytopenia in a patient with hepatosplenic Mansoni schistosomiasis [7]. The accumulated clinical data presume the important role of hepatic and splenic diseases in the pathogenesis of false PTP phenomenon.

In our clinical case the patient had a history of two confirmed novel coronavirus infection episodes. The American Society for Clinical Pathology studies have demonstrated that novel coronavirus (COVID-19) infection plays a role in the development of both transient PTP (within 3 weeks in a patient with acute severe COVID-19 pneumonia) and 9-month PTP that persisted after recovery in a 60-year-old male patient. Anti-nucleocapsid and coronavirus spike protein antibodies persisted in the blood of the patient for the whole period (9 months), which allowed the investigators to propose the association of EDTA and IgG/IgM to SARS-CoV-2. EDTA-pseudothrombocytopenia is also possible as a result of seroconversion due to the large-scale vaccination [6].

Thus, the causes of EDTA-dependent PTP in our patient could be variable, including non-alcoholic fatty liver disease due to diabetes mellitus or a prior coronavirus infection.

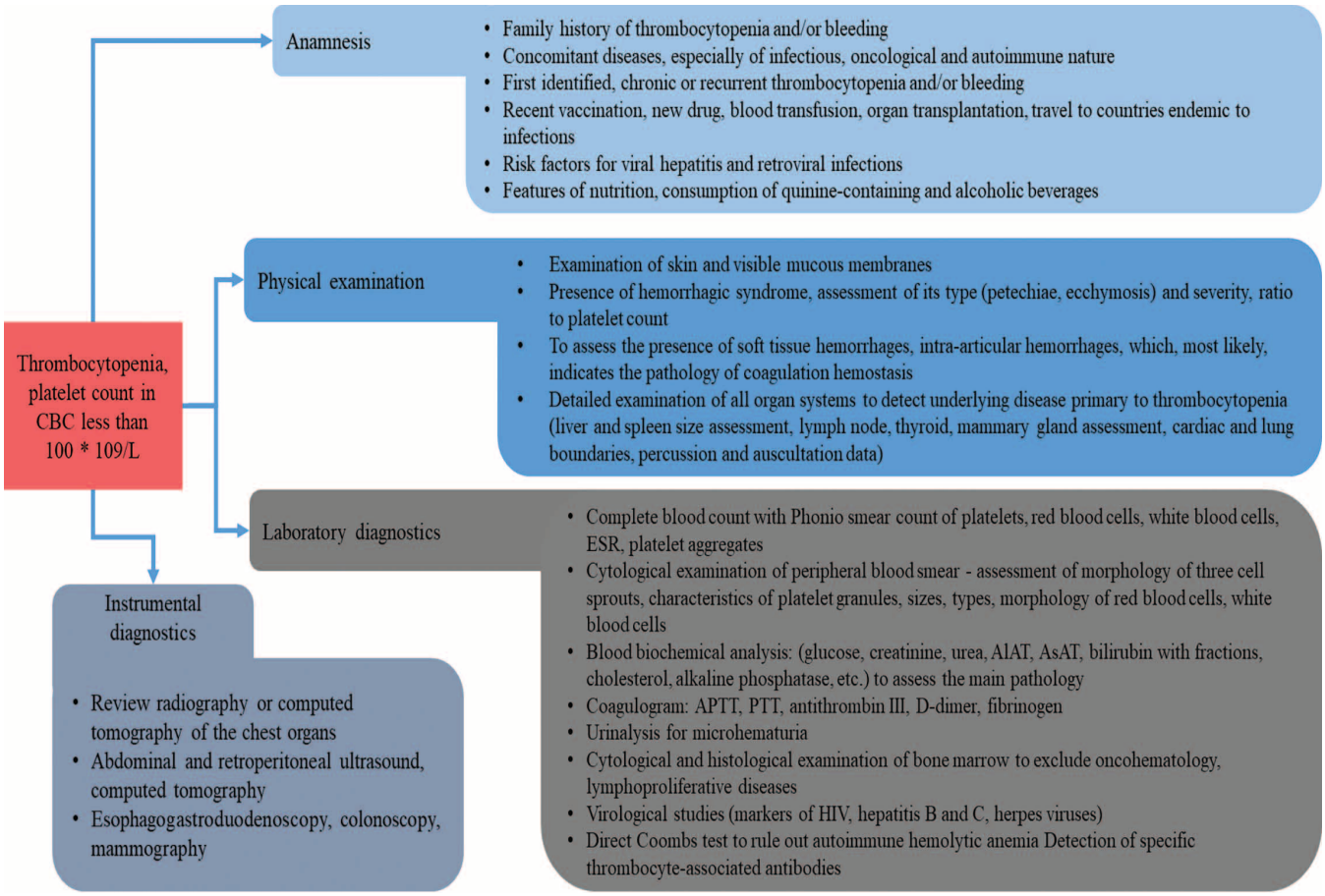

Figure 4. *Physician tactics when thrombocytopenia is detected in a complete blood count*

Note: CBC — complete blood count; ESR — erythrocyte sedimentation rate; AlAT — alanine aminotransferase; AsAT — asparagine aminotransferase; APTT — activated partial thromboplastin time; PTI — prothrombin index; HIV — human immunodeficiency virus

The study concerning the association of EDTA-associated thrombocytopenia and a genetic feature (fibrinogen platelet receptor gene polymorphism) has demonstrated the absence of statistically significant results regarding the value of this marker after the analysis of a limited patient group — further studies are required. Authors A.S. Polyakov and E.V. Goncharova have concluded that this laboratory phenomenon should not be considered a predictive factor for any diseases, though patients with pseudothrombocytopenia of this origin require periodic screening of blood parameters [2]. On the other hand, the author data confirm the high mortality level in patients with EDTA-PTP, as well as the fact that this phenomenon is an independent risk factor of malignancies [10].

M. Nagler et al. described an interesting observation that histograms of both platelets and white blood cells can change in patients with EDTA-dependent pseudothrombocytopenia. They demonstrated the activation of lymphocytic cells in response to EDTA-associated platelet aggregation in a clinical case of the patient with suspected acute leukemia. The automatic analyzer may count platelet aggregates as white blood cells, which leads to distorted complete blood count results. The authors ask for thorough evaluations of white blood cell and platelet histogram patterns, which can help to establish EDTA-dependent pseudothrombocytopenia and avoid treatment errors [11].

Currently it is impossible to establish the exact disease cause, though it is feasible to monitor the existing chronic diseases (essential hypertension, type 2 diabetes mellitus) with repeated blood tests.

Below is the physician tactics in cases of thrombocytopenia (Fig. 4).

Conclusion

The detection of thrombocytopenia in the complete blood count requires wide differential diagnosis. A large number of pathologies are accompanied by true thrombocytopenia. The treatment tactics should be initially determined with the correspondence of the laboratory data obtained to the clinical signs, which is the main difference of true pathology from the false phenomenon.

The presented clinical case demonstrates the importance of detecting laboratory phenomena in the outpatient setting.

It is necessary to inform attending physicians and laboratory personnel about the prevalence of false diagnostic phenomena and tactics upon their detection. The evaluation of the platelet count using hematological analyzers is a rather quick and cheap method, though it requires using an anticoagulant [12]. If the laboratory uses the EDTA anticoagulant preservative, it is feasible to inform the specialists about possible dependent thrombocytopenia and further tactics. After obtaining low platelet count in the automatic analyzer, one should count the platelets in the blood smear using the Phonio method, which is the reference and available method for the diagnosis of this condition.

The interdisciplinary interactions of clinical and laboratory physicians (or lab technicians, if the latter are missing), discussion of doubtful diagnostic cases, and mutual decisions are really important to confirm laboratory phenomena.

Besides, the correct diagnosis in the presented clinical case was determined by the correct interrogation, history collection, and physical examination of the patient, which helped to avoid tactical errors. Laboratory and instrumental diagnostic methods often yield artifacts which do not fit into the clinical pattern and history; they should always be critically evaluated by the attending physician. A serious hematological diagnosis was suspected in this patient, which could affect her quality of life, lead to increased anxiety and depression before the laboratory phenomenon verification.

Accounting for the modern availability of medical information and possibilities of self-examinations and interpretations of the data obtained by patients, the clinical physicians have to constantly enhance their knowledge not only about widespread pathologies, but also rare conditions, including laboratory phenomena.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

Ребровская М.М. (ORCID ID: https://orcid.org/0009-0005-5166-758X): разработка концепции и дизайна, анализ и интерпретация данных, обзор публикаций по теме статьи, написание текста статьи, одобрение окончательной версии статьи перед подачей для публикации

Климовская А.А. (ORCID ID: https://orcid.org/0009-0007-2399-991X): анализ и интерпретация данных, написание текста статьи, одобрение окончательной версии статьи перед подачей для публикации

Ефремова Е.В. (ORCID ID: https://orcid.org/0000-0002-7579-4824): анализ и интерпретация данных, обзор публикаций по теме статьи, написание текста статьи, научная консультация, одобрение окончательной версии статьи перед подачей для публикации

Шаповал Н.С. (ORCID ID: https://orcid.org/0000-0002-5642-3753): обзор публикаций по теме статьи, написание текста статьи, одобрение окончательной версии статьи перед подачей для публикации

Сигитова О.Н. (ORCID ID: https://orcid.org/0000-0001-8983-245X): обзор публикаций по теме статьи, написание текста статьи, научная консультация, одобрение окончательной версии статьи перед подачей для публикации

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Rebrovskaya M.M. (ORCID ID: https://orcid.org/0009-0005-5166-758X): development of concept and design, analysis and interpretation of data, review of publications on the topic of the article, writing of the article text, approval of the final version of the article before submission for publication

Klimovskaya A.A. (ORCID ID: https://orcid.org/0009-0007-2399-991X): analysis and interpretation of data, writing of the article text, approval of the final version of the article before submission for publication

Efremova E.V. (ORCID ID: https://orcid.org/0000-0002-7579-4824): analysis and interpretation of the data, review of publications on the topic of the article, writing of the article text, scientific consultation, approval of the final version of the article before submission for publication

Shapoval N.S. (ORCID ID: https://orcid.org/0000-0002-5642-3753): review of publications on the topic of the article, writing of the article text, approval of the final version of the article before submitting for publication

Sigitova O.N. (ORCID ID: https://orcid.org/0000-0001-8983-245X): review of publications on the subject of the article, writing of the article text, scientific consultation, approval of the final version of the article before submission for publication

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С.Т. Энгиноев[1,2]*, Ю.Б. Мартьянова[1], Е.В. Ефремова[3], И.И. Чернов[1]

[1] — ФГБОУ «Федеральный центр сердечно-сосудистой хирургии» Министерства здравоохранения Российской Федерации, Астрахань, Россия
[2] — ФГБОУ ВО «Астраханский ГМУ», Министерства здравоохранения Российской Федерации, Астрахань, Россия
[3] — ФГБОУ ВО «Ульяновский государственный университет», Ульяновск, Россия

КЛИНИЧЕСКИЙ СЛУЧАЙ УСПЕШНОГО ЛЕЧЕНИЯ ДИССЕКЦИИ КОРОНАРНОЙ АРТЕРИИ И ТРОМБОЗА ЛЕВОГО ЖЕЛУДОЧКА У МОЛОДОГО МУЖЧИНЫ — НОСИТЕЛЯ ГЕНА ФАКТОРА V ЛЕЙДЕНА С ТРАНЗИТОРНОЙ ИШЕМИЧЕСКОЙ АТАКОЙ

S.T. Enginoev[1,2]*, Yu.B. Martyanova[1], E.V. Efremova[3], I.I. Chernov[1]

[1]- Federal Center for Cardiovascular Surgery of the Ministry of Health of the Russian Federation, Astrakhan, Russia
[2] — Astrakhan State Medical University of the Ministry of Health of the Russian Federation, Astrakhan, Russia
[3] — Ulyanovsk State University, Ulyanovsk, Russia

A clinical case of successful treatment of coronary artery dissection and left ventricular thrombosis in a young man carrier of factor V Leiden gene and transient ischemic attack

Резюме

Одной из причин транзиторной ишемической атаки или ишемического инсульта являются объемные образования левых отделов сердца, в том числе, интракардиальные тромбы. Одним из предрасполагающих факторов тромбообразования является наличие Лейденской мутации, как наиболее распространенной формы наследственной тромбофилии в европейской популяции. В то же время, одной из причин острой сосудистой катастрофы может являться спонтанная диссекция коронарных артерий. Особую сложность представляет дифференциальная диагностика, требующая дополнительных методов обследования (внутрисосудистое ультразвуковое исследование, оптическая когерентная томография) помимо проведения коронарографии. Представленный клинический случай описывает диагностику и успешное лечение спонтанной диссекции передней межжелудочковой артерии, тромбоза левого желудочка, выявление мутации гена фактора V Лейдена у молодого мужчины с анамнезом транзиторной ишемической атаки.

Ключевые слова: *тромб левого желудочка; опухоль сердца; образование сердца; тромбэктомия; транзиторная ишемическая атака*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

*Контакты: Сослан Тайсумович Энгиноев, e-mail: Soslan.enginoev@gmail.com
*Contacts: Soslan T. Enginoev, e-mail: Soslan.enginoev@gmail.com
ORCID ID: https://orcid.org/0000-0002-4344-2672

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Abstract

One of the causes of transient ischemic attack or ischemic stroke are mass formations in the left heart. One of the predisposing factors for thrombosis is the presence of the Leiden mutation, as the most common form of hereditary thrombophilia in the European population. At the same time, spontaneous dissection of the coronary arteries (SCA) can be one of the reasons of an acute vascular accident. Of particular difficulty is differential diagnosis, which requires additional examination methods (intravascular ultrasound, optical coherence tomography) in addition to coronary angiography. The presented clinical case describes the diagnosis and successful treatment of spontaneous anterior interventricular artery dissection, left ventricular thrombosis, detection of factor V Leiden gene mutation in a young man with a history of transient ischemic attack.

Key words: *left ventricular thrombus; heart tumor; heart formation; thrombectomy; transient ischemic attack*

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IVUS — intravascular ultrasound, DB — diagonal branch, CAG — coronary angiography, LV — left ventricle, MRI — magnetic resonance imaging, ACS — acute coronary syndrome, AIVA — anterior interventricular artery, SCAD — spontaneous coronary artery dissection, TIA — transient ischemic attack, PE — pulmonary embolism, EF — ejection fraction, HR — heart rate.

Introduction

Thrombotic mass lesions located in left heart chambers are one of the causes of transient ischemic attacks (TIA) or ischemic strokes. Depending on the clot morphology, remote risks for embolic and cardiovascular events increase up to 22–37 % [1, 2]. Leiden mutation is one of the predisposing factors for clotting. It is one of the most common forms of hereditary thrombophilia in the European population [3]. Leiden mutation belongs to "classic" hereditary thrombophilias with antithrombin deficiency. Deep vein thrombosis and pulmonary embolism (PE) are considered the most common manifestations of thrombotic complications, though other thrombotic locations are possible, including cerebral, portal, and hepatic ones [4, 5].

At the same time, spontaneous coronary artery dissection (SCAD) may be considered one of the causes of vascular accidents. According to the scientific literature, 1–4 % of all ACS cases are associated with SCAD [6, 7]. Meanwhile, true SCAD incidence is unknown, accounting for non-specific clinical signs and difficult diagnosis. The disease is more common among young females; less than one third of cases is reported in males [8, 9]. The purpose of Inspire International Community supported by the The Women Heart Support Community is the collection and distribution of data regarding the female patients suffered from SCAD. Coronary angiography (CAG) in SCAD reveals the following: intimal flap in the arterial lumen, contrast extravasation, true and false vascular lumina (double vascular lumen), vascular lumen shrinkage due to hematoma. The J. Saw classification defines three SCAD types: type 1 with evident arterial wall contrasting; type 2 with diffuse stenosis of variable degree; type 3 mimicking atherosclerosis [10]. However, CAG data are not always enough for correct diagnosis. Differential SCAD search may require additional examination methods (intravascular ultrasound (IVUS), optical coherence tomography). Clinical cases with predisposing factors and patient comorbidities are especially difficult. Single SCAD cases associated with factor V (Leiden) mutation are described in the scientific literature. Hereby we present a proper case study describing the treatment of spontaneous anterior interventricular artery dissection with left ventricular (LV) thrombosis and TIA in a young man carrying the mutation of factor V (Leiden) mutation gene.

Case Study

The male patient A., 36 years old, was hospitalized on January 10, 2022 into the Cardiac Surgery Department No. 1 of the Federal State Budget Institution "Federal Center of Cardiovascular Surgery", Ministry of Health of the Russian Federation (Astrakhan), complaining of dyspnea on mild physical exertion, worsening fatigue.

History: the patient has been sick for about a year, when he developed dyspnea on physical exertion, pain in calf muscles during prolonged walking, worsening fatigue. According to the patient (no medical documents available), he was hospitalized in 2017–2018 due to deep vein thrombosis of the right upper extremity, right great saphenous vein; he was treated conservatively with short-term oral anticoagulants. The patient's current condition was worsening since January 5, 2022, when during car driving he felt weakness in the left extremities and the left side of the face. The symptoms regressed 10–15 min later; the neurologist considered this a TIA. The patient underwent transthoracic echocardiography at place of residence, where the mass lesion was detected in the LV. The patient was referred for hospitalization to the Federal State Budget Institution "Federal Center of Cardiovascular Surgery", Ministry of Health of the Russian Federation (Astrakhan) with the diagnosis of mass LV lesion. On admission the patient took the following medications: rivaroxaban 20 mg, acetylsalicylic acid 100 mg, clopidogrel 75 mg. The patient had significant cardiovascular family history — his father had a stroke. Bad habits: 10-year smoking history (previously) with a 5-year break; at the time of hospitalization, the patient was smoking e-cigarettes. The patient did not suffer from COVID-19.

Preliminary diagnosis on admission: LV lesion. Coronary artery disease (confirmation required). TIA (January 5, 2022). Chronic heart failure, Stage 2A, NYHA Functional Class II.

On admission, the overall condition was satisfactory. The patient's consciousness was clear. Hypersthenic constitution (body mass index 34.3 kg/m^2). The skin was clear, of physiological color, without cyanosis. Body temperature: 36.7 °C. Oxygen saturation: 98 %. Pulmonary auscultation revealed vesicular breathing with no rales; respiratory rate was 16/min. Cardiac auscultation revealed regular rhythm with the heart rate (HR) of 68/min; cardiac sounds were muffled, no pathological murmurs were auscultated. The pulse in radial arteries was symmetric, of satisfactory filling; no deficit was reported. Blood pressure: 140/90 mm Hg in both arms. No carotid bruits were detected. The tongue was moist and clear. The abdomen was soft and nontender on superficial palpation. No peripheral edema was detected.

The complete blood count on admission revealed lymphocytosis (48.4 %). The homocysteine level in blood was 13.3 mmol/L (reference values 5.46–16.2 mmol/L); anti-phospholipid antibodies did not exceed 10 U/mL. Antithrombin III activity was 85 % (reference values 83–128 %), Protein C concentration 124 % (reference values 70–140 %), free Protein S concentration 97.4 % (reference values 74.1–146.1 %). The urinalysis on admission revealed proteinuria (0.38 g/L).

Transthoracic echocardiography (January 10, 2022): end-diastolic LV volume 85 mL; end-systolic LV volume 40 mL; LV ejection fraction (EF, Simpson) 55 %; right ventricle: basal part 3 cm; left atrium 3.3 cm; left atrial volume 42 mL. Cardiac chambers were not enlarged. Global myocardial contractility was normal. Local contractility disorders of LV segments: apical LV hypokinesia. A mobile hyperechogenic pedunculated lesion sized

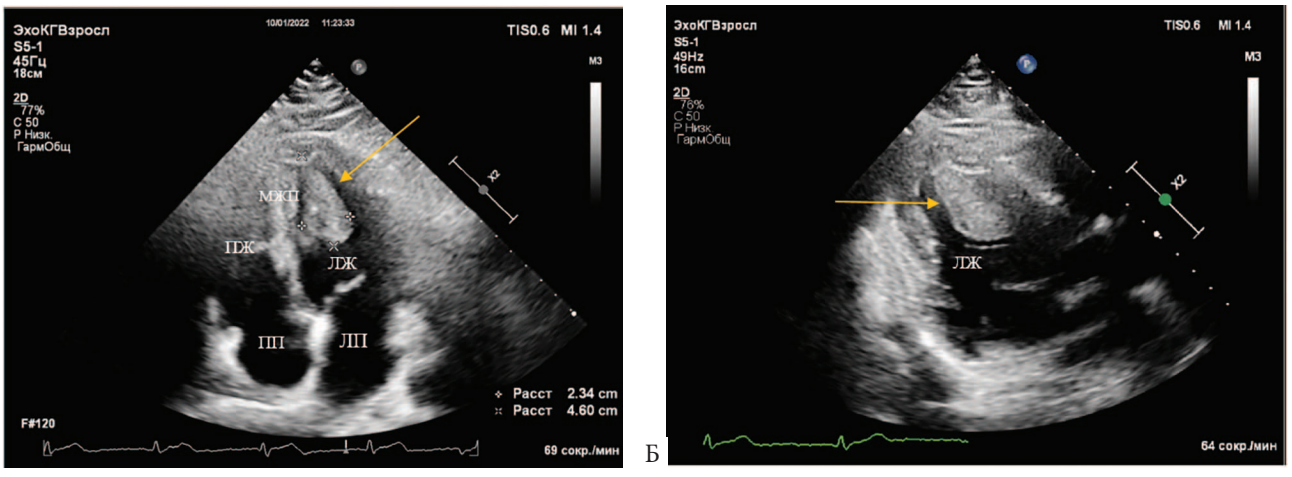


Figure 1. *Transthoracic echocardiography of patient*

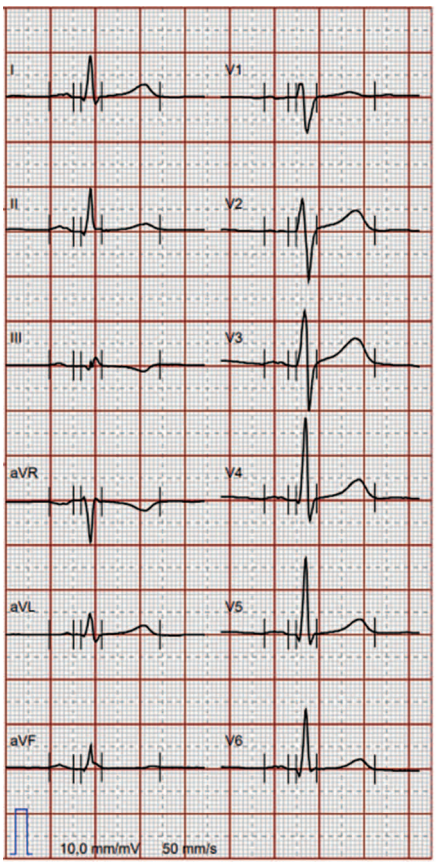
Note. Transthoracic echocardiography. a — apical approach, four-chamber position in the diastolic phase. In the LV cavity, a mobile hyperechogenic mass on a pedicle is visualized, attached to the apex, 4.6 x 2.3 cm in size. b — parasternal approach, position along the long axis in the diastolic phase

4.6 x 2.3 cm and attached to the apex was located in the LV cavity (thrombus? tumor?). Diastolic LV function was not impaired. Systolic right ventricular function was not impaired. Systolic pressure in the pulmonary artery 24 mm Hg. Pericardial and pleural cavities were normal (Fig. 1).

Electrocardiography (January 10, 2022): sinus rhythm with HR 76 beats per minute. Electrical axis of the heart was horizontal (Fig. 2).

GAG (January 10, 2022): eccentric atherosclerotic plaque 40 % in the middle third of the anterior interventricular artery (AIVA) (Fig. 3).

The patient underwent cardiac magnetic resonance imaging (MRI) with intravenous contrast enhancement (January 11, 2022): cine-MRI revealed no decrease in the global LV contractility (EF 56 %). Apical hypokinesis was detected; no other segmental LV contractility disorders were observed. Enhanced trabecularity of anterior and lateral LV walls at the level of middle and apical segments not reaching criteria for trabecular myocardium was detected. The interventricular septum was not thickened at the level of basal and middle segments.



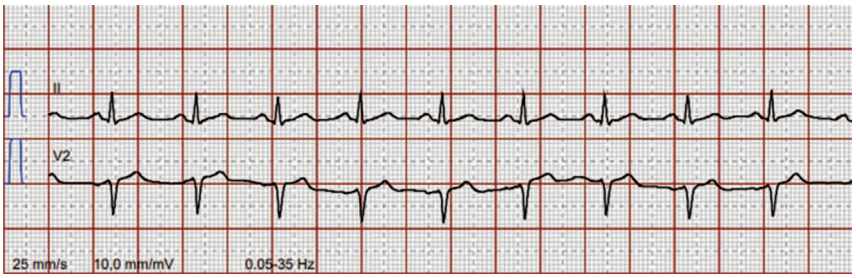


Figure 2. *Electrocardiography of patient*
Note. Sinus rhythm with a heart rate of 76 beats per minute. The electrical axis of the heart is horizontal

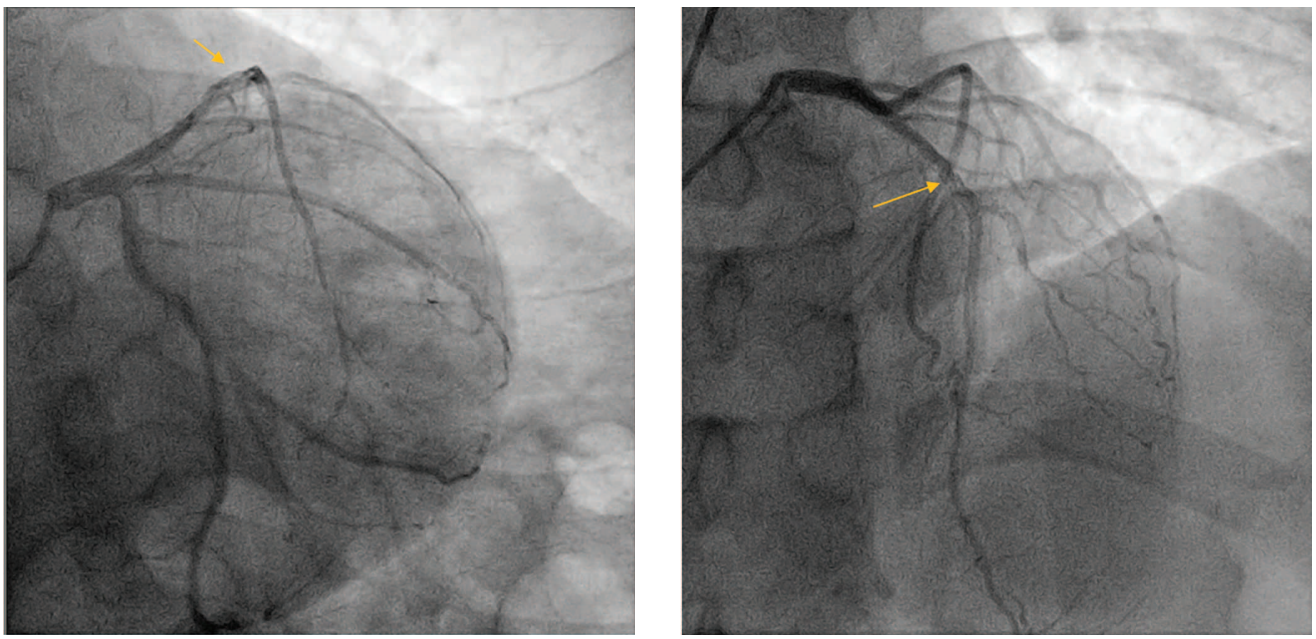


Figure 3. *Coronary angiography of patient at admission*
Note. An eccentric atherosclerotic plaque of 40 % is determined in the anterior interventricular artery (AIA) in the middle third

Myocardial hypertrophy of the apex (1.06 cm) and inferior wall (0.8 cm) of the apical LV segment. A clot sized 4.4×2.4 cm was detected attached to the LV apex. After contrast administration, its transmural accumulation was confirmed in the apex and anterior LV wall (apical segment) (Fig. 4).

Brain MRI (January 11, 2022) was ordered to exclude ischemic foci in the patient's brain. According to its results, no mass lesions, ischemic changes, and intracerebral hemorrhages were detected.

Due to the high risk of embolic complications, thrombectomy (January 13, 2022) was selected.

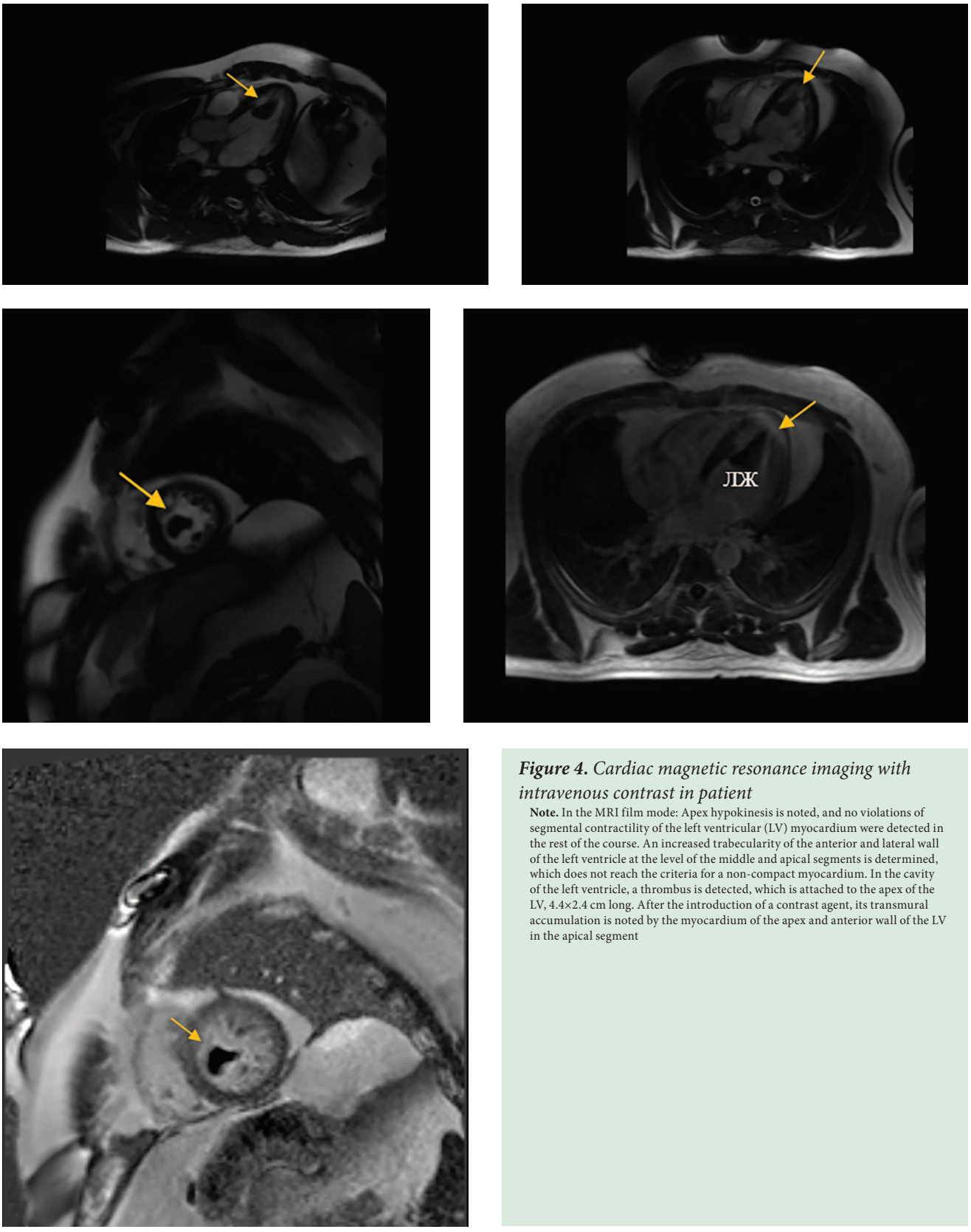


Figure 4. *Cardiac magnetic resonance imaging with intravenous contrast in patient*

Note. In the MRI film mode: Apex hypokinesis is noted, and no violations of segmental contractility of the left ventricular (LV) myocardium were detected in the rest of the course. An increased trabecularity of the anterior and lateral wall of the left ventricle at the level of the middle and apical segments is determined, which does not reach the criteria for a non-compact myocardium. In the cavity of the left ventricle, a thrombus is detected, which is attached to the apex of the LV, 4.4×2.4 cm long. After the introduction of a contrast agent, its transmural accumulation is noted by the myocardium of the apex and anterior wall of the LV in the apical segment

Intraoperative transesophageal echocardiography (January 13, 2022): LV ejection fraction (Simpson) 55 %. Cardiac chambers were not enlarged. Global myocardial contractility was normal. Apical LV hypokinesis was detected. A mobile hyperechogenic lesion on a thin pedicle sized 4.6×2.3 cm and attached to the apex was located in the LV cavity. Mild mitral and tricuspid regurgitation was detected (Fig. 5).

The mass tumor-like lesion was removed from LV via the right-sided mini-thoracotomy in the 4th intercostal space (Fig. 6). Intraoperative revision: a solid piriform LV lesion lacking a capsule, 4 cm long, 1–2 cm wide, fixed with a solid fibrotic based to the myocardium of the LV apex. The lesion was excised within the limits of normal tissues; the section demonstrated the sarcotic structure with solid fibrotic areas.

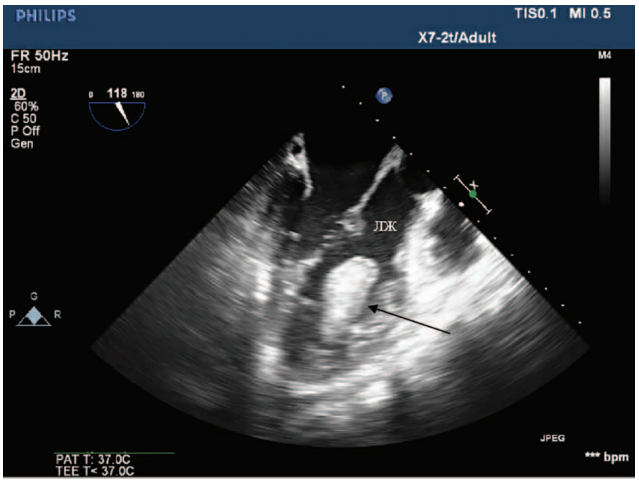


Figure 5. *Intraoperative transesophageal echocardiography of patient*

Note. In the cavity of the left ventricle, a mobile hyperechoic formation on a thin stalk is located, attached to the apex, 4.6×2.3 cm in size

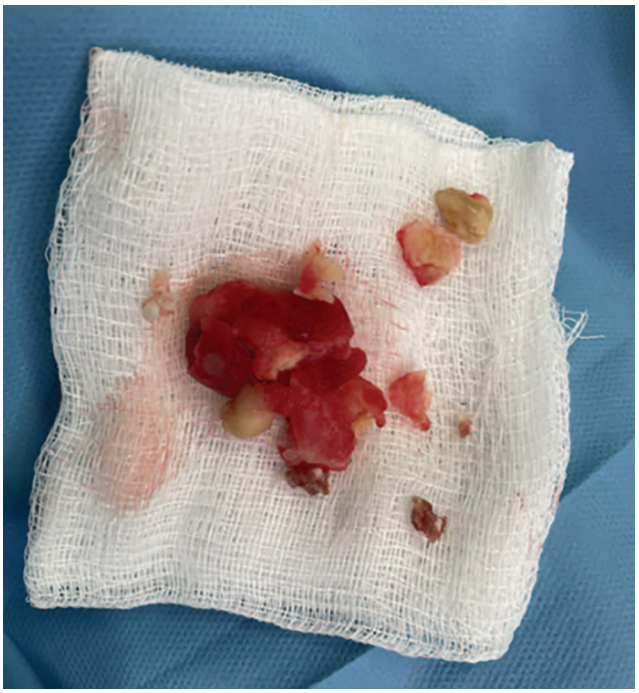


Figure 6. *Intraoperative view of the left ventricular mass*

The histological material was sent to the pathology center for examination. The following conclusion was made: "thrombotic masses with focal organization".

Accounting for thrombotic masses based on MRI and the histology results, CAG was analyzed again to verify the ischemic origin of clinical signs — AIVA dissection was suspected. It was decided to order the intravascular ultrasound (IVUS).

The repeated coronary angiography (Day 6 after the admission) detected a prolonged area of duplicated lumen with narrowing up to 75 % (Fig. 7A) in the AIVA and second diagonal branch. IVUS revealed a duplicated dissection lumen, 45–50 mm long, which was partially thrombotic and formed against the background of atherosclerotic plaque; true arterial lumen in distal areas was completely obturated with the IVUS catheter (Type 1 chronic AIVA dissection with thrombus recanalization) (Fig. 7B). AIVA was stented with drug-eluting stents (PROMUS, Boston Scientific, Massachusetts, USA) 2.75 x 32 mm and 3.5 x 32 mm (Fig. 8). The follow-up CAG confirmed the elimination of AIVA stenosis, with the artery patent along the whole length and preserved distal circulation.

Accounting for the disease history, clinical signs, and examination results, the patient was tested for the gene of Factor V Leiden mutation — a polymorphism variant predisposing to impaired folate cycle (heterozygous form).

Based on the data obtained, the following diagnosis was verified in the patient: "Thrombophilia (Factor V Leiden heterozygote)".

On Day 8, the patient was discharged home with the following clinical diagnosis:

Main disease: LV lesion (thrombus). ICD-10 code: D15.1

Main disease: Non-stenotic atherosclerosis of coronary arteries. Dissection of AIVA and the diagonal branch (DB) (Type 1 based on IVUS data). ICD-10 code: I25.1

Complication of the main disease: TIA (cardioembolic subtype) in the territory of the right middle cerebral artery (January 5, 2022). Heart failure with preserved EF (EF 55 %), Stage 2A (Strazhesko-Vasilenko staging), Functional Class II (NYHA). ICD-10 code: I50.0

Surgery: Excision of the mass LV lesion on January 13, 2022. Percutaneous transluminal coronary angioplasty of AIVA with the implantation of PROMUS stents 2.75 x 32 mm and 3.5 x 32 mm (January 16, 2022).

Concomitant diseases: Venous thromboses of the right upper and lower extremities (in 2017, 2018). Thrombophilia (Factor V Leiden heterozygote).

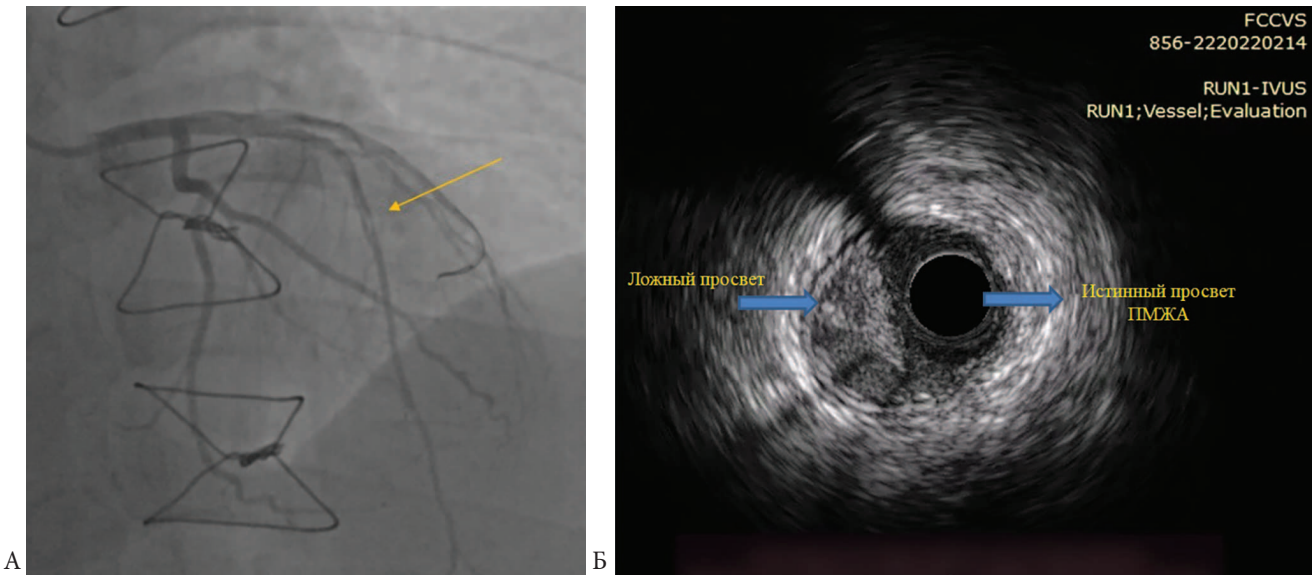


Figure 7. *Coronary angiography and IVUS after surgery (on the 6th day from admission) of Patient A., 36 years old*
Note. А — coronary angiography in the postoperative period (dissection of the anterior interventricular artery type 1 with recanalized thrombus; Б — intravascular ultrasound (IVUS)

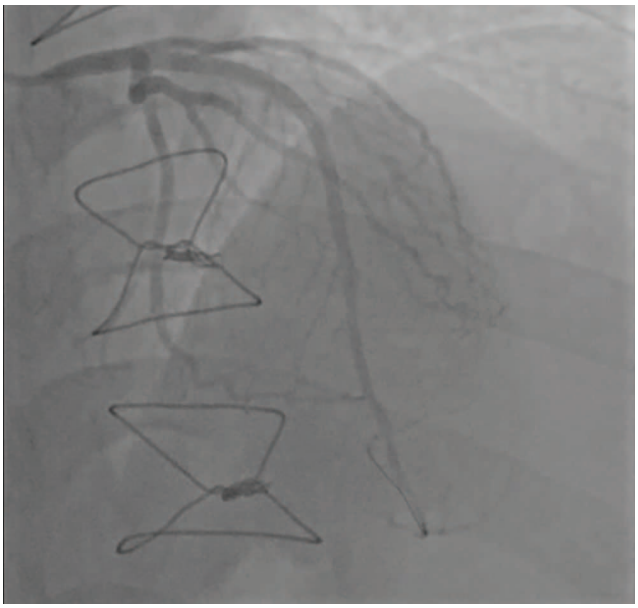


Figure 8. *Control coronary angiography after, anterior interventricular artery stenting of Patient A., 36 years old*
Abbreviations: IVUS, intravascular ultrasound, AVA, anterior interventricular artery

The patient was given the following recommendations on drug therapy: triple antithrombotic therapy for 6 months (rivaroxaban 20 mg + acetylsalicylic acid 75 mg + clopidogrel 75 mg QD), followed by dual antithrombotic therapy for another 6 months (clopidogrel 75 mg + rivaroxaban 20 mg QD), then rivaroxaban monotherapy 20 mg QD should be continued; nebivolol 7.5 mg QD, fixed perindopril 5 mg + indapamide 1.25 mg QD with BP monitoring; spironolactone 25 mg QD (for 1 month with potassium level and glomerular filtration rate monitoring, and subsequent decision on treatment adjustment); rosuvastatin 40 mg QD (with low-density lipoprotein monitoring).

When the patient was followed up later, thromboembolic complications did not relapse, and the patient was in satisfactory condition.

Subsequently, the patient discontinued the therapy administered himself and developed the acute cerebrovascular accident (7 months after discharging). The treatment is currently resumed to a complete extent.

Discussion

If a mass cardiac lesion is suspected in patients, echocardiography is traditionally used as the primary imaging method [11]. However, the differential diagnosis of cardiac lesions based on echocardiography data is complex, especially in young patients. Though transthoracic echocardiography is highly specific (98 %), it is less sensitive than cardiac MRI (29 % vs. 82–88 %) [12]. Contrast-enhanced cardiac MRI provides an additional valuable diagnostic information, which is especially important when planning the surgical intervention; this method specificity reaches 100 % [13]. According to cardiac MRI, LV thrombosis was detected in our patient. In order to exclude thrombosis development (or formation) as CAD/MI complication (or against the background of ischemic events), CAG was arranged in the patient [14]. However, primary CAG evaluation did not demonstrate overt causes of thrombus formation. SCAD was suspected only with repeated expert evaluation.

The latest decade has demonstrated changes in the concept of clinical SCAD evaluation as a non-atherosclerotic non-traumatic cause of acute coronary syndrome (ACS) and sudden cardiac death [6]. SCAD is an uncommon, but rather well-known clinical condition, which may manifest as ACS, syncope, or heart failure. The prevalence of this condition is 0.1–0.24 % among all patients that undergo CAG for stable coronary artery disease or CAG [7]. It is often difficult to detect the coronary artery dissection only with coronary angiography data (as in our case) — such additional examinations as optical coherent tomography or IVUS are required [6, 7, 10].

SCAD treatment options include conservative treatment, early revascularization with percutaneous intervention (PCI), or coronary bypass. PCI is predominant in isolated single-vessel dissection, coronary bypass is more suitable for patients with the dissection of the left coronary artery or several vessels [9].

AIVA stenting was selected in the case study presented, which led to the restoration of the arterial patency. TIA and LV thrombosis in the differential diagnosis of the patient led to the diagnosis "Thrombophilia (Factor V Leiden heterozygote)". Meanwhile, despite the acute thrombosis, administered anticoagulants, and comorbidities, the genetic test (polymerase chain reaction) helps to detect the Leiden mutation [15].

Single cases with SCAD combinations in patients with the Leiden mutation are described in the literature. Tahir Khan et al. (2013) described a rare SCAD case (in the right coronary artery) with the Factor V Leiden mutation in a 31-year-old male [16]. Stents were implanted in that patient. J.H. Joo et al. (2019) published another SCAD and LV thrombosis case in a 64-year-old female with successful conservative management [17].

Further patient management in the clinical case presented presumes long-term antithrombotic treatment. The patient compliance with the treatment is mandatory for the prevention of possible cardiovascular accidents [18]. Treatment compliance does not exceed 50 % with long-term secondary cardiovascular prevention [19]. From the perspective of patient-oriented approach and treatment continuity, high-tech medical care should be followed with outpatient recommendations at place of residence, which is not always possible in real clinical practice. Despite adequate patient awareness about possible unfavorable events with treatment discontinuation, further follow-up revealed unsatisfactory compliance with the recommendations, which led to the acute cerebrovascular accident. Subsequently the patient resumed the administered treatment and is constantly followed up at place of residence.

Conclusion

The described clinical case raises several important and unsolved issues of interdisciplinary patient management, including the inclusion of SCAD into the differential diagnosis of cardiovascular accidents — this presumes combined diagnosis with IVUS. One should account for the comorbidity of patients, including the history of cardiovascular events. Accounting for the age, risk factors, and the character of cardiovascular diseases, timely diagnosis of thrombophilia improves the prognosis in patients. The treatment of patient with thrombophilia after SCAD and intracardiac thrombosis presumes that the correct and timely cardiosurgical tactics is inseparably associated with conservative therapy providing the prevention of cardiovascular events. Therapy continuation, satisfactory treatment compliance, and monitoring the compliance with recommendations form the basis of the comorbid patient treatment that helps to improve the prognosis. Any successful cardiosurgical treatment will not be able to prevent further relapses in the absence of compliance with long-term conservative therapy, which is literally confirmed by the described clinical case.

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Энгиноев С.Т. (ORCID ID: https://orcid.org/0000-0002-4344-2672): разработка концепции и дизайна, обзор публикаций по теме статьи, написание текста статьи, одобрение окончательной версии статьи перед подачей для публикации

Мартьянова Ю.Б. (ORCID ID: https://orcid.org/0000-0002-4344-2672): анализ и интерпретация данных, написание текста статьи, одобрение окончательной версии статьи перед подачей для публикации

Шапошникова Е.И. (ORCID ID: https://orcid.org/0000-0001-9065-1189): анализ и интерпретация данных, написание текста статьи, одобрение окончательной версии статьи перед подачей для публикации

Ефремова Е.В. (ORCID ID: https://orcid.org/0000-0002-7579-4824): обзор публикаций по теме статьи, научная консультация, одобрение окончательной версии статьи перед подачей для публикации

Чернов И.И. (ORCID ID: https://orcid.org/0000-0002-9924-5125): анализ и интерпретация данных, написание текста статьи, одобрение окончательной версии статьи перед подачей для публикации

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Enginoev S.T. (ORCID ID: https://orcid.org/0000-0002-4344-2672): development of the concept and design, review of publications on the topic of the article, writing the text of the article, approval of the final version of the article before submission for publication

Martyanova Yu.B. (ORCID ID: https://orcid.org/0000-0002-4344-2672): data analysis and interpretation, writing the text of the article, approval of the final version of the article before submission for publication

Shaposhnikova E.I. (ORCID ID: https://orcid.org/0000-0001-9065-1189): data analysis and interpretation, writing the text of the article, approval of the final version of the article before submission for publication
Efremova E.V. (ORCID ID: https://orcid.org/0000-0002-7579-4824): review of publications on the topic of the article, scientific consultation, approval of the final version of the article before submission for publication
Chernov I.I. (ORCID ID: https://orcid.org/0000-0002-9924-5125): data analysis and interpretation, writing the text of the article, approval of the final version of the article before submission for publication

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