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МЕЖДУНАРОДНЫЙ МЕДИЦИНСКИЙ РЕЦЕНЗИРУЕМЫЙ ЖУРНАЛ

Издается под эгидой Евразийской аритмологической ассоциации врачей кардиологов и терапевтов

ЭКО • ВЕКТОР

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СОДЕРЖАНИЕ

Dear colleagues!

The first issue of the journal that was initiated by the Eurasian Arrhythmology Association together with the Mechnikov North-Western State Medical University is now presented to the readers. The publications that focused on the problems of arrhythmias nowadays publish materials for a small target audience of doctors. This journal is intended for a wide range of specialists despite the impression of narrow specialization. This is a distinguishing characteristic of the journal. After all, heart rhythm and conduction disorders can often be manifestations of comorbid pathology.

The contemporary healthcare system cannot be developed without meaningful professional communication. We hope that the journal will become a debate platform for discussions on topical issues of heart diseases and comorbid conditions that are complicated by heart rhythm and conduction disorders. Moreover, we hope that it will help to ensure scientific communication and exchange of ideas and results of our research and contribute to the introduction of new scientific research results into healthcare practice. Currently, the conversational interaction and exchange of scientific knowledge enable arrhythmologists, cardiologists, cardiovascular surgeons, and scientists of other specialties to diversify clinical arrhythmology problems. We are convinced that such a multidisciplinary approach will significantly improve the quality of medical care for patients, not only with cardiac arrhythmias but also with various diseases that are the root cause or contribute to their development.

The journal publishes clinical guidelines, original articles, article reviews, clinical cases, lectures/discussion reports, and notes on the activities of the Eurasian Arrhythmology Association. All articles are subject to double-blind peer review by authoritative scientists and specialists reputable in the field of knowledge of the published article.

The journal is published in Russian and English quarterly, both in electronic and printed versions. All articles are translated by the publisher and are free for the authors of the publication.

On behalf of the editorial board, I proffer you close cooperation. We look forward to receiving articles and reviews from you.

Respectfully yours,
S.A. Saiganov

Глубокоуважаемые коллеги!

Инициатива создания журнала принадлежит Евразийской аритмологической ассоциации вместе с Северо-Западным государственным медицинским университетом им. И.И. Мечникова. Сейчас вы знакомитесь с первым номером журнала. На сегодняшний день в изданиях, посвященных проблемам аритмий, публикуют материалы для небольшой целевой аудитории врачей. Этот журнал, несмотря на то, что название создает впечатление об узкой специализации, предназначен для широкого круга специалистов. Это является особенностью журнала. Ведь нарушения ритма и проводимости сердца зачастую бывают проявлениями коморбидной патологии.

Развитие современного здравоохранения невозможно без содержательной профессиональной коммуникации. Мы надеемся, что журнал станет дискуссионной площадкой для обсуждения актуальных вопросов заболеваний сердца и коморбидных состояний, осложненных нарушениями сердечного ритма и проводимости, поможет обеспечить научную коммуникацию, обмен идеями и результатами собственных исследований, а также будет способствовать внедрению новых научных разработок в практику здравоохранения. В настоящее время диалог и обмен научными знаниями аритмологов, кардиологов, сердечно-сосудистых хирургов и ученых других специальностей позволит разносторонне освещать проблемы клинической аритмологии. Уверены, что такой мультидисциплинарный подход позволит в значительной степени улучшить качество оказания медицинской помощи пациентам не только с аритмиями сердца, но и с тем широким кругом заболеваний, являющихся первопричиной или способствующих их развитию.

В журнале публикуются клинические рекомендации, оригинальные статьи, обзоры статей, клинические случаи, лекции/доклады дискуссии и заметки о деятельности Евразийской аритмологической ассоциации. Все статьи проходят двойное слепое рецензирование авторитетными учеными, специалистами, имеющими признание в области знаний публикуемой статьи.

Журнал публикуется на русском и английском языках ежеквартально, как в электронном, так и печатном вариантах. Все переводы статей осуществляются издательством и являются для авторов публикации бесплатными.

От имени редколлегии, приглашаю к тесному сотрудничеству. Ждем от вас статей и отзывов.

С уважением,
главный редактор С. А. Сайганов

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The Role of Hyperuricemia in the Development of Atrial Fibrillation

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Atrial fibrillation (AF) is one of the most common cardiac arrhythmias. We have discussed the role of hyperuricemia as a predisposing factor for the onset of AF. Numerous clinical and experimental investigators demonstrated the correlation between serum uric acid (SUA) level and arrhythmia development and its complications. The development and progression of AF are connected to a complex of changes in atrial cardiac muscle tissue. The electrical, structural, contractile remodeling, neurohumoral systems, inflammation, fibrosis, oxidative stress, endothelial dysfunction, activation of NLRP3 inflammasome induced by crystals of monosodium urate (MSU), heat shock proteins (HSP), cytokines – all have a role in the development of this process. Furthermore, the role of xanthine oxidase (XO) is considered in the pathogenesis of AF through activation of systemic inflammation and oxidative stress, preparing that substrate for AF. The overwhelming data suggest a direct pathophysiological role of the increased SUA and XO activity as risk factors for AF. This article offers a comprehensive review of investigations that shows the interrelation between hyperuricemia and the risk of AF.

Keywords: atrial fibrillation; uric acid; hyperuricemia; myocardial remodeling; oxidative stress; xanthine oxidase; uric acid transporters; heat shock proteins (HSP); NLRP3 inflammasome; cytokines.

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Роль гиперурикемии в развитии фибрилляции предсердий

Т.Л. Борисенко, В.А. Снежицкий

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Фибрилляция предсердий (ФП) — одно из наиболее распространенных нарушений сердечного ритма. В настоящее время обсуждается роль гиперурикемии как одного из предрасполагающих факторов возникновения ФП. Результаты многочисленных клинических и экспериментальных исследований продемонстрировали взаимосвязь повышения уровня мочевой кислоты (МК) относительно развития аритмии и ее осложнений. Развитие и прогрессирование ФП связаны с комплексом изменений ткани миокарда предсердий — электрическим, структурным, сократительным ремоделированием, известна роль нейрогуморальных систем, воспаления, фиброза, оксидативного стресса, эндотелиальной дисфункции, активации инфламмасомы NLRP3, индуцированной кристаллами моноурата натрия (МУН), белков теплового шока (HSP), цитокинов в развитии данного процесса. Накопленные данные позволяют предположить существование прямой патофизиологической роли повышенного уровня МК в сыворотке крови и активности ксантиноксидазы с риском ФП. Роль ксантиноксидазы в патогенезе ФП рассматривается через активацию системного воспаления и оксидативного стресса, формируя тем самым субстрат для ФП. Настоящая статья посвящена обзору исследований о взаимосвязи гиперурикемии с риском развития ФП.

Ключевые слова: фибрилляция предсердий; мочевая кислота; гиперурикемия; ремоделирование миокарда; оксидативный стресс; ксантиноксидаза; переносчики уратов; белки теплового шока (HSP); инфламмасома NLRP3; цитокины.

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ЭКО•ВЕКТОР

Atrial fibrillation (AF) is a supraventricular tachycardia characterized by uncoordinated electrical atrial activity [1]. This is one of the most widespread heart arrhythmias and causes about 80% of paroxysmal supraventricular tachycardia cases. The occurrence of AF in the general population reaches 2% and continues to increase [2]. AF morbidity is expected to double in the next 50 years. This increase is directly associated with an aging population, an increase of congestive heart failure prevalence, and improvements in diagnostics of this kind of arrhythmia disease [3]. In addition, AF deteriorates a patient's quality of life and increases the risk of lethal cardiovascular complications [4]. AF is prognostically unfavorable because it is followed by a growth of overall mortality and, in particular, cardiovascular mortality. The mortality rate is higher in AF patients than in patients with sinus rhythm. It also can be associated with a large number of thromboembolic complications [5].

Many epidemiological studies report that hyperuricemia is considered to be a significant AF risk factor as well as age, male sex, inheritance, obesity, hypercholesterolemia, tobacco smoking, strenuous physical activity, arterial hypertension, valvular heart disease, coronary heart disease, heart failure, and diabetes mellitus [6].

The role of uric acid (UA) in developing the most widespread cardiovascular diseases was first reported in the 1950s. Nowadays, the interest in studying purine metabolism and UA as its end-product is increasing. This is associated with an observable growth of both asymptomatic and clinically manifested hyperuricemia [7–10].

For the last decades, the spread of hyperuricemia has been considerably increasing worldwide. The data show a verifiable growth of hyperuricemia prevalence in the U.S. over the past decade from 19.1% to 21.4% [11]. A meta-analysis published by B. Liu et al. reported that the overall prevalence of hyperuricemia made up 21.6% for males and 8.6% for females, according to 59 Chinese studies sampled for meta-analysis, which were performed over the recent years [12]. It was demonstrated that the risk of hyperuricemia was increased among males in the age above 30 and females in the age above 50. The predominance of hyperuricemia prevalence among males was observed in other studies as well [13]. In the aforementioned Chinese study, it has been revealed that hyperuricemia among males has been found four times more often than among females [12]. Furthermore, a distinct age range of hyperuricemia prevalence: from 14.7% at a young age to 20.5% at the age of 55–64 was observed [14].

Hyperuricemia increases the UA concentration in the blood serum above 360 μmol/L for females and 400 μmol/L for males. However, these values could be subjected to various factors, such as race, sex, regular consumption of certain food products (red meat, seafood, alcohol) [15–17]. 5%–8% of the population has an asymptomatic increase in UA level, and only 5%–20% of them suffer from gout [18]. UA is a weak organic acid generated

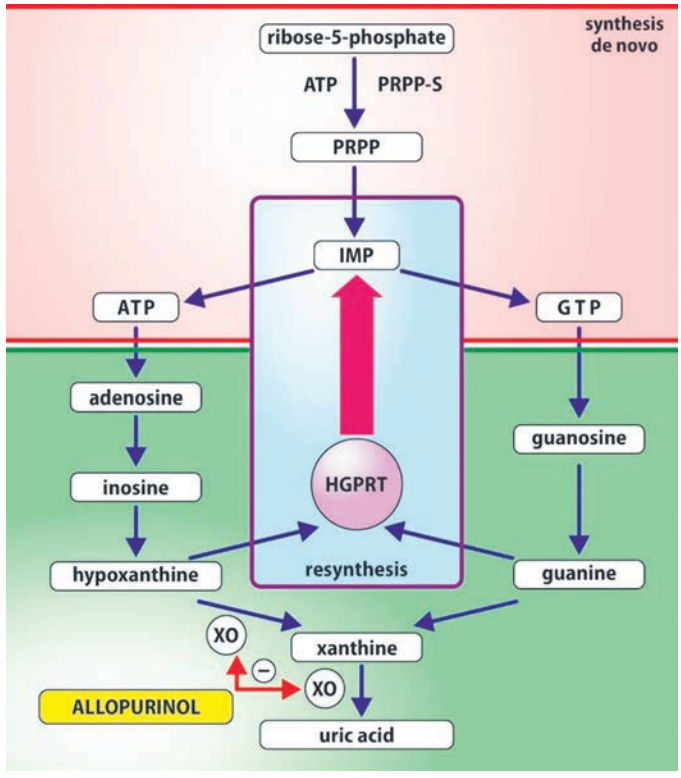

Fig. 1. De novo purine synthesis. Phosphoribosyl pyrophosphate synthetase (PRPP-S), adenosine triphosphate (ATP), phosphoribosyl pyrophosphate (PRPP), inosine monophosphate (IMP), guanosine triphosphate (GTP), hypoxanthine-guanine phosphoribosyltransferase (HGPRT), xanthine oxidase (XO).

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during the elimination of purine metabolism wastes. The key enzyme is phosphoribosyl pyrophosphate synthetase (PRPP-S). It launches several stages through which inosine monophosphate (IMP) produces adenosine triphosphate (ATP) and guanosine triphosphate (GTP). While performing their functions, ATP and GTP undergo a disintegration process which results in hypoxanthine, produced as a result of ATP degradation, and guanine made as a result of GTP degradation. Thus, they act as UA metabolic predecessors. These nitrogenous bases are oxidizing to xanthine, which in turn undergo oxidative transformation to the UA. The critical enzyme at this stage is the enzyme of xanthine oxidase (XO) (Fig. 1) [6].

Recent studies have confirmed a XO activity in the human heart (MacGowan et al., 1995) [19] and its allocation in microvascular endothelial cells, macrophages, and mast cells. The highest activity of XO becomes apparent in the endothelium. Endothelial XO plays a crucial role in vascular oxidative stress, which contributes to the development of AF [20]. The accumulated data allow us to propose a direct pathophysiological role of the increased UA concentration in the blood serum and XO activity with a risk of AF [21].

Ischemia and cellular damage facilitate to accumulation of xanthine, creating a substrate for XO. This enzyme participates in the purine degradation of the UA that is a source of superoxide radicals. This enzyme uses molecular oxygen as an electron acceptor and leads to the superoxide anion free radicals, thus contributing to oxidative stress. Superoxide anion can create hydrogen peroxide through the activity of superoxide dismutase, if Ferrum is present, it is a hydroxyl radical.

Moreover, the superoxide anion interacts with nitric oxide (NO) and composes a toxic molecule of peroxynitrite. Together, hydroxyl radicals and peroxynitrite induce cellular reactions ranging from subtle changes of cell functions to severe oxidative damage to affected macromolecules, leading to necrosis and apoptosis. Thus, XO is an inductor of oxidative stress, and emerging free radicals directly damage cardiomyocytes [20].

The development and progression of AF are connected to a complex of changes in atrial cardiac muscle tissue: electrical, structural, contractile remodeling, including secondary cardiovascular alterations in the left atrium due to remodeling of the left ventricle as a result of a pressure overload [22].

Structural remodeling during AF is characterized by atrial dilation and fibrosis, massive connective tissue accumulation, and individual myocytes' disruption. Fibrosis is a substrate of the micro-reentry mechanism, the circular movement of the excitation wave in the atrial cardiac muscle [23].

The electrophysiological mechanism of AF consists of electrical remodeling and abnormal automaticity, characterized by reduction of the cardiac action potential duration and effective refractory period. The autonomic dysfunction and the direct tachycardia influence on functions of ion channels are determined as possible sources of changes in atrial electrophysiological properties. Atrial automaticity can be associated with dysregulation of the intracellular Ca^{2+} concentration. Dysregulation of Ca^{2+} causes its release from the sarcoplasmic reticulum (SR) during the diastole periods and increases inward currents in cell membrane due to Na^{+}/Ca^{2+} exchange activation, which in turn induce afterdepolarization associated with triggered activity, thus facilitating aggravation of AF [24]. In addition, automaticity through triggered activity in the pulmonary veins (PV) becomes a trigger to AF, supporting the reentry mechanism at the boundaries between PV and the atrium [25]. As well as ischemia, fast atrial contraction can lead to a shortening of the refractory period due to high-energy phosphate depletion and activation of ATP-sensitive K^{+} channels, as well as to Ca^{2+} atrial cardiac muscle overload [26]. Furthermore, decreasing Na^{+} currents and transient outward potassium current (/to) reduces the refractory period and decreases cardiac conduction [27]. Together, these mechanisms facilitate the generation of multiple excitation waves in the atria, frequent activation of the atria, and refractory dispersion [28].

The role of neurohumoral systems, in particular, renin-angiotensin-aldosterone system, inflammation, fibrosis oxidative stress, and endothelial dysfunction (for example, through a decrease of the NO production by endothelium), activation of the NLRP3 inflammasome, induced by monosodium urate (MSU) crystals, was revealed in the development of that process [26].

The link between hyperuricemia and changes in cardiac structure was examined in mice. The increase of the UA was followed by increased XO activity in cardiac tissue, which caused cardiomyocyte hypertrophy, myocardial oxidative stress, interstitial fibrosis, and disturbance of diastole relaxation due to activation of S6 kinase beta-1, profibrotic TGF-β1/Smad2/3 signaling. These results improved after the allopurinol administration. Thus, XO may facilitate an aggravation of AF. However, no prospective clinical studies have yet been performed to test the possibility of xanthine oxidase inhibitor's ability to prevent a genesis of AF [29].

Mouse cardiomyocytes were found to express at least 4 UA transporters (UAT): URATv1/GLUT9, ABCG2, MRP4, and MCT9. According to Maharani et al., urate transporters help activate a protein in voltage-dependent Kv1.5 potassium channels. This results in an inducement of ultrarapid delayed rectifier current (/Kur) with the decrease of atrial action potential and, in this way, influencing the development of arrhythmogenic substrate [30].

The inhibition of the UA-influx by a UAT with benzbromarone attenuated the enhancement of Kv1.5 protein expression by decreasing intracellular UA. In contrast, inhibition of ABCG2, the UA-efflux transporter, accelerated an expression of Kv1.5 protein. Accumulated intracellular UA induced cellular damage due to oxidative stress. Blocking the enhanced Kv1.5 protein expression was abolished by the *N*-acetylcysteine antioxidant and apocynin, the inhibitor

of NADPH oxidase. This makes it possible to assume that antioxidants may be a new therapeutical approach in the AF treatment in patients with hyperuricemia [30].

One of the promising approaches in modern-day cardiology is the study of the impact of heat shock proteins (HSP) on the state of the cardiovascular system. HSP is synthesized in all nucleus cells, and its expression is increased during any stressful exposure (inflammation, hypoxia, intoxication). In stressful conditions, heat shock protein 70 (Hsp70) prevents the protein misfolding and the Kv1.5 protein aggregation, which expression is regulated by heat shock factor 1 (HSF1). HSF1 activation and Hsp70 associated increase are crucial factors that help cells overcome stress and reduce the risk of damage [29]. Taufiq et al. researched a UA inducement mechanism for boosting a Kv1.5 expression and revealed how intracellular accumulation of the UA facilitates HSF1 activation and Hsp70 increase. HSF1 is activated by oxidative stress, and HSF1 activation increases HSP expression. It has been proved that an inducement of HSP synthesis could be observed during hyperuricemia [31].

According to various experimental, epidemiological, and cohort observational studies, inflammation plays a vital role in the AF onset and preservation [32, 33]. AF is associated with an elevation of several inflammatory markers in the blood plasma, such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP). NLRP3 inflammasome is a multi-protein complex, which consists of NLRP3, ASC, and procaspase-1 enzymes. In addition, NLRP3 inflammasome launches the production of bioactive caspase-1, which contributes to the maturation of active IL-1β and IL-18 [34]. Macrophages and myoblasts release these cytokines as components of the inflammatory response [35].

An increased UA level (more than 400 μmol/L) in the blood serum induces the concretion of monosodium urate (MSU) crystals and directly activates the NLRP3 inflammasome. MSU utilizes caspase-1 by activating the NLRP3 inflammasome, resulting in IL-1β and IL-18 output in the human monocytic cell line (THP1). In an inflammasome-deficient mice model, neutrophil influx induced by MSU was markedly impaired. Moreover, colchicine, the medicine used to prevent the first stage of gout inflammation, can block IL-1β maturation caused by MSU. NLRP3 inflammasome activity was increased in atrial cardiomyocytes of patients with paroxysmal and permanent AF. In addition, NLRP3 and caspase-1 levels in the right atrium were increased in patients with permanent AF [36].

An AF inducement has been demonstrated in a knock-in mouse model, which constantly expressed active NLRP3. MCC950, a selective inhibitor of the NLRP3 inflammasome, interrupts the NLRP3 inflammasome complex assembly and suppresses AF induction. The activation of the NLRP3 inflammasome, specific to cardiomyocytes, induces electrical and structural remodeling of atria, exhibiting abnormal release of Ca^{2+} from the SR, efficient contraction of the atrial effective refractory period, and atrial enlargement. On the contrary, NLRP3 knockdown suppressed the AF induction and restored the normal levels of mRNA, Ryr2, Kcna5, Girk1, and Girk4. This data demonstrates that MSU activates the NLRP3 inflammasome, associated with AF pathophysiology [37].

CRP and TNF-α proinflammatory cytokines participate in cellular signal activation and are associated with fibrosis, apoptosis, and hypertrophy. The level of TNF-α, an inflammatory mediator, was considerably increased in patients with a history of diastolic heart failure (DHF) and AF in a cohort of patients with DHF [37]. TNF-α changed the expression or distribution of connexin 40 and connexin 43 and directly changed the Ca^{2+} processing in cardiomyocytes [38]. Also, it has been revealed that TNF-α increases the apoptosis of cardiomyocytes and myolysis. This leads to the dilation of atria and conduction heterogeneity [39]. The level of circulating CRP is higher in patients with a history of AF than in patients without AF. For patients with permanent AF, the CRP level is higher compared to patients with paroxysmal AF [40]

Performed experimental and clinical studies prove the negative effect of proinflammatory cytokines on AF aggravation. The study showed that mice with increased TNF-α expression had an increased risk of AF aggravation. Furthermore, the influence of proinflammatory cytokines on AF aggravation was estimated in an experiment in dogs. It was concluded that the growth of IL and TNF-α concentrations in plasma significantly increases the risk of AF aggravation and prescription of infliximab, a TNF-α inhibitor, prevents the onset of arrhythmia [4].

Data collected for the last several years indicate thin most cases of hyperuricemia associated with gout are more likely connected with acid underexcretion than overproduction. In total, 300–600 mg (1.8–3.6 mmol) of the UA is excreted in 24 hours. Approximately 95% of the UA is excreted in urine as a result of glomerular filtration. However, almost all UA later undergo subsequent reabsorption of underexposed urate transporters (URAT-1) and organic anion transporters in proximal tubules. After that, it is again secreted in the distal tubules in urine, and later 80 % of the acid is completely reabsorbed into the blood, and 20 % is excreted in the urine. An increase in the UA level in the blood serum influences endothelial cells and vascular smooth muscles, resulting in microvascular kidney damage. As a result, kidneys may have a crucial role in the UA inadequate excretion and thus become a reason for hyperuricemia [6].

Hyperuricemia is significantly associated with AF. In addition, the results of numerous clinical and experimental studies demonstrated an interlink between an increase of UA and the development of arrhythmia with complications [41].

A retrospective study of 49,292 medical records, completed by Japanese scientists Kuwabara M. et al. in 2016 revealed that hyperuricemia is a significant independent and competing risk factor of AF in a healthy person, as well as old age, male sex, high body mass index, low FEV1/FVC ratio, and increased hemoglobin levels [42].

Lots of studies have found a positive correlation between the UA concentration and AF. For example, a prospective cohort study of 123,238 Chinese patients enrolled in the study from 2006 to 2014 showed that high UA concentration and its increase with time was associated with an increased risk of AF. Furthermore, in another cohort study, gout resulting from hyperuricemia was associated with a moderately increased risk of AF [1].

According to the meta-analysis of clinical studies performed by Chinese scientists Chun-Hong Zhang et al. in 2015, the UA increased level in the blood serum was associated with the risk of paroxysmal and persistent AF occurrence in the general population and also in patients subjected to coronary artery bypass surgery. This connection can be explained by the influence of oxidative stress and activation of the systemic inflammatory response [43].

A study of 140 patients, performed by Deshko M.S. et al. in 2015, demonstrated the connection of the higher level of UA in the blood serum in patients with permanent AF, regardless of whether they have AHT and/or CAD, compared with those without arrhythmia. Furthermore, an increase of XO activity facilitated the increase in the UA level, xanthine dehydrogenase conversion in XO (boosting the velocity of synthesis), adenosine triphosphate degradation to adenosine and hypoxanthine (boosting the quantity of substrate), and also a competitive decrease of the UA excretion in the kidney proximal tubules due to lactic acid increased production [44, 45]. A high level of UA may be an AF predictor. This is confirmed by a large-scale cohort study of 6,308 people in the general population of Norway (Nyrnes A. et al., 2014) [46].

To this date, the treatment of AF appears to be one of the most significant challenges for public health. The results of numerous clinical and experimental studies demonstrated the prognostic significance of the UA level increase to the development of arrhythmia and its complications. Hence, it is necessary to focus on monitoring the UA level in the blood serum in rheumatic patients and decreasing cardiovascular and kidney disease risks. Furthermore, assessing the patient's clinical status and understanding of subtle mechanisms of arrhythmogenesis make it possible to discuss specific treatment courses aligned with a current view of precision medicine.

ADDITIONAL INFORMATION

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REFERENCES

1. Taufiq F, Li P, Miake J, Hisatome I. Hyperuricemia as a risk factor for atrial fibrillation due to soluble and crystalized uric acid. *Circ Rep*. 2019;1(11):469–473. DOI: 10.1253/circrep.CR-19-0088

2. Krijthe BP, Kunst A, Benjamin EJ, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J*. 2013;34(35):2746–2751. DOI: 10.1093/eurheartj/eht28027462751

3. Zozulya IS, Gandzha TI, Suprun AO, Olefirenko AS. Provision of emergency medical care for atrial fibrillation. *Medicina neotlozhnykh sostoyanij*. 2016;3–4:60–61. (In Russ.).

4. Podzolkov VI, Tarzimanova AI, Gataulin RG, et al. The role of obesity in the development of atrial fibrillation: current problem status. *Cardiovascular Therapy and Prevention*. 2019;18(4):109–114. (In Russ.). DOI: 10.15829/1728-8800-2019-4-109-114

5. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation — developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J*. 2012;33(21):2719–2747. DOI: 10.1093/eurheartj/ehs253

6. Zhernakova Yu. Hyperuricemia as a risk factor for cardiovascular disease - what's new? *Medical Alphabet*. 2020;(13):5–11. (In Russ.). DOI: 10.33667/2078-5631-2020-13-5-11

7. Bilchenko A. Hyperuricemia as a risk factor of cardiovascular morbidity and mortality.Korrekciya giperurikemii kak faktora riska serdechno-sosudistoj zabolevaemosti i smertnosti // Novosti mediciny i farmacii. 2011;5(389):53–58. (In Russ.).

8. Donskov A, Balkarov I, Dadina Z, et al. Urate kidney damage and metabolic changes in patients with arterial hypertension. *Terapevticheskij Arkhiv*. 1999;(6):53–56. (In Russ.).

9. Becker JF, Schumacher HR Jr, Wortmann RL. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med*. 2005;353:2450–2461. DOI: 10.1056/NEJMoa050373

10. France LV, Pahor M, Di Bari M, et al. Serum uric acid, diuretic treatment and risk of cardiovascular events in the Systolic Hypertension in the elderly Program (SHEP). *J Hypertens*. 2000;18(8):1149–1154. DOI: 10.1097/00004872-200018080-00021

11. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population. The National Health and Nutrition

Examination Survey 2007–2008. *Arthritis Rheum.* 2011;63(10): 3136–3141. DOI: 10.1002/art.30520

12. Liu B, Wang T, Zhao HN, et al. The prevalence of hyperuricemia in China: a meta-analysis. *BMC Public Health.* 2011;11:832. DOI: 10.1186/1471-2458-11-832

13. Qiu L, Cheng X, Wu J, et al. Prevalence of hyperuricemia and its related risk factors in healthy adults from Northern and Northeastern Chinese provinces. *BMC Public health.* 2013;13:664. DOI: 10.1186/1471-2458-13-664

14. Shal'nova SA, Deev AD, Artamonova GV, et al. Hyperuricemia and its correlates in the Russian population (results of the ESSE-RF epidemiological study). *Rational Pharmacotherapy in Cardiology.* 2014;10(2):153–159. (In Russ.).

15. Wu AH, Gladden JD, Ahmed M, et al. Relation of serum uric acid to cardiovascular disease. *Int J Cardiol.* 2016;213:4–7. DOI: 10.1016/j.ijcard.2015.08.110

16. Hou L, Zhang M, Han W, et al. Influence of salt intake on association of blood uric acid with hypertension and related cardiovascular risk. *PLoS One.* 2016;11(4):e0150451. DOI: 10.1371/journal.pone.0150451

17. Ando K, Takahashi H, Watanabe T, et al. Impact of serum uric acid levels on coronary plaque stability evaluated using integrated backscatter intravascular ultrasound in patients with coronary artery disease. *J Atheroscler Thromb.* 2016;23(8):932–939. DOI: 10.5551/jat.33951

18. Bespalova I, Kalyuzhin V, Medyantsev Yu. Asyptomatic hyperuricemia as a metabolic syndrome component. *Bulletin of Siberian Medicine*. 2012;11(3):14–17. (In Russ.). DOI: 10.20538/1682-0363-2012-3-14-17

19. MacGowan S, Regan M, Malone C, et al. Superoxide radical and xanthine oxidoreductase activity in the human heart during cardiac operations. *Ann Thorac Surg.* 1995;60(5):1289–1293. DOI: 10.1016/0003-4975(95)00616-S

20. Korantzopoulos P, Letsas K, Liu T. Xanthine oxidase and uric acid in atrial fibrillation. *Front Physiol.* 2012;3:150. DOI: 10.3389/fphys.2012.00150

21. Letsas K, Korantzopoulos P, Filippatos G, et al. Uric acid elevation in atrial fibrillation. *Hellenic J Cardiol.* 2010;51(3):209–213.

22. Yatskevich ES, Snezhitskiy VA. The influence of aldosterone and its antagonists on myocardial remodeling in ratients with atrial fibrillation. *Journal of Grodno State Medical University*. 2012;(4(40)):5–9. (In Russ.).

23. Delcayre C, Swynghedauw B. Molecular mechanisms of myocardial remodelling. The role of aldosterone. *J Mol Cell Cardiol.* 2002;34(12):1577–1584. DOI: 10.1006/jmcc.2002.2088

24. Schotten U, Verheule S, Kirchhof P, Goette A. Pathophysiological mechanisms of atrial fibrillation: A translational appraisal. *Physiol Rev.* 2011;91(1):265–325. DOI: 10.1152/physrev.00031.2009

25. Patterson E, Jackman WM, Beckman KJ, et al. Spontaneous pulmonary vein firing in man: Relationship to tachycardia-pause early afterdepolarizations and triggered arrhythmia in canine pulmonary veins in vitro. *J Cardiovasc Electrophysiol.* 2007;18(10):1067–1075. DOI: 10.1111/j.1540-8167.2007.00909.x

26. Zholbaeva A, Tabina A, Goluhova E. Molecular mechanisms of atrial fibrillation: "ideal" marker searching. *Creative Cardiology.* 2015;(2):40–53. (In Russ.). DOI: 10.15275/kreatkard.2015.02.04

27. Dobrev D, Friedrich A, Voigt N, et al. The G protein-gated potassium current I(K,ACh) is constitutively active in patients with chronic atrial fibrillation. *Circulation.* 2005;112(24):3697–3706. DOI: 10.1161/CIRCULATIONAHA.105.575332

28. Snezhitskiy V. Electrophysiological atrial and sinus nodal remodeling phenomenon: mechanisms of development and pathogenesis. *Clinical Medicine (Russian Journal).* 2004;82(11): 10–14. (In Russ.).

29. Jia G, Habibi J, Bostick BP, et al. Uric acid promotes left ventricular diastolic dysfunction in mice fed a Western diet. *Hypertension.* 2015;65(3):531–539. DOI: 10.1161/HYPERTENSIONAHA.114.04737

30. Maharani N, Ting YK, Cheng J, et al. Molecular mechanisms underlying urate-induced enhancement of Kv1.5 channel expression in HL-1 atrial myocytes. *Circ J.* 2015;79(12):2659–2668. DOI: 10.1253/circj.CJ-15-0416

31. Niforou K, Cheimonidou C, Trougakos IP. Molecular chaperones and proteostasis regulation during redox imbalance. *Redox Biol.* 2014;2:323–332. DOI: 10.1016/j.redox.2014.01.017

32. Giannopoulos G, Cleman MW, Deftereos S. Inflammation fueling atrial fibrillation substrate: Seeking ways to "cool" the heart. *Med Chem.* 2014;10(7):663–671. DOI: 10.2174/1573406410666140318110100

33. Bubeshka DA, Snezhitskiy VA, Shulika VR. Biomarkers of inflammation in patients with nonvalvular atrial fibrillation and left ventricular systolic dysfunction. *Medical News.* 2017;(4):69–72. (In Russ.)

34. Levy M, Thaiss CA, Elinav E. Taming the inflammasome. *Nat Med.* 2015;21(3):213–215. DOI: 10.1038/nm.3808

35. Bruins P, te Velthuis H, Yazdanbakhsh AP, et al. Activation of the complement system during and after cardiopulmonary bypass surgery: Postsurgery activation involves C-reactive protein and is associated with postoperative arrhythmia. *Circulation.* 1997;96(10):3542–3548. DOI: 10.1161/01.cir.96.10.3542

36. Yao C, Veleva T, Scott LJ, et al. Enhanced cardiomyocyte NLRP3 inflammasome signaling promotes atrial fibrillation. *Circulation.* 2018;138(20):2227–2242. DOI: 10.1161/CIRCULATIONAHA.118.035202

37. Putko BN, Wang Z, Lo J, et al. Circulating levels of tumor necrosis factor-alpha receptor 2 are increased in heart failure with preserved ejection fraction relative to heart failure with reduced ejection fraction: Evidence for a divergence in pathophysiology. *PLoS One.* 2014;9(6):e99495. DOI: 10.1371/journal.pone.0099495

38. Liew R, Khairunnisa K, Gu Y, et al. Role of tumor necrosis factor-α in the pathogenesis of atrial fibrosis and development of an arrhythmogenic substrate. *Circ J.* 2013;77(5):1171–1179. DOI: 10.1253/circj.cj-12-1155

39. Hu YF, Chen YJ, Lin YJ, Chen SA. Inflammation and the pathogenesis of atrial fibrillation. *Nat Rev Cardiol.* 2015;12(4):230–243. DOI: 10.1038/nrcardio.2015.2

40. Chung MK, Martin DO, Sprecher D, et al. C-reactive protein elevation in patients with atrial arrhythmias: Inflammatory

mechanisms and persistence of atrial fibrillation. *Circulation.* 2001;104(24):2886–2891. DOI: 10.1161/hc4901.101760

41. Chen Y, Xia Y, Han X, et al. Association between serum uric acid and atrial fibrillation: A cross-sectional community-based study in China. *BMJ Open.* 2017;7(12):e019037. DOI: 10.1136/ bmjopen-2017-019037

42. Kuwabara M, Niwa K, Nishihara S, et al. Hyperuricemia is an independent competing risk factor for atrial fibrillation. *Int J Cardiol.* 2017;231:137–142. DOI: 10.1016/j.ijcard.2016.11.268

43. Zhang CH, Huang DS, Shen D. Association between serum uric acid levels and atrial fibrillation risk. *Cell Physiol Biochem*. 2016;38(4):1589–1595. DOI: 10.1159/000443099

44. Deshko M, Snezhitskiy V, Madekina G, et al. Prognostic value of hyperuricemia in patients with atrial fibrillation and heart failure with preserved ejection fraction. *Cardiology.* 2015;55(10):52–57. (In Russ.). DOI: 10.18565/cardio.2015.10.52-57

45. Kepurko TL, Snezhitskiy VA. Hyperuricemia as a risk factor for atrial fibrillation progression. *Cardiology in Belarus.* 2018;10(1): 125–132.

46. Nyrnes A, Toft I, Njølstad I. Uric acid is associated with future atrial fibrillation: an 11-year follow-up of 6308 men and women-the Tromso Study. *Europace*. 2014;16(3):320–326. DOI: 10.1093/europace/eut260

СПИСОК ЛИТЕРАТУРЫ

1. Taufiq F., Li P., Miake J., Hisatome I. Hyperuricemia as a risk factor for atrial fibrillation due to soluble and crystalized uric acid // Circ. Rep. 2019. Vol. 1, No. 11. P. 469–473. DOI: 10.1253/circrep.CR-19-00882.

2. Krijthe B.P., Kunst A., Benjamin E.J., et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060 // Eur. Heart J. 2013. Vol. 34, No. 35. P. 2746–2751. DOI: 10.1093/eurheartj/eht2803.

3. Зозуля И.С., Ганджа Т.И., Супрун А.О., Олефиренко А.С. Оказание неотложной медицинской помощи при фибрилляции предсердий // Медицина неотложных состояний. 2016. Т. 3–4. С. 60–61.

4. Подзолков В.И., Тарзиманова А.И., Гатаулин Р.Г. и др. Роль ожирения в развитии фибрилляции предсердий: современное состояние проблемы // Кардиоваскулярная терапия и профилактика. 2019. Т. 18, № 4. С. 109–114. DOI: 10.15829/1728880020194109114

5. Camm A.J, Lip G.Y., De Caterina R. et al. 2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation — developed with the special contribution of the European Heart Rhythm Association // Eur. Heart J. 2012. Vol. 33, No. 21. P. 2719–2747. DOI: 10.1093/eurheartj/ehs253

6. Жернакова Ю.В. Гиперурикемия как фактор риска сердечно-сосудистых заболеваний — что нового? // Медицинский алфавит. 2020. № 13. С. 5–11. DOI: 10.33667/2078-5631-2020-13-5-11

7. Бильченко А.В. Коррекция гиперурикемии как фактора риска сердечно-сосудистой заболеваемости и смертности // Новости медицины и фармации. 2011. № 5(389). С. 53–58.

8. Донсков А.С., Балкаров И.М., Дадина З.М. и др. Уратное поражение почек и метаболические сдвиги у пациентов с артериальной гипертензией // Терапевтический Архив. 1999. № 6. С. 53–56.

9. Becker J.F., Schumacher H.R.Jr., Wortmann R.L. Febuxostat compared with allopurinol in patients with hyperuricemia and gout // N. Engl. J. Med. 2005. Vol. 353, No. 23. P. 2450–2461. DOI: 10.1056/NEJMoa050373

10. France L.V., Pahor M., Di Bari M. et al. Serum uric acid, diuretic treatment and risk of cardiovascular events in the Systolic Hypertension in the elderly Program (SHEP) // J. Hypertens. 2000. Vol. 18, No. 8. P. 1149–1154. DOI: 10.1097/00004872-200018080-00021

11. Zhu Y., Pandya B.J., Choi H.K. Prevalence of gout and hyperuricemia in the US general population. The National Health and Nutrition Examination Survey 2007–2008 // Arthritis. Rheum. 2011. Vol. 63, No. 10. P. 3136–3141. DOI: 10.1002/art.30520

12. Liu B., Wang T., Zhao H.N. et al. The prevalence of hyperuricemia in China: a meta-analysis // BMC Public Health. 2011. Vol. 11. P. 832. DOI: 10.1186/1471-2458-11-832

13. Qiu L., Cheng X.Q., Wu J. et al. Prevalence of hyperuricemia and its related risk factors in healthy adults from Northern and Northeastern Chinese provinces // BMC Public health. 2013. Vol. 13. P. 664. DOI: 10.1186/1471-2458-13-664

14. Шальнова С.А., Деев А.Д., Артамонова Г.В. и др. Гиперурикемия и ее корреляты в российской популяции (результаты эпидемиологического исследования ЭССЕ-РФ) // Рациональная Фармакотерапия в Кардиологии. 2014. Т. 10, No. 2. С. 153–159.

15. Wu A.H., Gladden J.D., Ahmed M. et al. Relation of serum uric acid to cardiovascular disease // Int. J. Cardiol. 2016. Vol. 213. P. 4–7. DOI: 10.1016/j.ijcard.2015.08.110

16. Hou L., Zhang M., Han W. et al. Influence of salt intake on association of blood uric acid with hypertension and related cardiovascular risk // PLoS One. 2016. Vol. 11, No. 4. P. e0150451. DOI: 10.1371/journal.pone.0150451

17. Ando K., Takahashi H., Watanabe T. et al. Impact of serum uric acid levels on coronary plaque stability evaluated using integrated

backscatter intravascular ultrasound in patients with coronary artery disease // J. Atheroscler. Thromb. 2016. Vol. 23, No. 8. P. 932–939. DOI: 10.5551/jat.33951

18. Беспалова И.Д., Калюжин В.В., Медянцев Ю.А. Бессимптомная гиперурикемия как компонент метаболического синдрома // Бюллетень сибирской медицины. 2012. Т. 11, № 3. С. 14–17. DOI: 10.20538/1682-0363-2012-3-14-17

19. MacGowan S., Regan M., Malone C. et al. Superoxide radical and xanthine oxidoreductase activity in the human heart during cardiac operations // Ann. Thorac. Surg. 1995. Vol. 60, No. 5. P. 1289–1293. DOI: 10.1016/0003-4975(95)00616-S

20. Korantzopoulos P., Letsas K., Liu T. Xanthine oxidase and uric acid in atrial fibrillation // Front. Physiol. 2012. Vol. 3. P. 150. DOI: 10.3389/fphys.2012.00150

21. Letsas K., Korantzopoulos P., Filippatos G. et al. Uric acid elevation in atrial fibrillation // Hellenic J. Cardiol. 2010. Vol. 51, No.3. P. 209–213.

22. Яцкевич Е.С., Снежицкий В.А. Влияние альдостерона и его антагонистов на ремоделирование миокарда у пациентов с фибрилляцией предсердий // Журнал Гродненского государственного медицинского университета. 2012. № 4(40). С. 5–9.

23. Delcayre C., Swynghedauw B. Molecular mechanisms of myocardial remodelling. The role of aldosterone // J. Mol. Cell. Cardiol. 2002. Vol. 34, No. 12. P. 1577–1584. DOI: 10.1006/jmcc.2002.2088

24. Schotten U., Verheule S., Kirchhof P., Goette A. Pathophysiological mechanisms of atrial fibrillation: A translational appraisal // Physiol. Rev. 2011. Vol. 91, No. 1. P. 265–325. DOI: 10.1152/physrev.00031.2009

25. Patterson E., Jackman W.M., Beckman K.J. et al. Spontaneous pulmonary vein firing in man: Relationship to tachycardia-pause early afterdepolarizations and triggered arrhythmia in canine pulmonary veins in vitro // J. Cardiovasc. Electrophysiol. 2007. Vol. 18, No. 10. P. 1067–1075. DOI: 10.1111/j.1540-8167.2007.00909.x

26. Жолбаева А.З., Табина А.Е., Голухова Е.З. Молекулярные механизмы фибрилляции предсердий: в поиске «идеального» маркера // Креативная кардиология. 2015. № 2. С. 40–53. DOI: 10.15275/kreatkard.2015.02.04

27. Dobrev D., Friedrich A., Voigt N. et al. The G protein-gated potassium current I(K,ACh) is constitutively active in patients with chronic atrial fibrillation // Circulation. 2005. Vol. 112, No. 24. P. 3697–3706. DOI: 10.1161/CIRCULATIONAHA.105.575332

28. Снежицкий В.А. Феномен электрофизиологического ремоделирования предсердий и синусового узла: механизмы развития и патогенез // Клиническая медицина. 2004. Т. 82, № 11. С. 10–14.

29. Jia G., Habibi J., Bostick B.P. et al. Uric acid promotes left ventricular diastolic dysfunction in mice fed a Western diet // Hypertension. 2015. Vol. 65, No. 3. P. 531–539. DOI: 10.1161/HYPERTENSIONAHA.114.04737

30. Maharani N., Ting Y.K., Cheng J. et al. Molecular mechanisms underlying urate-induced enhancement of Kv1.5 channel expression in HL-1 atrial myocytes // Circ. J. 2015. Vol. 79, No. 12. P. 2659–2668. DOI: 10.1253/circj.CJ-15-0416

31. Niforou K., Cheimonidou C., Trougakos I.P. Molecular chaperones and proteostasis regulation during redox imbalance // Redox. Biol. 2014. Vol. 2. P. 323–332. DOI: 10.1016/j.redox.2014.01.017

32. Giannopoulos G., Cleman M.W., Deftereos S. Inflammation fueling atrial fibrillation substrate: Seeking ways to "cool" the heart // Med. Chem. 2014. Vol. 10, No. 7. P. 663–671. DOI: 10.2174/15734064106661403181101000

33. Бубешка Д.А., Снежицкий В.А., Шулика В.Р. Биомаркеры воспаления у пациентов с неклапанной фибрилляцией предсердий и систолической дисфункцией левого желудочка // Медицинские новости. 2017. № 4. С. 69–72.

34. Levy M., Thaiss C.A., Elinav E. Taming the inflammasome // Nat. Med. 2015. Vol. 21, No. 3. P. 213–215. DOI: 10.1038/nm.3808

35. Bruins P., te Velthuis H., Yazdanbakhsh A.P. et al. Activation of the complement system during and after cardiopulmonary bypass surgery: Postsurgery activation involves C-reactive protein and is associated with postoperative arrhythmia // Circulation. 1997. Vol. 96, No. 10. P. 3542–3548. DOI: 10.1161/01.cir.96.10.3542

36. Yao C., Veleva T., Scott L.D. Jr. et al. Enhanced cardiomyocyte NLRP3 inflammasome signaling promotes atrial fibrillation // Circulation. 2018. Vol. 138, No. 20. P. 2227–2242. DOI: 10.1161/CIRCULATIONAHA.118.035202

37. Putko B.N., Wang Z., Lo J. et al. Circulating levels of tumor necrosis factor-alpha receptor 2 are increased in heart failure with preserved ejection fraction relative to heart failure with reduced ejection fraction: Evidence for a divergence in pathophysiology // PLoS One. 2014. Vol. 9, No. 6. P. e99495. DOI: 10.1371/journal.pone.0099495

38. Liew R., Khairunnisa K., Gu Y. et al. Role of tumor necrosis factor-α in the pathogenesis of atrial fibrosis and development of an arrhythmogenic substrate // Circ. J. 2013. Vol. 77, No. 5. P. 1171–1179. DOI: 10.1253/circj.cj-12-1155

39. Hu Y.F., Chen Y.J., Lin Y.J., Chen S.A. Inflammation and the pathogenesis of atrial fibrillation // Nat. Rev. Cardiol. 2015. Vol. 12, No. 4. P. 230–243. DOI: 10.1038/nrcardio.2015.2

40. Chung M.K., Martin D.O., Sprecher D. et al. C-reactive protein elevation in patients with atrial arrhythmias: Inflammatory mechanisms and persistence of atrial fibrillation // Circulation. 2001. Vol. 104, No. 24. P. 2886–2891. DOI: 10.1161/hc4901.101760

41. Chen Y., Xia Y., Han X. et al. Association between serum uric acid and atrial fibrillation: A cross-sectional community-based study in China // BMJ Open. 2017. Vol. 7, No. 12. P. e019037. DOI: 10.1136/ bmjopen-2017-019037

42. Kuwabara M., Niwa K., Nishihara S. et al. Hyperuricemia is an independent competing risk factor for atrial fibrillation // Int. J. Cardiol. 2017. Vol. 231. P. 137–142. DOI: 10.1016/j.ijcard.2016.11.268

43. Zhang C.H., Huang D.S., Shen D. et al. Association between serum uric acid levels and atrial fibrillation risk // Cell. Physiol. Biochem. 2016. N. 38, No. 4. P. 1589–1595. DOI: 10.1159/000443099

44. Дешко М.С., Снежицкий В.А., Мадекина Г.А. и др. Прогностическое значение гиперурикемии у пациентов с фибрилляцией предсердий и сердечной недостаточностью с сохранной фракцией выброса // Кардиология. 2015. Т. 55, № 10. С. 52–57. DOI: 10.18565/cardio.2015.10.52-57

45. Кепурко Т.Л., Снежицкий В.А. Гиперурикемия как фактор риска развития фибрилляции предсердий // Кардиология в Беларуси. 2018. Т. 10, № 1. С. 125–132.

46. Nyrnes A., Toft I., Njølstad I. et al. Uric acid is associated with future atrial fibrillation: an 11-year follow-up of 6308 men and women-the Tromso Study // Europace. 2014. Vol. 16, No. 3. P. 320–326. DOI: 10.1093/europace/eut260

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Application of Hemostatic Agent "Haemoblock" for Pocket Hematoma Reduction. Design of the PEGAS Study: a Multicenter Clinical Trial

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Pocket hematoma is a common complication of pacemaker implantations which prolongs hospitalization and may demand surgical revision in some cases. According to the data from different researchers PH rate varies from 2 to 7%. It depends on number of factors including a need for anticoagulation therapy. We present a review of design of multicenter clinical trial evaluating safety and efficacy of application of hemostatic agent "Haemoblock" for pocket hematoma reduction in patients taking oral anticoagulants.

Keywords: Pacemaker pocket hematoma; oral anticoagulants; haemoblock.

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Применение препарата “Гемоблок” для снижения риска формирования гематом ложа электрокардиостимулятора. Протокол многоцентрового клинического исследования ПЕГАС

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Гематома ложа (ГЛ) является известным осложнением процедур имплантации электрокардиостимулятора (ЭКС), приводящим к увеличению продолжительности нахождения в стационаре и, в некоторых случаях, к проведению хирургической ревизии ложа ЭКС. Частота ГЛ, по мнению разных авторов, составляет 2–7% и зависит от ряда факторов, в том числе от необходимости приема антитромботической терапии. В данной статье представлен анонс стартовавшего многоцентрового проспективного слепого рандомизированного плацебо-контролируемого клинического исследования по изучению безопасности применения отечественного гемостатического препарата «Гемоблок» при имплантации ЭКС и его эффективности в профилактике формирования ГЛ ЭКС у пациентов, принимающих оральные антикоагулянты.

Ключевые слова: гематома ложа электрокардиостимулятора; оральные антикоагулянты; гемоблок.

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ЭКО•ВЕКТОР

INTRODUCTION

The pocket hematoma (PH), a common complication of pacemaker implantations, is detected in 2%–7% of cases [1, 2]. PH is clinically manifested by a sensation of local discomfort and pain and is associated with infiltration of the subcutaneous tissue [3]. Furthermore, this complication may require surgical intervention [2], which increases the risk of infection of the endocardial system [4] and prolongs hospitalization [5]. Hence, the search for ways to prevent bleeding from the pacemaker pocket is of great practical interest.

According to a study by Bernard M. et al., up to 50% of patients undergoing implantation of antiarrhythmic devices have indications for antithrombotic therapy, which elevates the risk of pacemaker PH significantly in them [6]. Several authors have proposed to perform a complete or partial withdrawal of these drugs for the period before the surgery and in the early postoperative period. In our opinion, such an approach in most cases is potentially hazardous to patients' health, especially in the case of patients who have previously undergone surgical correction of valve insufficiency or who have undergone percutaneous endovascular interventions. The strategy of continuing the intake of oral anticoagulants (OAC) without interruption or transition to bridge therapy before implantation has been demonstrated to be efficient and safe [7]. Meanwhile, patients taking OACs constitute a high-risk cohort of postoperative PH [8] and require particular alertness in this complication. The use of local hemostatic drugs is a promising method for increasing intraoperative hemostasis efficiency. All currently used and known local hemostatic agents aim to imitate specific stages of natural hemostasis and their acceleration or form a fibrin clot rapidly bypassing these stages [9]. Experience of using the topical hemostatic drugs to prevent PH in implanted devices is represented by a small number of studies that resulted in conflicting findings and had limitations associated with a small number of participants and a single-center design. Thus, the efficiency of the use of fibrin glue (24% PH in the control group versus 0% PH in the experimental group) was demonstrated in patients receiving heparin or warfarin [10]. Previously, a significant decrease in the frequency of PH of pacemakers was observed with local application of tranexamic acid (7.7% versus 26.5%) [11] and Arista AH® hemostatic powder (4% versus 9%) [12].

Another work studied the possibilities of the HemostatTM drug (which includes collagen and thrombin) for the implantation of pacemakers without discontinuation of OAC or when taking dual antiplatelet therapy. The results indicated a complete failure of hemostatic drugs compared with the use of vacuum drainage of the pacemaker pocket (8.5% of PH requiring surgical revision, 6.1% of infectious complications versus 0% of endpoints in the drainage group, n = 82 patients, p = 0.01 and p = 0.06, respectively) [13]. Therefore, the PerClot® polysaccharide hemostatic system was suggested to use. Due to dehydration of the pocket contents, it was supposed to provide a high concentration of erythrocytes, platelets, and procoagulant proteins, creating a reliable matrix that stops bleeding. Meanwhile, the clinical use of PerClot® did not affect the frequency of PH in some cases. Further, it also caused a pronounced inflammatory response, which forced the study to be terminated early [14].

Despite the ambiguity of the data on the possibilities of local hemostatic drugs in ensuring the prevention of PH of implanted devices, there is an active search for new pharmacological agents that can solve this problem. One of such agents is the Russian drug "Haemoblock" which exerts its hemostatic effect by forming a clot with blood plasma proteins (mainly albumin). A polyacrylic matrix complex is formed at stage 1 of the drug action, containing albumin molecules in the cells. At the next stage, albumin molecules reduce silver ions, forming polyacrylate anions with a strong bond with positively charged protein molecules. This structure is packed in several microlayers, creating a solid polymethacrylate film on the wound surface. Subsequently, the surface structure designed is replaced by fibrin, and the polyacrylate matrix is plasmolyzed within one day [15].

The Russian drug "Haemoblock" has already demonstrated its hemostatic potential in general surgical practice [16], orthopedics [17], and endoscopic interventions [16]. However, the possibilities of "Haemoblock" in preventing pacemaker PH have not been studied and may require further investigations. Therefore, we set out a new study to assess the safety of using the hemostatic drug "Haemoblock" during implantation of pacemakers to monitor its efficiency in preventing the PH of pacemakers in patients taking OAC.

STUDY DESIGN

The study will be conducted following the protocol, the rules of Good Clinical Practice, and the legislation of the Russian Federation. The clinical study protocol was reviewed and approved at a meeting of the Ethics Committee of the Ryazan State Medical University of the Ministry of Health of Russia (Protocol No. 18 of 08/25/2020).

Participants and planned sample size

This multicenter, prospective, blind, randomized, placebo-controlled clinical study will enroll patients aged 40–85 years with indications for implantation of a single- or dual-chamber pacemaker, taking OACs for at least seven days before surgery and at least seven days in the early postoperative period. The study design will not imply the choice of the preferred drug for anticoagulant therapy or change of the OAC at preparation for surgical treatment. Preferred dosing regimens for previously prescribed medications will be used according to the patient's clinical characteristics (comorbidity, risk of stroke) and the presence of risk factors for hemorrhage. OAC can be changed if the kidney pathology is detected and performed following current clinical guidelines [18].

The study will not include patients with hypoalbuminemia, severe arterial hypertension (systolic blood pressure ⩾ 200 mm Hg and/or diastolic blood pressure ⩾ 110 mm Hg), varying forms of coronary heart disease, severe chronic renal failure (creatinine clearance less than 40 ml/min), heart failure (left ventricular ejection fraction less than 35%), hemoglobin level less than 90 g/l; as well as those having verified impairments in one of the links of hemostasis (thrombocytopenia, abnormal values of prothrombin index, fibrinogen, and international normalized ratio above 3.0). Additional exclusion criteria include the need to take two or more antithrombotic drugs, the presence of known contraindications to the study drug administration in patients, the period of pregnancy and lactation, and participation in another study. Based on the optimal sample size calculation required to test the hypothesis (study power 80%, significance level 0.05), it is estimated to include at least 200 patients in the study.

Randomization

After signing informed consent, the patients will be centrally randomized using a random number generator. According to the randomization results, a control group and the leading group will be formed.

Pacemaker implantation

Before the surgery, the patient will be prevented from infectious complications by administering an antibacterial drug, according to the scheme adopted in each clinic, at least 30 minutes before the intervention. The pacemaker stimulation mode VVI(R) or DDD(R) is chosen according to the clinical recommendations of the All-Russian Society of Arrhythmology for electrophysiological studies, catheter ablation, and the use of implantable antiarrhythmic devices [19]. The surgery will be performed under local anesthesia. The pacemaker is implanted according to the generally accepted technique under the skin in the left or right subclavian region. The pacemaker pocket location is chosen by the surgeon individually. It is preferable to form a pocket in the subcutaneous tissue without damaging the fascia of the musculus pectoralis major. A gauze wad soaked in 15 ml of “Haemoblock” (leading group) or 15 ml of 0.9% NaCl solution (control group) is placed in the pocket formed. The wads are removed immediately before immersion of the pacemaker in the pocket.

The choice of venous approach and electrode fixation system (active, passive) is determined by the surgeon individually. Electrocoagulation is actively used intraoperatively. Before suturing the subcutaneous tissue,

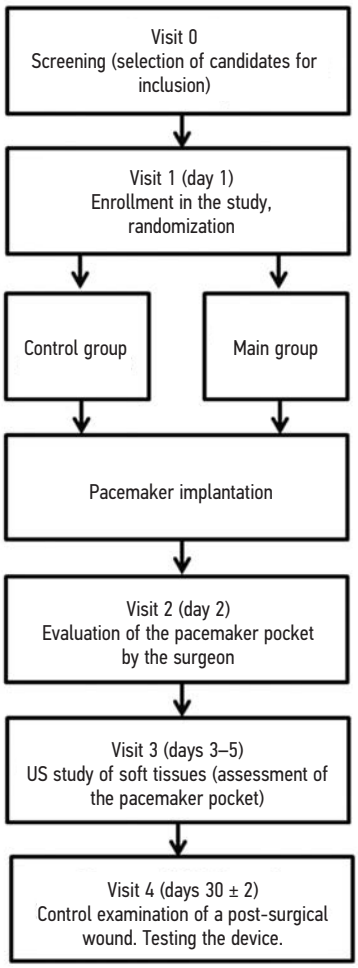

Fig. 1. Study design

the pocket is irrigated with 5 ml of "Haemoblock" solution without subsequent rinsing. In the presence of diffuse bleeding, which, according to the surgeon, can lead to a hematoma of the pacemaker pocket, a Bülau drain is installed. In all cases, after implantation, bed rest is prescribed following the clinic's standards of patient management, but not less than 3 hours [20]. Upon the patient's return to the ward, a cold compress with a load is applied to the postoperative wound area for 60 minutes.

Management of patients in the early postoperative period

The study design does not provide bridge therapy or discontinuation of the OAC before and after the pacemaker implantation. It is forbidden to prescribe hemostatic treatment in the first two days after the pacemaker implantation. On day three after implantation, it is allowed to prescribe an intravenous drip-feed infusion of 100 ml of the aminocaproic acid solution and/or 5 ml of tranexamic acid solution intravenously. With severe bleeding from the pacemaker pocket and the need to maintain drainage, antibiotic therapy continues until the Bülau drain is removed. If necessary, in the first two days after implantation, drainage of the pacemaker pocket is allowed in a dressing room. All manipulations performed, including drainage and hemostatic therapy, are registered in the patient's medical care. All patients undergo ultrasound study of soft tissues on days 3–5, verifying the presence of fluid (blood) in the pacemaker pocket and counting the volume of accumulated fluid. The follow-up period for patients will be 30 ± two days after the pacemaker implantation (Fig. 1).

Study indicators

The primary endpoint is the presence of free fluid (blood) in the pacemaker pocket in the early postoperative period, diagnosed by soft tissue ultrasound. In addition, the presence of a hematoma (fluid) in the pocket before the US study can be verified after the operating surgeon's examination, which detects palpable infiltration that smooths the pacemaker contour and the presence of a fluctuation effect.

Secondary endpoints include intraoperative installation of Bülau drain, duration of the Bülau drain, the need for postoperative drainage of the pacemaker pocket, imbibition of soft tissues on the side of pacemaker implantation, hemostatic therapy, exceeding the average number of bed-days, cerebral stroke, transient ischemic attacks, bleeding, pericarditis, cardiac tamponade, and infectious complications.

Research methods

Patients will undergo general clinical diagnostics following the nosological standard. Obligatory components of the examination are diagnostics of hemostasis pathology (complete blood count with platelet count, prothrombin index, fibrinogen, international normalized ratio), determination of the blood level of albumin, verification of the status of renal failure (creatinine clearance), and heart failure (echocardiography with left ventricular ejection fraction measurement according to Simpson), US study of soft tissues around the pacemaker pocket.

Statistical processing of the research materials will be performed using the methods of parametric and nonparametric analysis. The accumulation, correction, and systematization of the initial information and visualization of the results obtained will be performed in Microsoft Office Excel 2010 spreadsheets. Statistical analyses will be performed using the IBM SPSS Statistics 23 program. To assess the effect of the study drug on the endpoints, the odds ratio will be calculated, and a correlation analysis is planned.

STUDY TIMING AND EXPECTED RESULTS

The study was registered with the USA National Institute of Health (NCT04559646). The enrollment of patients had been started, and the first randomization was performed on September 28, 2020. Thus, the research base will be fully formed by the end of 2021, and the first results will be presented in quarter 1 of 2022. The use of the hemostatic drug "Haemoblock" during the pacemaker implantation is expected to reduce the risk of PH formation in patients taking OAC.

ADDITIONAL INFORMATION

Conflict of interest. The study's sponsor was the "Moscow Regional Scientific Research Institute of Blood," which provided the drug "Haemoblock" to research centers free of charge. No additional financial remuneration was provided to the research participants.

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

REFERENCES

1. Ilov N, Nechepurenko A, Abdulkadyrov A, et al. Arguments to apply epinephrine for pocket hematoma reduction. The MAITRE Study. *J Atr Fibrillation.* 2016;9(1):1391. DOI: 10.4022/jafib.1391

2. Notaristefano F, Angeli F, Verdecchia P, et al. Device-pocket hematoma after cardiac implantable electronic devices. *Circ Arrhythm Electrophysiol.* 2020;13(4):361–363. DOI: 10.1161/CIRCEP.120.008372

3. De Sensi F, Miracapillo G, Cresti A, et al. Pocket hematoma: a call for definition. *Pacing Clin Electrophysiol*. 2015;38(8):909–913. DOI: 10.1111/pace.12665

4. Essebag V, Verma A, Healey JS, et al. Clinically significant pocket hematoma increases long-term risk of device infection: BRUISE CONTROL INFECTION study. *J Am Coll Cardiol.* 2016;67(11): 1300–1308. DOI: 10.1016/j.jacc.2016.01.009

5. Sridhar ARM, Yarlagadda V, Yeruva MR, et al. Impact of haematoma after pacemaker and CRT device implantation on hospitalization costs, length of stay, and mortality: A popu-lation-based study. *Europace.* 2015;17(10):1548–1554. DOI: 10.1093/europace/euv075

6. Essebag V, Healey JS, Joza J, et al. Effect of direct oral anticoagulants, warfarin, and an-tiplatelet agents on risk of device pocket hematoma: Combined analysis of BRUISE CON-TROL 1 and 2. *Circ Arrhythm Electrophysiol.* 2019;12(10):e007545. DOI: 10.1161/CIRCEP.119.007545

7. Birnie DH, Healey JS, Wells GA, et al. Pacemaker or Defibrillator Surgery without Inter-ruption of Anticoagulation. *N Engl J Med.* 2013;368(22):2084–2093. DOI: 10.1056/nejmoa1302946

8. Sridhar ARM, Yarlagadda V, Kanmanthareddy A, et al. Incidence, predictors and out-comes of hematoma after ICD implantation: An analysis of a nationwide database of 85,276 patients. *Indian Pacing Electrophysiol J.* 2016;16(15):159–164. DOI: 10.1016/j.ipej.2016.10.005

9. Lucevich O.Eh. Peculiarities of application of local hemostatic materials in surgery. *Moscow Surgical Journal.* 2016;(3(49)):12–20. (In Russ.).

10. Tereshchenko SG, Plotkin AV, Mecheva LV. Intraorgan use of Hemoblock for prevention and arrest of bleedings in endoscopic excision of gastric polyps. *Russian Sklifosovsky Journal Emergency Medical Care.* 2019;8(1):30–34. DOI: 10.23934/2223-9022-2019-8-1-30-34

11. Tscholl V, Spann F, Moses J, et al. Prospective randomized study evaluating the effects of PerClot® (Polysaccharide Hemostatic System) application in patients with high bleeding risk undergoing cardiac rhythm device implantation. *Int J Cardiol.* 2017;248:84–91. DOI: 10.1016/j.ijcard.2017.08.038

12. Reynbakh O, Akhrass P, Souvaliotis N, et al. Use of MPH hemostatic powder for elec-trophysiology device implantation reduces postoperative rates of pocket hematoma and infec-tion. *Curr Med Res Opinion.* 2018;34(10):1861–1867. DOI: 10.1080/03007995.2018.1476847

13. Degovtsov EN, Kolyadko PV, Kolyadko VP, Satinov AV. first results of a randomized controlled trial of hemoblock in patients with large incisional hernias. *Russian Sklifosovsky Journal of Emergency Medical Care.* 2019;8(4):430–436. (In Russ.). DOI: 10.23934/2223-9022-2019-8-4-430-436

14. Kolesov SV, Grin AA, Slinyakov LY, et al. Efficiency of using polyacrylic acid silver salt in decompression and stabilization surgery on the lumbar spine involving 1 to 3 segments. *Spine Surgery.* 2019;16(2):73–80. (In Russ.). DOI: 10.14531/ss2019.2.73–80

15. Revishvili ASh, Shlyakhto EV, Popov SV, et al. Clinical recommendations for the use of electrophysiological study, catheter ablation and implantable cardiac electronic devices. Moscow; 2017. (In Russ.).

16. Makarova NV, Durmanov SS, Kozlov AV, et al. Does early activa-tion of patients after pacemaker implantation affect the rate of post-intervention complications? *Journal of Arrhythmology*. 2013;(74):40–44. (In Russ.).

СПИСОК ЛИТЕРАТУРЫ

1. Ilov N., Nechepurenko A., Abdulkadyrov A. et al. Arguments to apply epinephrine for pocket hematoma reduction. The MAITRE Study // J. Atr. Fibrillation. 2016. Vol. 9, No. 1. P. 1391. DOI: 10.4022/jafib.1391

2. Notaristefano F., Angeli F., Verdecchia P. et al. Device-Pocket hematoma after cardiac implantable electronic devices // Circ. Arrhythm. Electrophysiol. 2020. Vol. 13, No. 4. P. 361–363. DOI: 10.1161/CIRCEP.120.008372

3. De Sensi F., Miracapillo G., Cresti A. et al. Pocket hematoma: a call for definition // Pacing Clin. Electrophysiol. 2015. Vol. 38, No. 8. P. 909–913. DOI: 10.1111/pace.12665

4. Essebag V., Verma A., Healey J.S. et al. Clinically significant pocket hematoma in-creases long-term risk of device infection: BRUISE CONTROL INFECTION study // J. Am. Coll. Cardiol. 2016. Vol. 67, No. 11. P. 1300–1308. DOI: 10.1016/j.jacc.2016.01.009

5. Sridhar A.R.M., Yarlagadda V., Yeruva M.R. et al. Impact of haematoma after pacemaker and CRT device implantation on hospitalization costs, length of stay, and mortali-ty: A population-based study // Europace. 2015. Vol. 17, No. 10. P. 1548–1554. DOI: 10.1093/europace/euv075

6. Essebag V., Healey J.S., Joza J. et al. Effect of direct oral anticoagulants, warfarin, and antiplatelet agents on risk of device pocket hematoma: Combined analysis of BRUISE CONTROL 1 and 2 // Circ. Arrhythm. Electrophysiol. 2019. Vol. 12, No. 10. P. e007545. DOI: 10.1161/CIRCEP.119.007545

7. Birnie D.H., Healey J.S., Wells G.A. et al. Pacemaker or Defibrillator Surgery with-out Interruption of Anticoagulation // N. Engl. J. Med. 2013. Vol. 368, No. 22. P. 2084–2093. DOI: 10.1056/nejmoa1302946

8. Sridhar A.R.M., Yarlagadda V., Kanmanthareddy A. et al. Incidence, predictors and outcomes of hematoma after ICD implantation: An analysis of a nationwide database of 85,276 patients // Indian Pacing Electrophysiol. J. 2016. Vol. 16, No. 15. P. 159–164. DOI: 10.1016/j.ipej.2016.10.005

9. Луцевич О.Э. Особенности применения гемостатических материалов местного действия в хирургии // Московский хирургический журнал. 2016. № 3(49). С. 12–20.

10. Терещенко С.Г., Плоткин А.В., Мечева Л.В. Внутриорганное применение гемостатического средства «Гемоблок» для профилактики и остановки кровотечений при эндоскопическом удалении полипов желудка // Журнал им. Н.В. Склифосовского Неотложная медицинская помощь. 2019. Т. 8, № 1. С. 30–34. DOI: 10.23934/2223-9022-2019-8-1-30-34

11. Tscholl V., Spann F., Moses J. et al. Prospective randomized study evaluating the effects of PerClot® (Polysaccharide Hemostatic System) application in patients with high bleeding risk undergoing cardiac rhythm device implantation // Int. J. Cardiol. 2017. Vol. 248. P. 84–91. DOI: 10.1016/j.ijcard.2017.08.038

12. Reynbakh O., Akhrass P., Souvaliotis N. et al. Use of MPH hemostatic powder for elec-trophysiology device implantation reduces postoperative rates of pocket hematoma and infec-tion // Curr. Med. Res. Opinion. 2018. Vol. 34, No. 10. P. 1861–1867. DOI: 10.1080/03007995.2018.1476847

13. Деговцов Е.Н., Колядко П.В., Колядко В.П., Сатинов А.В. Первые результаты рандо-мизированного контролируемого исследования применения гемоблока у пациентов с большими вентральными послеоперационными грыжами // Журнал им. Н.В. Склифосовского Неотложная медицинская помощь. 2019. Т. 8, № 4. С. 430–436. DOI: 10.23934/2223-9022-2019-8-4-430-436

14. Колесов С.В., Гринь А.А., Слиняков Л.Ю. и др. Эффективность использования серебряной соли полиакриловой кислоты при декомпрессионно-стабилизирующих операциях на поясничном отделе позвоночника с захватом 1–3 сегментов // Хирургия позвоночника. 2019. Т. 16, № 2. С. 73–80. DOI: 10.14531/ss2019.2.73–80

15. Ревишвили А.Ш., Шляхто Е.В., Попов С.В. и др. Клинические рекомендации по проведению электрофизиологических исследований, катетерной абляции и применению имплантируемых антиаритмических устройств. М., 2017.

16. Макарова Н.В., Дурманов С.С., Козлов А.В. и др. Влияет ли ранняя активизация пациентов после имплантации электрокардиостимуляторов на частоту послеоперационных осложнений? // Вестник аритмологии. 2013. № 74. С. 40–44.

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Late Electrode Sepsis: Clinical Features, Diagnostics and Management. Clinical Cases

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In clinical practice diagnostics and treatment of infection of cardiac implantable electronic devices (CIEDs) is connected with significant difficulties, because distinctive features of electrode sepsis are extremely low information content of Duke criteria, disease propensity for a long flow in various clinical forms as well as in the form of a septic syndrome. An important practical issue in management of patients with CIEDs remains working out of effective strategies to prevent occurrence of late electrode sepsis (arising in a year or more after implantation of the device). The article describes two cases of typical course of late recurrent infection of the CIEDs.

Keywords: infective endocarditis; electrode sepsis; infection of cardiac implantable electronic devices.

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Поздний электродный сепсис: особенности клинического течения, диагностики и ведения. Клинические случаи

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Диагностика и лечение пациентов с инфекцией имплантированных в сердце устройств в клинической практике сопряжены с существенными трудностями, поскольку отличительными особенностями электродного сепсиса считаются крайне низкая информативность критериев Duke, склонность заболевания длительно протекать в виде ряда клинических масок, в том числе септического синдрома. Важным практическим аспектом ведения пациентов с имплантированными в сердце устройствами остается выработка эффективной стратегии профилактики позднего электродного сепсиса (возникающего через год и более после имплантации устройства). В статье приведено описание двух случаев типичного течения позднего рецидивирующего одонтогенного инфекционного эндокардита имплантированного в сердце устройства.

Ключевые слова: инфекционный эндокардит; электродный сепсис; инфекция имплантированных в сердце устройств.

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ЭКО•ВЕКТОР

Abbreviations

ARVI — acute respiratory viral infection
AV block — atrioventricular block
CIED — cardiac implantable electronic device
CRP — C-reactive protein
ECG — electrocardiography
ES — electrode sepsis
ESR — erythrocyte sedimentation rate
IE — infectious endocarditis
MSCT, multispiral CT — multispiral computer tomography
PE — pulmonary embolism
TEE — transesophageal electrocardiography
TTE — transthoracic echocardiographic examination
TV — tricuspid valve

INTRODUCTION

Modern cardiology is impossible without implantation of intracardiac devices, such as cardiac pacemakers, resynchronization therapy devices, implantable cardioverter-defibrillators. Meanwhile, as the number of implanted devices increases, so does the number of cases of their infection [1]. At present, sufficient clinical material has been accumulated, demonstrating the obvious features of the course of this type of IE, leading to late diagnosis, the spread of infection to the tricuspid valve and, as a result, to a poor prognosis. The frequency of purulent complications after implantation of pacemakers is from 0.6 to 5.7%; mortality rate varies from 0.13% in local purulent inflammation to 19.9% in bacterial endocarditis and sepsis [2].

Abroad, term electrode sepsis is widely used to reflect the main features of the course of cardiac implantable electronic device infection, which are the predominance of systemic inflammation symptoms and the long-term absence of heart damage signs.

We present two typical cases of the course of cardiac implantable electronic device infection, illustrating the difficulties of diagnosing and treating this disease.

CLINICAL CASE 1

Patient A., 27 years old. At the age of 15, he was implanted with a two-chamber pacemaker for congenital (as it was regarded at that time) subtotal AV block. Seven years later, the pacemaker power supply was replaced due to exhausted battery. Five years later, in September 2018, the patient developed night sweats and rises in body temperature to 40–41°C. He denied invasive interventions, diseases or other conditions that could be accompanied by bacteremia over the past 6 months.

The patient was examined in a hospital (from September 27, 2018 to October 11, 2018) and the diagnosis of community-acquired left-sided lower-lobe pneumonia was established based on lung X-ray data. Lung Multispiral CT was not performed. Blood tests showed leukocytosis, left shift, 10-fold increase in CRP, Staphylococcus Haemolyticus was found in blood cultures. According to transthoracicEcho-KG, no pathology was revealed. The patient underwent a 12-day course of ceftriaxone and leflobact with positive dynamics of clinical, instrumental and laboratory data: during the week before discharge, there was no fever, pneumatization of the lungs according to the control radiographs recovered completely, the level of leukocytes and CRP returned to normal. Control blood cultures were not performed. However, just one week after discharge, the patient was re-hospitalized due to recurrence of fever. Again, leukocytosis and left shift were observed, procalcitonin exceeded normal values by 150 times. This time Staphylococcus Aureus was found in blood cultures (October 19, 2018). On the fourth day of hospitalization with echocardiography, vegetation was first detected on one of the pacemaker electrodes. Based on the data obtained, acute IE associated with the implanted pacemaker was diagnosed. The total duration of antibiotic therapy was 25 days. Unfortunately, there was no detailed information on the antibiotics used in the discharge reports. In order to find out the primary source of infection, the patient was examined by a dentist. An orthopantomogram (OPTG) revealed multiple granulomas of the upper and lower jaws. There were signs of periodontitis on teeth 15, 13, 12, 11, 21, 22, 23, 26, 27, 37, 45, 46; signs of chronic pulpitis 24, 25, 38, 35, 34, 33, 43, 44 (Fig. 1). It turned out that the

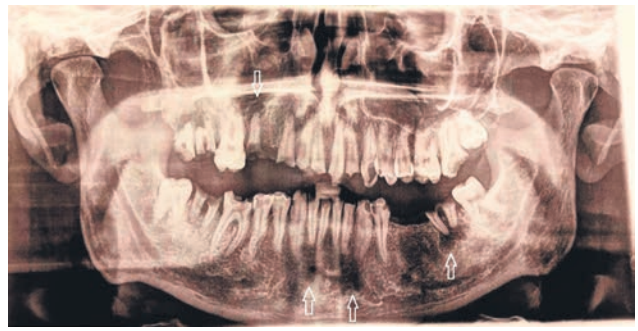

Fig. 1. Orthopantomogram of patient A. Arrows indicate multiple granulomas of the roots of the teeth of the upper and lower jaws.

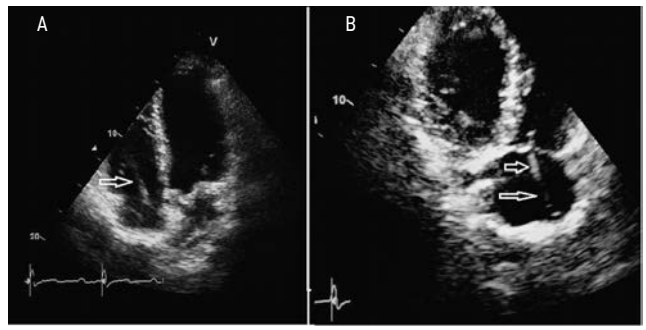

Fig. 2. Echocardiograms of patient A. Arrows indicate uneven compaction and thickening of the electrode sections located in the right chambers of the heart. Reliable formations in the projection of the electrodes are not determined. A — Four-chambered apical section; B — Modified three-chambered apical section (through the inflow sections of the right ventricle).

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patient himself did not attach much importance to the state of the oral cavity and had not visited the dentist in recent years. Considering the large extent of the lesion, a phased debridement of the oral cavity was started. By the time of discharge (November 13, 2018), there were no symptoms, the CBT and procalcitonin values returned to normal. The control culture showed the absence of microflora growth, with the control TTE there were no reliable vegetations in the area of the electrodes. Indications for surgical treatment of IE have not been formulated.

A month after discharge, fever recurred, and this time, in addition to the symptoms already listed earlier, there was hyperemia and soreness in the area of the pacemaker bed. In early December 2018, the patient was hospitalized with a diagnosis of "pacemaker bed abscess". In control TTE and TEE, no reliable vegetation was found in the projection of electrodes, valves, and free endocardium. There was only uneven compaction and thickening of some areas of the

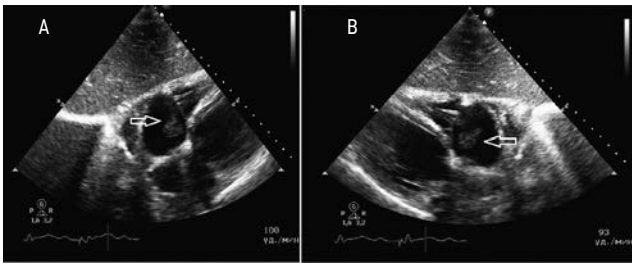

Fig. 3. Echocardiogram of patient A., 04.2019 A — Four-chambered apical section; B — Three-chambered subcostal modified section. The arrows indicate a large loose vegetation located on the electrode near the TV structures.

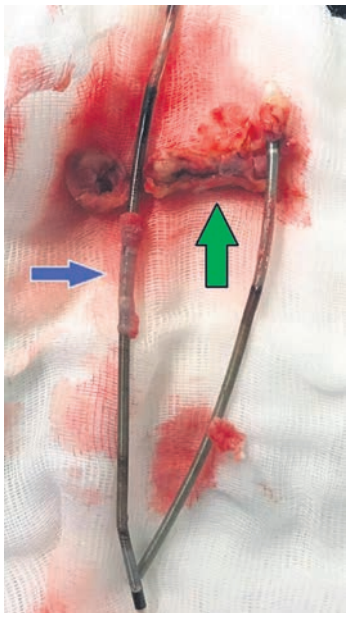

Fig. 4. Postoperative photography: fragments of removed electrodes. There are two types of vegetation fixed on electrodes: classic giant vegetation, reaching a length of 5.5 cm (green arrow); vegetation, braiding the electrode like a "sleeve" or "stocking" (blue arrow).

electrode (Fig. 2). Staphylococcus Aureus was re-isolated in blood cultures. The therapy was carried out with vancomycin (1 g) with gentamicin (80 mg) for 25 days. After sanitation of the abscess and with antibiotic therapy, regression of all symptoms was again noted, with complete normalization of blood counts.

Diagnosis at discharge (December 28, 2018): Subacute infectious odontogenic endocarditis with the formation of a pacemaker bed abscess.

Sanitation of the oral cavity was accompanied by standard antibiotic therapy: on the day of the dental intervention, the patient received a single oral dose of 2 g of amoxicillin orally, or 600 mg of clindamycin. In addition, intravenous gentamicin courses were repeated due to recurrent fever. Each course was accompanied by a rapid normalization of the clinical condition, normalization of temperature and laboratory parameters. In repeated cultures of blood, there was no growth, reliable vegetation on the electrodes was absent. The surgical stage of treatment for this patient was postponed until the complete sanitation of the oral cavity. Moreover, the opinions of the doctors involved regarding the need for surgical treatment were by no means unambiguous. Sanitation, including the phased removal of the infected teeth, took a considerable amount of time.

By April 2019, the patient's condition deteriorated rapidly: weight loss (-8 kg), febrile rises in temperature, enlargement of the liver and spleen, severe weakness, a tendency to arterial hypotension (90–80/60–55 mm Hg), severe anemia, lungs X-ray showed pneumonic infiltration again. Blood tests revealed an increase in anemia, thrombocytosis, leukocytosis, and an increase in ESR by 4.2 times. The growth of Staphylococcus epidermidis was noted in blood cultures. ECG revealed large loose vegetation on the electrodes in the immediate vicinity of the MC (Fig. 3), however, there were no reliable signs of the involvement of MCs in the infectious process.

It was during this hospitalization, with the background of massive antibiotic therapy, that the oral cavity sanitation was urgently completed, and on May 07, 2019, 7.5 months after the onset of the disease, during an open surgical intervention, the system of constant electrocardiostimulation was completely removed and the heart chambers were sanitized while extracorporeal circulation and cold cardioplegia. On both electrodes, multiple vegetations were found, both ordinary — large formations on the "stem" fixed to the electrodes, and vegetation of the "sleeve" type (Fig. 4). During the surgical revision, vegetation was revealed on the anterior cusp of the TV, which necessitated partial resection and suture plasty of the anterior cusp of the TV. Fortunately, there were no indications for pacemaker reimplantation, since in the preoperative period it turned out that the patient was predominantly in sinus rhythm, there were no signs of AV block (both subtotal and complete). The early postoperative period was complicated by two episodes of ventricular tachycardia on the 2nd and 4th days after surgery

with outcome in ventricular fibrillation and sudden death. Resuscitation measures were successful.

In the postoperative period, the patient received antibiotic therapy (meronem 1 g, vancomycin 1 g) for 6 weeks. During the dynamic observation of the patient during the next year, there were no complaints, the temperature remained normal, laboratory markers of inflammation were absent.

CLINICAL CASE 2

Patient B., 64 years old. Suffers from diabetes mellitus. In 2015, a complete AV block developed, complicated by Morgagni-Adams-Stokes attacks, which is why a two-chamber pacemaker was implanted. There were no other invasive interventions, injuries, or infectious diseases. Since the fall of 2017, the patient periodically (once a week) experienced attacks of chills and pronounced "night" sweating, as well as a decrease in body weight. Since December 2018, unexplained sudden rises in temperature up to 38.5°C have appeared. According to the patient, the local therapist diagnosed angina and prescribed a course of antibiotic therapy with a positive effect. Over the next two months, the state of health remained satisfactory.

In March 2019, fever and night sweats resumed, and therefore the patient was hospitalized with a diagnosis of ARVI, acute bronchitis. In laboratory data, leukocytosis, a twofold increase in ESR, and a 12-fold excess of CRP were noted. Blood cultures were not performed. Lung x-ray showed no pathology. Within 17 days the patient received the following treatment: ceftriaxone 2 g, levofloxacin 500 mg, metronidazole 500 mg. By the time of discharge, the clinical condition and laboratory readings had returned to normal. For the next 4 months after the discharge, the patient felt well. However, in mid-July 2019, fever and bouts of night sweats resumed. By the beginning of August 2019, shortness of breath again joined the general symptoms of inflammation, and therefore the patient was again hospitalized. In laboratory tests, leukocytosis, a 55-fold increase in CRP, and mild anemia were present. Staphylococcus epidermidis was isolated from blood cultures. Orthopantomogram revealed signs of chronic periodontitis 26, 43, 47 teeth. Contrast multispiral CT of the lungs revealed embolic, destructive left-sided lower lobe pneumonia complicated by abscess, as well as multiple PE (segmental branches) on both sides. The finding with transthoracic echocardiography was initially regarded as a vegetation in the projection of the TV, although later, with TEE, classical vegetations on the atrial and ventricular paceaker electrodes were reliably identified (Fig. 5), as well as local uneven thickening and echogenicity of the electrode fragments, regarded as 'sleeve' type vegetation (Fig. 6). There were no reliable signs of TV damage.

The duration of antibiotic therapy, including blood cultures and doxycycline 100 mg 2 r/day and ciprofloxacin 200 mg 2 r/day, was 6.5 weeks. With the antibiotic therapy, a rapid positive clinical dynamic was observed — manifestations of

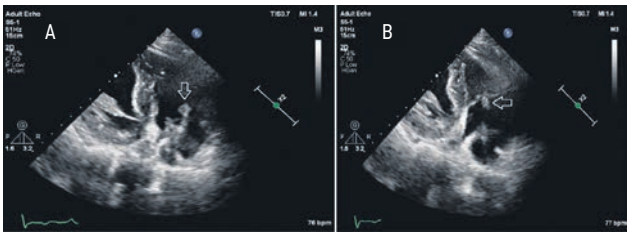

Fig. 5. Echocardiography of patient B. Loose vegetation, fixed on the ventricular electrode near the tricuspid valve. Modified three-chambered apical section: A — Diastole, tricuspid valve open; B — Systole, tricuspid valve closed. Formation is fixed to the electrode; the cusps of the own tricuspid valve appear intact.

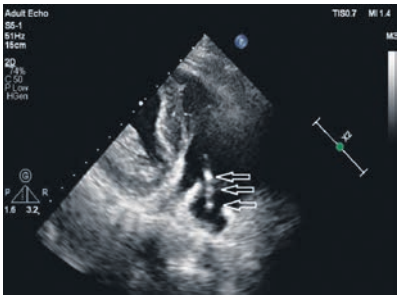

Fig. 6. EchoCG of patient B. Modified 3-chamber apical section. Uneven thickening and echogenicity of the area of the ventricular electrode located above the cusps of the tricuspid valve. This picture was regarded as a probable vegetation of the "sleeve" type.

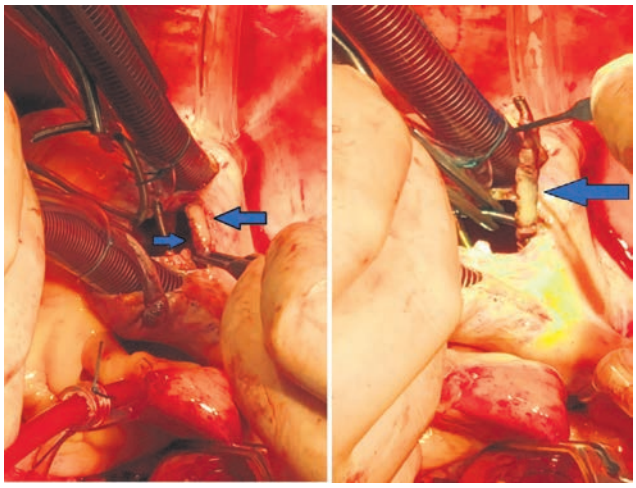

Fig. 7. Intraoperative photographs. Massive vegetation of the "sleeve" type on intracardiac fragments of the electrodes (blue arrows).

respiratory failure disappeared, temperature and laboratory changes returned to normal.

Nevertheless, even after a 6.5-week course of antibiotic therapy, according to EchoCG and TEE, vegetation on the intracardiac electrodes in the immediate vicinity of the TV valves was present. All ECGs showed P-dependent ventricular pacing. With the planned programming of the pacemaker, the patient's dependence on the stimulator was confirmed.

On 10.10.2019, 11 months after the onset of the disease, the pacemaker endocardial system was extracted, and the

permanent pacemaker was reimplanted into the epicardial position under artificial circulation. Intraoperatively, the presence of massive vegetation of 'sleeve' type on the electrodes was confirmed (Fig. 7), and vegetation on the TV was also detected, which required its removal and plastic surgery of the TV according to De Vega.

In the postoperative period, the patient underwent a 2-week course of antibiotic therapy with vancomycin, 2 g/day. Over the next 6 months, the patient's condition remained stable, there were no complaints, there were no markers of inflammation, and the body temperature did not rise.

CASE DISCUSSION

IE is known to often develop as a result of bacteremia, the cause of which can be identified by taking anamnesis: invasive procedures (dental, urological, gynecological) or obvious concomitant infectious diseases. Meanwhile, it is often overlooked that spontaneous activation of chronic foci of infection can become the cause of bacteremia. In particular, odontogenic foci are the most frequent sources of microflora that causes the development of infective endocarditis.

When studying the role of chronic focal infection of the oral cavity in the development of infective endocarditis, it was found that foci of stomatogenic infection were detected in 93.7% of cases [3], and in 70.9% these foci were chronic. these foci were recognized to be the immediate cause of the development of infective endocarditis in 22.2% of cases [4]. A study by S.N. Krutov (2010) revealed a direct correlation between the microbial DNA of the gingival sulcus and the DNA of the IE causative agent from vegetation [5].

An important aspect of the preoperative preparation of any cardiac surgery (including the implantation of intracardiac devices) is the sanitation of chronic foci of oral cavity infection at least 2 weeks before the intervention, which significantly reduces the risk of developing infectious complications in the postoperative period. This rule is strictly observed when performing major cardiac surgery such as implantation of valve prostheses or vascular grafts. Unfortunately, it seems that this rule is not always fulfilled regarding the implantation of endovascular and intracardiac devices.

For a long time, the main manifestation of the disease is septic syndrome, the course of which has changed and does not always correspond to previous ideas. In many cases, modern septic syndrome is characterized by a chronic or subacute course, under one or more masks, successively replacing each other, or stably combined with each other. Typical masks of IE APU are rheumatologic syndrome, local infection of the device bed, and respiratory syndrome. We shall consider each of these masks in sequence.

Rheumatological syndrome includes fever, night sweats, arthralgias, unexplained weight loss, polyserositis, moderate enlargement of the liver and spleen, and changes in urinary sediment.

In young people and middle-aged people, a febrile increase in temperature is typical, while in elderly and weak people, high fever is often absent, giving way to a prolonged subfebrile condition. A stable manifestation of septic syndrome in such patients can only be a change in daily body temperature by more than one degree. Abnormal temperature is usually accompanied by profuse night sweats. Over time, patients experience weight loss. When performing instrumental studies, manifestations of polyserositis in the form of minor hydrothorax and hydropericardium can be detected. The septic syndrome is also characterized by the addition of nephritis. In patients with multiple comorbidities, such findings are usually interpreted as manifestations of chronic pathology.

Local infection of the bed of the intracardiac device is often perceived as a local and potentially curable infection. This belief is supported by the fact that during therapy, usually all local symptoms undergo rapid regression, creating the illusion of recovery. Meanwhile, it should be noted that infection of the device pocket can only be called a local infection, since in the overwhelming majority of cases of local inflammation in the area of the device bed, the infection eventually spreads to the intracardiac electrodes. So, in the study by D. Klug et al. (2007) demonstrated that in patients with isolated infection of the stimulator bed and the absence of obvious manifestations of generalized infection, cultures from intravascular segments of the electrodes were positive in 72% of cases [6]. Thus, any infectious process in the area of extracardiac elements of the device is potentially a manifestation of CIED and should be the reason for the removal of the entire system (recommendation class I, level of evidence C).

Respiratory Syndrome. One of the earliest and most typical complications of electrode sepsis is infarction pneumonia, the manifestations of which vary widely: from asymptomatic to clinically severe pneumonia. The source of embolism is fresh vegetation formed on the electrodes, which are located in the right chambers of the heart. Since until recently the main method for diagnosing community-acquired pneumonia remained the x-ray of the chest, which is not sensitive enough to detect pneumonia infarction in comparison with multispiral CT of the lungs, the embolic nature of pneumonia for the time being remains unclear, and patients for some time are being treated against common community-acquired pneumonia or bronchitis. Unfortunately, multispiral CT in routine clinical practice is usually performed much later, with recurrent pneumonia. Meanwhile, the presence of CIED infection in a patient with suspected inflammatory lung disease is the basis for performing MSCT as a first-line method to exclude infarction pneumonia and stratification of the risk of IE.

Comprehensive consideration of all clinical masks of IE is a more sensitive approach than taking into account the Duke criteria, which are not very informative in relation to ES. The latter can proceed for a long time without the formation of classical vegetation — mobile, rather large formations on the electrodes, similar to those that occur with valvular

lesions. With CIED infection, a typical vegetation "braids" the electrode like a "sleeve" and looks atypical during EchoCG examination, in the form of extended seals on the electrode, falsely perceived as fibrous tissue on the electrode. In the early stages, classical vegetation is unstable and, probably, can come off and disappear, including against the background of ongoing therapy, which is often mistakenly interpreted as positive dynamics or even recovery. Massive, obvious, persistent vegetation on the electrodes is most likely characteristic of the late stage of IE, associated with an extensive clinical picture of sepsis and the probable spread of infection to the TV. Another feature of CIED infection diagnostics is significant difficulties in early detection of TV lesions. In both presented cases, TV vegetation was detected only intraoperatively, because Artifacts of the electrodes and/or vegetation located on the electrodes in the immediate vicinity of the TV make it difficult to assess the valve itself, and the absence of significant tricuspid regurgitation speaks against the leaflet lesions. The described clinical cases have shown that with ES duration ⩾ 6 months, TV is usually involved into the infectious process. However, it is impossible to say for sure that exactly six months is the period after which the TV is always affected, since there is no serious evidence base / large studies on this. The duration of ES is undoubtedly directly proportional to the likelihood of TV infection, being an additional argument in favor of the earliest possible removal of CIED in case of suspected ES.

In our opinion, a more important consequence of this pattern is the need to remove the entire pacemaker system not only with confirmed ES (which is very difficult to prove at the early stages), not only with local infection of the device bed, but also with a reasonable suspicion of a septic condition without a proven source in patients with CIED. This suspicion is the basis for considering the issue of complete removal of the "suspicious" CIED and prolonged antibiotic therapy according to the recommendations of the European Society of Cardiology 2015. An additional diagnostic tool for CIED-associated sepsis is a combined positron emission and X-ray computed tomography (PET/CT) scan with 18F-FDG [7]. The isolated use of antibiotics without radical removal of CIED worsens the prognosis, because persistent intracardiac infection ultimately leads to the progression of sepsis and the involvement of TV structures in the infectious process, which, even after the cure of CIED infection, becomes a severe clinical problem.

CONCLUSION

• The course of infective endocarditis of the device implanted in the heart differs from the classical clinical picture of valvular IE. The key to early diagnosis of electrode sepsis is knowledge of typical clinical CIED masks and the features of the modern course of septic syndrome.

• With a long course of electrode sepsis, the likelihood of involvement of tricuspid valve structures in infective endocarditis is directly proportional to the time from debut to surgery.

• Early and complete removal of CIED in combination with antibacterial therapy, the duration and volume of which corresponds to international clinical guidelines, is a guarantee of favorable short-term and long-term prognosis.

• In our opinion, the systematic sanitation of chronic foci of infection, especially odontogenic infection, can become an effective preventive measure against CIED infection.

• Thorough debridement of chronic foci of infection before ISU implantation should be as necessary a procedure as before open cardiac surgery.

ADDITIONAL INFORMATION

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REFERENCES

1. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology. *Eur Heart J.* 2015;36(44):3075–3128. DOI: 10.1093/eurheartj/ehv319

2. Sazhin AV, Tyagunov AE, Murman MV. Treatment of suppurative complications of constant pacing. *Russian Journal of Thoracic and Cardiovascular Surgery*. 2012;(1):31–36. (In Russ.).

3. Prokhvatilov GI, Shelkovskii VN. Chronic odontogenic infection and its role in the development of diseases of internal organs (infective endocarditis). Lecture. Saint Petersburg: Military medical academy of S.M. Kirov; 2010. (In Russ.).

4. Shelkovskii VN. Surgical debridement of foci of odontogenic infection in treatment and prevention of infective endocarditis [dissertation]. Saint Petersburg; 1999. (In Russ.).

5. Krutova SN. Features of dental preparation of patients with infective endocarditis for heart surgery [dissertation]. Tver; 2010. (In Russ.).

6. Klug D, Balde M, Pavin D, et al. Risk factors related to infections of implanted pacemakers and cardioverter — defibrillators: result of a large prospective study. *Circulation.* 2007;116:1349–1355. DOI: 10.1161/CIRCULATIONAHA.106.678664

7. Kalinin DA, Mikhaylov EN, Ryzhkova DV, et al. Difficult diagnosis of sepsis associated with pacemaker lead , infection in the elderly: the role of positron emission tomography. *Journal of Arrhythmology.* 2019;26(2):55–57. DOI: 10.35336/VA-2019-2-55-57. (In Russ.).

8. Gupalo EM, Stukalova OV, Mironova NA, et al. Potentialities of heart MRI in detection of inflammation in patients with idiopathic abnormalities of cardiac conduction and clinical syndrome of dilated cardiomyopathy. *Journal of Arrhythmology*. 2014;(77):32–41. (In Russ.).

СПИСОК ЛИТЕРАТУРЫ

1. Habib G., Lancellotti P., Antunes M.J. et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology // Eur. Heart J. 2015. Vol. 36, No. 44. P. 3075–3128. DOI: 10.1093/eurheartj/ehv319

2. Сажин А.В., Тягунов А.Е., Мурман М.В. Лечение гнойных осложнений, возникающих на фоне постоянной электрокардиостимуляции // Грудная и сердечно-сосудистая хирургия. 2012. № 1. С. 31–36.

3. Прохватилов Г.И., Шелковский В.Н. Хроническая одонтогенная инфекция и ее роль в развитии заболеваний внутренних органов (инфекционного эндокардита). Лекция. СПб.: Военно-медицинская академия имени С.М. Кирова, 2010.

4. Шелковский В.Н. Хирургическая санация очагов одонтогенной инфекции в лечении и профилактике инфекционных эндокардитов: автореф. дис. ... канд. мед. наук. СПб., 1999.

5. Крутова С. Н. Особенности стоматологической подготовки больных инфекционным эндокардитом к операции на сердце: автореф. дис. ... канд. мед. наук. Тверь, 2010.

6. Klug D., Balde M., Pavin D. et al. Risk factors related to infections of implanted pacemakers and cardioverter — defibrillators: result of a large prospective study // Circulation. 2007. Vol. 116. P. 1349–1355. DOI: 10.1161/CIRCULATIONAHA.106.678664

7. Калинин Д.А., Михайлов Е.Н., Рыжкова Д.В. и др. Трудности диагностики при ассоциированном с инфекцией электродов электрокардиостимулятора сепсисе в пожилом возрасте: роль позитронной эмиссионной томографии // Вестник аритмологии. 2019. Т. 26, № 2(96). С. 55–57. DOI: 10.35336/VA-2019-2-55-57

8. Гупало Е.М., Стукалова О.В., Миронова Н.А. и др. Возможности магнитно-резонансной томографии сердца в выявлении воспаления у больных с идиопатическими нарушениями проводимости сердца и у больных с клиническим синдромом дилатационной кардиомиопатии // Вестник аритмологии. 2014. № 77. С. 32–41.

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Nuances of Cardiac Resynchronization Therapy in Patients with Dilated Cardiomyopathy and Atrial Fibrillation (a Clinical Case)

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Dilated cardiomyopathy is a steadily developing disease characterized by progressive chronic heart failure resistant to drug therapy. Cardiac resynchronization therapy significantly improves the prognosis in these patients if they have indications for implantation of resynchronization devices. The article presents a clinical case of successful implantation of a cardiac resynchronization device with defibrillator in a patient suffering from DCM in combination with permanent atrial fibrillation. The nuances of ventricular rate control and the role of the catheter procedure for modifying the atrioventricular junction are discussed.

Keywords: dilated cardiomyopathy; cardiac resynchronization therapy; atrial fibrillation.

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Нюансы сердечной ресинхронизирующей терапии у пациентов с дилатационной кардиомиопатией и фибрилляцией предсердий (клинический случай)

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Дилатационная кардиомиопатия — неуклонно прогрессирующее заболевание, характеризующееся резистентной к медикаментозной терапии прогрессирующей хронической сердечной недостаточностью. Сердечная ресинхронизирующая терапия существенно улучшает прогноз у таких пациентов при наличии у них показания к имплантации ресинхронизирующих устройств. В статье представлен клинический случай успешной имплантации сердечного ресинхронизирующего устройства с функцией кардиоверсии-дефибрилляции пациенту, страдающему ДКМП в сочетании с постоянной формой фибрилляции предсердий. Обсуждены нюансы контроля частоты желудочковых сокращений и роль катетерной процедуры модификации атриовентрикулярного соединения.

Ключевые слова: дилатационная кардиомиопатия; сердечная ресинхронизирующая терапия; фибрилляция предсердий.

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ЭКО•ВЕКТОР

INTRODUCTION

DCM is a primary myocardial damage, which develops as a result of exposure to various genetic and nongenetic factors and is characterized by pronounced dilatation of the heart chambers with a decrease in the systolic function of the ventricles. [1].

Criteria for the diagnosis of DCM:

1. Dilation of the heart chambers. The diagnostic criterion is an increase in the left ventricular (LV) of size/volume index > 112% in relation to the mean value for a given age + 2 SD.

2. Decreased LV ejection fraction (EF). EF should be calculated in 2D or 3D using the Simpson method. EF less than 45% is considered a diagnostic criterion [2].

The leading clinical sign of DCM is progressive chronic heart failure (CHF) resistant to drug therapy. In the natural course of the disease without therapy, the annual mortality of patients with DCM is 10-50% [3].

CRT significantly improves the prognosis in patients with DCM having indications for implantation of resynchronizing devices [4–6]. The presence of a sinus rhythm in the patient makes it possible to synchronize the work of all chambers of the heart. In patients with AF, it is impossible to synchronize the work of the atria and ventricles. CRT is recommended for such patients only in the case of providing close to 100% biventricular stimulation (using medication or catheter procedures) [7, 8].

MATERIALS AND METHODS

Case histories, discharge epicrisis, results of instrumental examinations of patient B. for the period 1918–2021.

PURPOSE OF THE STUDY

Show the features of management of patients with DCM in combination with AF after implantation of a cardiac resynchronization device.

RESULTS AND ITS DISCUSSION

Patient B., born 05.09.1947. He considers himself ill since September 2018, when for the first time, against the background of the first episode of AF in his life, clinical signs of CHF appeared. The patient was hospitalized. Examination revealed a decrease in EF to 36%, complete left bundle branch block according to ECG with a QRS complex width of 160 ms. Sinus rhythm was restored by electro-pulse therapy. Ischemic cardiomyopathy was diagnosed. The following therapy was prescribed: metoprolol with succinate, perindopril, eplerinone, torasemide, apixaban, atorvastatin. Coronary angiography (CAG) is recommended routinely to verify the diagnosis.

In April 2019, in presence of ongoing therapy, an episode of stable hemodynamically significant ventricular tachycardia (VT), accompanied by loss of consciousness, was recorded for the first time.

In May 2019, CAG and ventriculography were performed. Coronary arteries showed no pathology. EF was visually estimated at about 40%. After CAG, the diagnosis was changed to DCM.

The ongoing optimal drug therapy did not lead to an improvement in the patient's condition. Hemodynamically significant VT, complicated by syncope, recurred. AF became permanent.

In view of repeated VT and indications for implantation of a cardiac resynchronization device, a 3-chamber pacemaker with a cardioversion-defibrillation function (CRT-D) was implanted in August 2019. After CRT-D implantation, adequate control of atrioventricular (AV) conduction was ensured by medication with a dose of metoprolol succinate titrated up to 200 mg per day; full biventricular stimulation, approaching 100%, took place. Against this background, 4 weeks after CRT-D implantation, not only the patient's condition improved, but also the EF normalized (EF 65%). In September 2019, due to several triggers of an implanted cardioverter-defibrillator for persistent VT, metoprolol was replaced with sotalol at a daily dose of 160 mg.

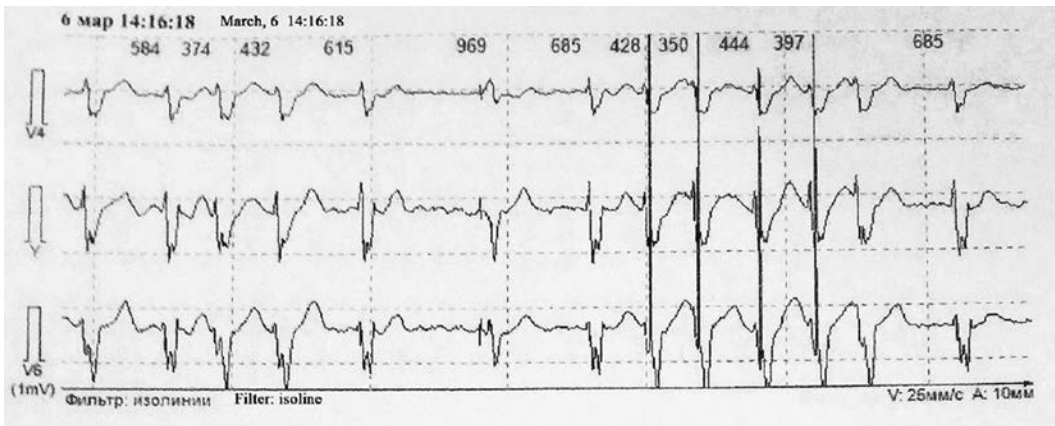

Fig. 1. Fragment of ECG monitoring after CRT-D implantation, explanation in the text.

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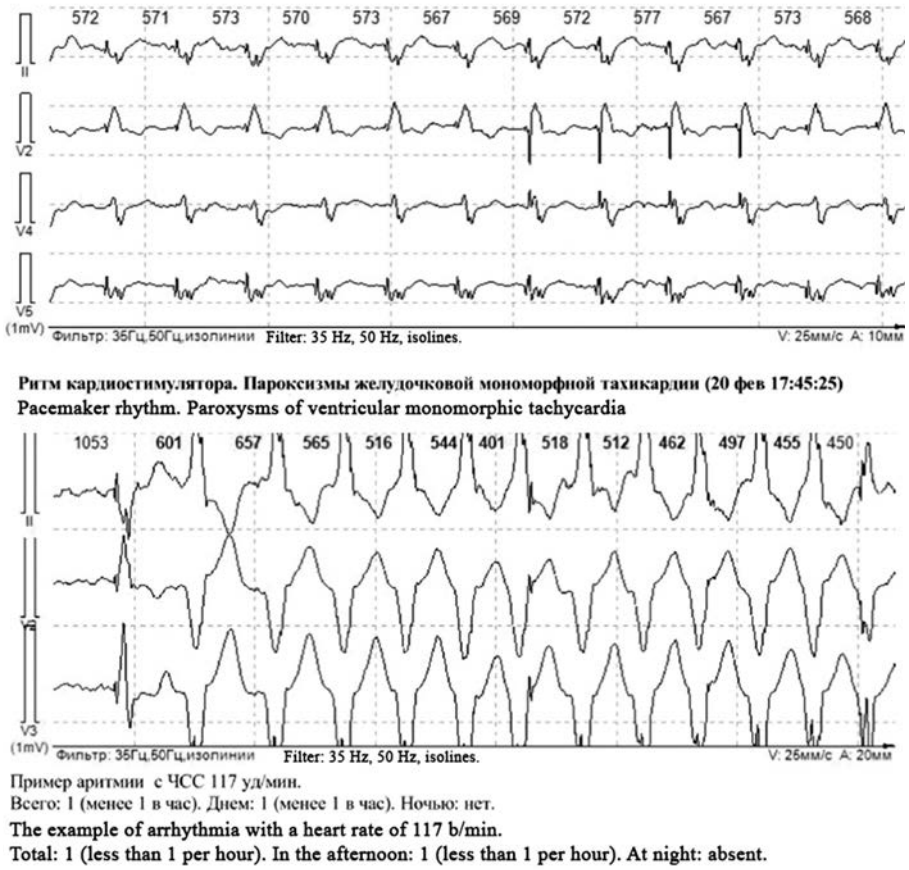

Fig. 2. Two fragments of 24-hour ECG monitoring after destruction of the AV junction. Explanation in the text.

Unfortunately, sotalol in a daily dose of 160 mg was unable to adequately control AV conduction. The percentage of biventricular stimulation decreased to 70%. With underlying critically low values of biventricular stimulation in February 2020, dyspnea reappeared and began to increase.

Hospitalized with decompensated CHF. When programming the pacemaker, a low percentage of biventricular stimulation due to tachysystolic AF and inadequate drug control of AV conduction was observed.

According to 24-hour ECG monitoring (from March 06, 2020): in presence of tachysystolic AF (heart rate up to 150 beats/min.), along with episodes of full-fledged biventricular pacing (Fig. 1), multiple loss of biventricular ventricular pacing with its replacement owithn triggered LV stimulation in the performed supraventricular and ectopic ventricular complexes was observed. From echocardiography (March 06,2020) a decrease in EF to 41.5% was revealed.

The following therapy was prescribed: metoprolol 150 mg per day, dabigatran etexilate 150 mg 2 times a day, spironolactone 25 mg per day. Due to hypotension, further titration of the metoprolol dose was not possible. For the same reason, inhibitors of the renin-angiotensin system were not prescribed. There were no signs of fluid retention and therefore no diuretics were prescribed. The therapy did not improve the clinical condition. Dyspnea persisted during household physical activity.

Indications for the destruction of the AV connection were established due to the impossibility of drug control of AV conduction. The procedure was planned and performed on March 20, 2020. After the destruction of the AV junction, which provided 100% biventricular stimulation, the clinical situation improved, the dyspnea disappeared.

According to echocardiography from February 20, 2021 there was a tendency to EF improvement (EF 42.6%).

According to the daily ECG monitoring from February 20, 2021: permanent AF; 3rd degree AV block; pacemaker rhythm in biventricular stimulation mode; VT episode without clinical manifestations, to which CRT-D did not respond (probably due to a lower (than the programmed) frequency rhythm disturbance was not perceived as VT) (Fig. 2).

CONCLUSIONS

The case presented by us illustrates the efficacy of CRT in patients with DCM in combination with AF under the condition of full, approaching 100% biventricular stimulation. Patients need rigid medication (or catheter procedures if medication is ineffective) control of AV conduction, since only suppression of the conduction of supraventricular complexes to the ventricles can provide full biventricular stimulation.

ADDITIONAL INFORMATION

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REFERENCES

1. Kardiologiya. Nacional'noe rukovodstvo. Ed. by E.V. Shlyakhto. Moscow: GEHOTAR-Media; 2019. (In Russ.).

2. Mathew T, Williams L, Navaratnam G, et al. Diagnosis and assessment of dilated cardiomyopathy: a guideline protocol from the British Society of Echocardiography. *Echo Res Pract.* 2017;4(2):G1–G13. DOI: 10.1530/ERP-16-0037

3. Novikov VI, Novikova TN. Kardiomiopatii. Moscow: MEDpress-inform; 2021. (In Russ.).

4. Hronicheskaya serdechnaya nedostatochnost'. Klinicheskie rekomendacii. 2020 [Internet]. Available from: https://scardio.ru/content/Guidelines/2020/Clinic_rekom_HSN.pdf. Accessed: Dec 13, 2021. (In Russ.).

5. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). *Eur J Heart Fail.* 2016;18(8):891–975. DOI: 10.1002/ejhf.592

6. McLeod CJ, Shen W-K, Rea RF, et al. Differential outcome of cardiac resynchronization therapy in ischemic cardiomyopathy and idiopathic dilated cardiomyopathy. *Heart Rhythm.* 2011;8(3):377–382. DOI: 10.1016/j.hrthm.2010.11.013

7. Upadhyay GA, Choudhry NK, Auricchio A, et al. Cardiac resynchronization in patients with atrial fibrillation: a meta-analysis of prospective cohort studies. *J Am Coll Cardiol.* 2008;52(15):1239–1246. DOI: 10.1016/j.jacc.2008.06.043

8. Lawin D, Stellbrink C. Change in indication for cardiac resynchronization therapy? *Eur J Cardiothorac Surg.* 2019;55(Suppl 1):i11–i16. DOI: 10.1093/ejcts/ezy488

СПИСОК ЛИТЕРАТУРЫ

1. Кардиология. Национальное руководство / под ред. Е.В. Шляхто. М.: ГЭОТАР-Медиа, 2019.

2. Mathew T., Williams L., Navaratnam G. et al. Diagnosis and assessment of dilated cardiomyopathy: a guideline protocol from the British Society of Echocardiography // Echo Res. Pract. 2017. Vol. 4, No. 2. P. G1–G13. DOI: 10.1530/ERP-16-0037

3. Новиков В.И., Новикова Т.Н. Кардиомиопатии. М.: МЕДпресс-информ, 2021.

4. Хроническая сердечная недостаточность. Клинические рекомендации. 2020 [Электронный ресурс]. Режим доступа: https://scardio.ru/content/Guidelines/2020/Clinic_rekom_HSN.pdf. Дата обращения: 13.12.2021.

5. Ponikowski P., Voors A.A., Anker S.D. et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) // Eur. J. Heart Fail. 2016. Vol. 18, No. 8. P. 891–975. DOI: 10.1002/ejhf.592

6. McLeod C.J., Shen W-K., Rea R.F. et al. Differential outcome of cardiac resynchronization therapy in ischemic cardiomyopathy and idiopathic dilated cardiomyopathy // Heart Rhythm. 2011. Vol. 8, No. 3. P. 377–382. DOI: 10.1016/j.hrthm.2010.11.013

7. Upadhyay G.A., Choudhry N.K., Auricchio A. et al. Cardiac resynchronization in patients with atrial fibrillation: a meta-analysis of prospective cohort studies // J. Am. Coll. Cardiol. 2008. Vol. 52, No. 15. P. 1239–1246. DOI: 10.1016/j.jacc.2008.06.043

8. Lawin D., Stellbrink C. Change in indication for cardiac resynchronization therapy? // Eur. J. Cardiothorac. Surg. 2019. Vol. 55, No. Suppl 1. P. i11–i16. DOI: 10.1093/ejcts/ezy488

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Clinical Experience of Use of Sacubitril/Valsartan in a Patient with Dilated Cardiomyopathy, Chronic Heart Failure with Reduced Ejection Fraction and Ventricular Arrhythmias

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Chronic heart failure is the final stage of the cardiovascular continuum, which is an important cause of disability and reduced life expectancy in developed countries. Optimal medical therapy recommended for patients with symptomatic HF and reduced left ventricular ejection fraction includes angiotensin-converting enzyme inhibitors (or angiotensin II receptor antagonists), beta-blockers and mineralocorticoid receptor antagonists. However, the use of optimal medical therapy does not always lead to the elimination of symptoms, improvement of the quality of life and functional capabilities of patients.

Sakubitril/valsartan is a novel combination drug that includes the angiotensin II receptor blocker valsartan and the neprilisin inhibitor sacubitril. In a large PARADIGM-HF clinical trial it demonstrated a 20% reduction in cardiovascular mortality and hospitalization due to decompensation of heart failure compared with standard therapy with enalapril. We report a case of successful use of sacubitril/valsartan in a 61-year-old patient with dilated cardiomyopathy, chronic heart failure with reduced ejection fraction and ventricular arrhythmias. After 6 months of therapy, the patient achieved marked positive dynamics of the clinical status, laboratory and instrumental parameters in absence of any adverse reactions and complications.

Keywords: sacubitril/valsartan; heart failure with reduced ejection fraction; dilated cardiomyopathy; ventricular arrhythmias; case report.

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Опыт использования препарата сакубитрил/валсартан у пациента с дилатационной кардиомиопатией, хронической сердечной недостаточностью сосниженной фракцией выброса и желудочковыми нарушениями ритма

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Хроническая сердечная недостаточность — конечная стадия сердечно-сосудистого континуума, которая является важной причиной нарушения трудоспособности и сокращения продолжительности жизни населения развитых стран. Оптимальная медикаментозная терапия, рекомендованная пациентам с симптоматической ХСН и сниженной фракцией выброса левого желудочка включает в себя ингибиторы ангиотензинпревращающего фермента (либо антагонисты рецепторов ангиотензина II), бета-адреноблокаторы и антагонисты рецепторов минералокортикоидов. Однако использование оптимальной медикаментозной терапии не всегда позволяет добиться устранения симптомов, улучшения качества жизни и функциональных возможностей пациентов.

Сакубитрил/валсартан — это новый комбинированный препарат, включающий в себя антагонист рецепторов ангиотензина II валсартан и ингибитор неприлизина сакубитрил. В крупном клиническом исследовании PARADIGM-HF он продемонстрировал 20%-е снижение сердечно-сосудистой смертности и частоты повторных госпитализаций в связи с декомпенсацией по сравнению со стандартной терапией эналаприлом.

В настоящем наблюдении представлен опыт успешного применения препарата сакубитрил/валсартан у 61-летнего пациента с дилатационной кардиомиопатией, хронической сердечной недостаточностью со сниженной фракцией выброса и желудочковыми нарушениями ритма. После 6 месяцев терапии у пациента отмечалась значительная положительная динамика клинического статуса, лабораторных и инструментальных показателей при отсутствии значимых побочных реакций и осложнений.

Ключевые слова: сакубитрил/валсартан; хроническая сердечная недостаточность со сниженной фракцией выброса; желудочковые аритмии; дилатационная кардиомиопатия; клинический случай.

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ЭКО•ВЕКТОР

INTRODUCTION

Dilated cardiomyopathy (DCM) is characterized by a poorly contracting dilated left ventricle with a normal or reduced left ventricular wall thickness, which leads to the development of congestive cardiac failure [1]. The progression of heart failure (HF) is associated with left ventricular remodeling, which manifests as gradual increases in left ventricular end-diastolic and end-systolic volumes, wall thinning, and a change in chamber geometry to a more spherical and less elongated shape. This process is usually associated with a steady reduction in left ventricular ejection fraction (LVEF). Other life-threatening complications of DCM include ventricular arrhythmias, thromboembolic events, syncope and sudden cardiac death [2, 3].

The primary direction of HF management is the early initiation of therapy. It is important not just to eliminate symptoms, but to improve patients' functional capacity and quality of life, prevent hospital admissions and reduce mortality [4]. Neuro-hormonal antagonists (ACE-inhibitors, MRAs and beta-blockers) for years have been the cornerstone of the treatment for heart failure with reduced ejection fraction (HFrEF). However a novel compound (LCZ696) that combines the moieties of an angiotensin II receptor blocker (valsartan) and a neprilysin inhibitor (sacubitril) has recently been shown to be superior to an ACE-inhibitor (enalapril) in reducing the risk of death and of hospitalization for HF in a PARADIGM-HF randomized controlled trial with strict inclusion/exclusion criteria [5–7]. Sacubitril/valsartan is therefore recommended to replace ACE-inhibitors in HFrEF patients who remain symptomatic despite optimal therapy and who fit these trial criteria [7].

In this article we report a case of a 61-year-old male patient with dilated cardiomyopathy possibly related to myocarditis, HFrEF and episodes of non-sustained ventricular tachycardia. Sacubitril/valsartan treatment was initiated after six months of standard treatment.

CASE PRESENTATION

In September 2020 a 61-year-old male patient was admitted to the Grodno Regional Clinical Cardiology Center presenting with dyspnea on exertion, reduced exercise tolerance, palpitations and ankle swelling. He had a previous medical history of vasospastic angina, hypertension and ventricular ectopy. He was a non-smoker and had no family history of cardiovascular disease. Present clinical symptoms have developed since March 2020, when, after episode of hypothermia, he had developed right-sided pneumonia (confirmed Covid-19 negative by RT-PCR test). The present clinical deterioration was noted during the last two weeks before hospital admission.

Current medications included metoprolol 25 mg b.i.d., ramipril 5 mg q.i.d., spironolactone 50 mg q.i.d., aspirin 75 mg PO q.i.d, and atorvastatin 10 mg q.i.d.

Upon his initial presentation, the patient had respiratory rate 22 breaths/min, heart rate of 82/min, blood pressure – 160/100 mm Hg and 97% oxygen saturation on ambient air. Cardiac auscultation revealed an audible S3 sound and a moderate systolic murmur, indicative of mitral regurgitation. Also he had edema in feet and ankles,

An electrocardiogram revealed sinus rhythm with heart rate of 77/min, left atrial enlargement and LV hypertrophy with secondary ST-T wave changes (see Fig. 1).

His baseline echocardiogram showed dilation of all heart chambers, pulmonary trunk and its branches, significant decrease in systolic function of the LV myocardium with severe *global hypokinesis.* His LVEF was 23% (Biplance). Also the patient had moderate mitral and tricuspid regurgitation (grade II), atherosclerotic lesions of the aorta and aortic valve, dilation of ascending aorta (42 mm), moderate aortic regurgitation (grade II) and pulmonary hypertension (SPAP — 49 mm Hg).

Ambulatory 24-hour Holter ECG monitoring (metoprolol 25 mg b.i.d.) revealed that patient had sinus rhythm with a heart rate from 78 to 114 b.p.m. His average heart rate during the day was 91 b.p.m, at night — 82 b.p.m., RR max. — 1345 msec. There were 10397 isolated polymorphic PVCs, 207 couplets and 64 episodes of non-sustained ventricular tachycardia (lasting for 3 beats) at a rate of 101 — 135 b.p.m (see Fig. 2). No ischemic changes of ST segment and T wave have been found.

The complete blood cell (CBC) count revealed normal white blood cell (WBC) count of 7.8 · 10^9/L, red blood count

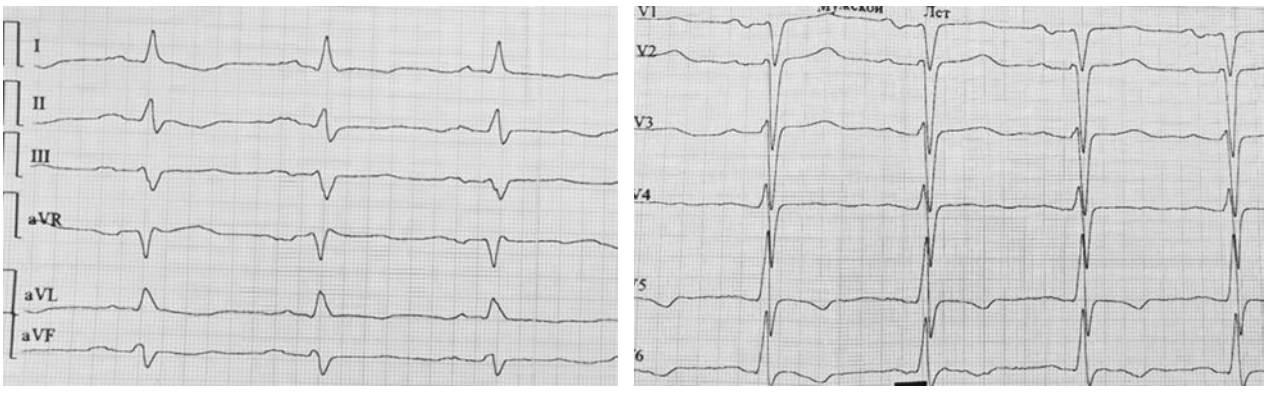

Fig. 1. Patient's electrocardiogram at admission to the hospital

of 4.62 · 10^{12}/L, hemoglobin of 143 g/L and platelet count of 163 · 10^{9}/L. His total cholesterol (5.54 mmol/L) and bilirubin (23.1 mmol/L) were slightly elevated, urea (2.5 mmol/L) and creatinine (113.4 mcmol/L) stayed within normal values with estimated GFR of 61 ml/min/1.73m^2). His coagulation testing showed no changes from reference values. Other notable admission labs included low potassium level 3.8 mmol/L, pro-brain natriuretic peptide 3203 pg/mL and d-dimer 840 ng/ml.

Taking into account his dyspnea on exertion and reduced exercise tolerance, the patient underwent coronary angiography, which revealed 75% proximal stenosis of the diagonal branch (D1) of his left anterior descending artery (LAD). His left circumflex coronary artery and right coronary artery didn't have any significant stenosis (see Fig. 3 and 4). Conservative treatment was recommended in absence of indications for percutaneous coronary intervention (SYNTAX Score — 2 points).

The patient was diagnosed with: Dilated cardiomyopathy, probably secondary to myocarditis (March 2020). Moderate mitral and tricuspid regurgitation (grade II). Frequent polymorphic ventricular ectopy, including episodes of non-sustained VT. Atherosclerosis of the aorta and coronary arteries (75% stenosis of the diagonal branch of LAD). Moderate pulmonary hypertension (SPAP — 49 mm Hg). HFrEF (LVEF — 23%), stage IIB (Vasilenko — Strazhesko), NYHA class III.

The treatment initiated in the cardiology department included carvedilol 6.25 mg b.i.d., spironolactone 50 mg b.i.d., furosemide 40 mg q.i.d. (i.v. and then orally), ringer's solution i.v., aspirin 75 mg q.i.d., atorvastatine 10 mg q.i.d. and amiodarone 200 mg b.i.d. Intravenous vasodilators and inotropic agents were not prescribed.

The treatment included aspirin and statins because patient was diagnosed with 75% proximal stenosis of the diagonal branch of LAD, which signified that he had concomitant ischemic heart disease and established coronary artery atherosclerosis. Before initiation of treatment with atorvastatine (6 years ago) patient was diagnosed with hyperlipidemia (total cholesterol — 7.65 mmol/L), which was another indication for lipid-lowering agents. In the 2016 ESC HF Guidelines statins continuation may be considered

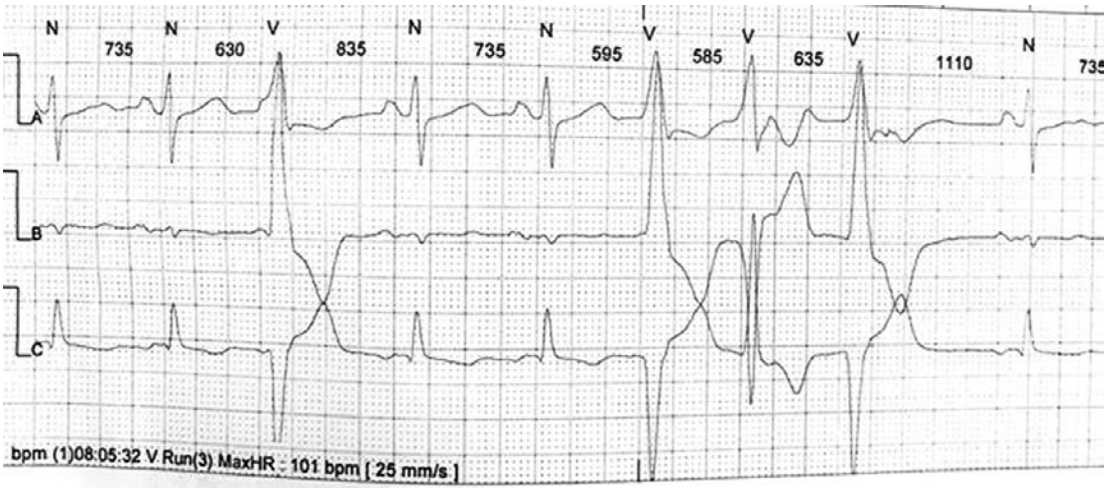

Fig. 2. Episode of non-sustained ventricular tachycardia (3 beats) at a rate of 101 b.p.m. and a solitary premature ventricular contraction

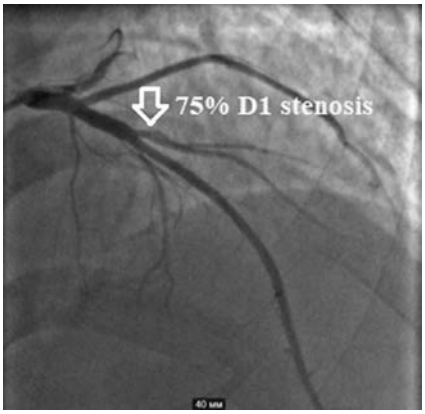

Fig. 3. 75% proximal stenosis of the diagonal branch (D1) of the left anterior descending artery

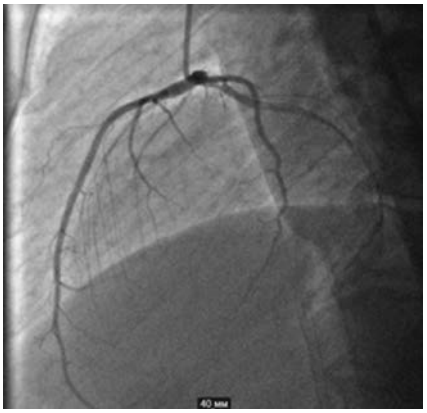

Fig. 4. Left anterior descending artery and circumflex artery without significant stenosis

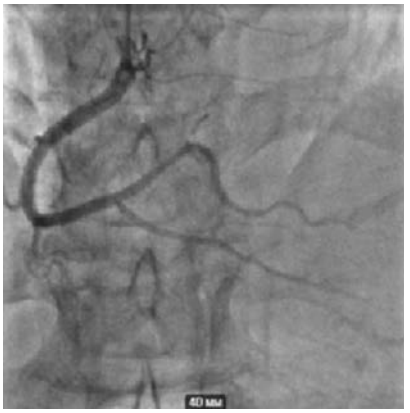

Fig. 5. Right coronary artery without significant stenosis

for those patients already on statins for prevention of CAD [5]. Also 2016 ESC HF Guidelines imply that aspirin should be given in patients with heart failure with accompanying CAD, although its use should be compounded by an adequate evaluation of the expected benefits and risks. Our patient had no major bleeding risk factors, that is why aspirin intake was continued.

Prior to hospital admission patient was treated with ramipril 5 mg b.i.d., but further dosage increase could not be achieved because of decrease in blood pressure.

Therefore, considering that the patient fitted the PARADIGM-HF trial inclusion criteria (see Table 1), ramipril was switched to sacubitril/valsartan in the initial dose of 24/26 mg b.i.d. after the recommended period of 36 hours after discontinuing ACE-inhibitor therapy.

After 7 days of treatment patient noted dyspnea reduction on exertion, absence of dyspnea at rest and a slight reduce in palpitations.

24-hour Holter ECG monitoring (carvedilol 6.25 mg b.i.d. + amiodarone 200 mg b.i.d.) revealed that patient had sinus rhythm with heart rate from 70 to 98 b.p.m. His average heart rate during the day was 80 b.p.m., at night — 73 b.p.m. There were 6546 isolated polymorphic PVCs and 78 couplets. No episodes of non-sustained ventricular tachycardia and ischemic changes of ST segment and T wave were recorded.

However, laboratory tests haven't demonstrated any changes in NT-proBNP level (3252 pg/mL vs. 3203 pg/mL at admission).

At discharge on the 14th day the following therapy was recommended: sacubitril/valsartan 24/26 mg b.i.d., carvedilol 6.25 mg b.i.d., eplerenone 50 mg b.i.d., aspirin 75 mg q.i.d., rosuvastatine 10 mg q.i.d. and amiodarone 200 mg q.i.d (for 1 month). Sacubitril/valsartan dosage was meant to be titrated slowly and doubled every 3–4 weeks to the maintenance dose of one tablet of 97/103 mg b.i.d., if tolerated by the patient.

For the primary prevention of sudden cardiac death, the insertion of implantable cardioverter-defibrillator was recommended; however, patient refused this intervention. It should be noted that according to the current ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, treatment with beta-blocker, MRA and sacubitril/valsartan reduces the risk of sudden cardiac death and is recommended for patients with HFrEF and ventricular arrhythmias (IA) [5]. It is associated with a decrease in the relative risk of SCD by 20% according to the results of the PARADIGM-HF trial [6].

After 4 weeks of treatment the dose of sacubitril/valsartan was increased up to the mid-range does of 49/51 mg b.i.d. The subsequent attempt to increase the dose was accompanied by a substantial decrease in blood pressure and couldn't be achieved.

In January 2021 during his follow-up visit to the doctor patient admitted a significant improvement of his quality of life: he could walk at longer distances and perform household chores without exertion, his sleep improved, ankle swelling and palpitation significantly reduced. He had respiratory rate 17 breaths/min, heart rate of 72/min, and blood pressure — 110/65 mm Hg.

In March 2021, after six months of treatment with sacubitril/valsartan, patient's NT-proBNP level decreased to 317 pg/mL. His CBC, coagulation testing and basic metabolic panel were within reference values (see Table 2).

His electrocardiogram revealed sinus rhythm with heart rate of 67/min, with LV hypertrophy with secondary ST-T wave changes. His echocardiogram revealed visible improvement in systolic function (LVEF — 52%), reduction in the size of both ventricles and atria, and absence of *hypokinesis of the left ventricle*. The dynamics of the echocardiography parameters is presented in Table 3.

His 24-hour Holter ECG monitoring (carvedilol 6.25 mg b.i.d.) revealed that patient had sinus rhythm with heart rate from 58 to 103 b.p.m. His average heart rate during the day was 78 b.p.m., at night — 75 b.p.m. There were only 2213 isolated PVCs, mostly monomorphic and 79 couplets. No episodes of non-sustained ventricular tachycardia were recorded (see Fig. 6).

Table 1. PARADIGM-HF trial inclusion criteria and patient's characteristics

PARADIGM-HF trial inclusion criteria	Patient's characteristics
18 years and older	61 y.o.
LVEF < 35%	LVEF — 23% (Biplance)
NYHA class II–IV	NYHA class III
ACE inhibitor or ARB in target dose	ramipril 5 mg b.i.d.
NT-proBNP ⩾ 600 pg/mL	NT-proBNP — 3203 pg/mL
eGFR ⩾ 30 ml/min/1.73 m^2	eGFR = 61 ml/min/1.73 m^2
systolic blood pressure ⩾ 95 mmHg,	systolic blood pressure — 110 mmHg,
serum potassium level < 5.4 mmol/L	serum potassium level — 3.8 mmol/L

Table 2. The dynamics of the basic metabolic panel parameters within 6 months of treatment with sacubitril/valsartan

Basic metabolic panel parameters	Baseline	6 months after sacubitril/ valsartan initiation	Reference values
Urea, mmol/L	2.5	6.53	2.2–7.5
Creatinine, mmol/L	113.4	100.9	62–124
Potassium, mmol/L	3.8	4,6	3.5–5.5
Soduim, mmol/L	142	141	135–150
Total cholesterol, mmol/L	5.54	4.47	0–5.16
Glucose (fasting), mmol/L	4.3	5.1	3.3–5.9
Bilirubin, mmol/L	23.1	7.8	5–21

Table 3. The dynamics of the echocardiography parameters within 6 months of treatment with sacubitril/valsartan

Echocardiography parameters	Baseline	6 months after sacubitril/valsartan initiation
Diastolic LV internal dimension, mm	72	62
Systolic LV internal dimension, mm	65	45
LV end-diastolic volume, mL	283	192
LV end-systolic volume, mL	227	92
LVEF (%), Biplance	23	52
Left atrial diameter, mm	49 x 67	44 x 64
Right atrial diameter, mm	44 x 57	42 x 54
Right ventricle diameter, mm	32	29

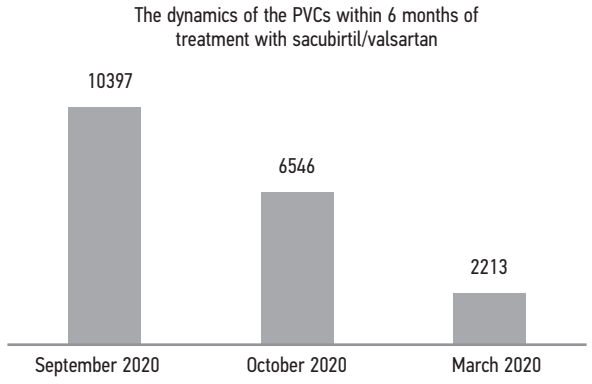

Fig. 6. The dynamics of the PVCs within 6 months of treatment with sacubitril/valsartan.

The patient subsequently reported improved exercise tolerance and quality of life. His clinical condition has improved to NYHA class II and now he continues his optimal medical therapy including sacubitril/valsartan 49/51 mg b.i.d.

DISCUSSION

Nowadays we can see significant improvements in therapeutic approaches for HFrEF [8]. With the beginning of the angiotensin receptor blocker/ neprilysin inhibitors (ARNI) era, a new effective tool for better management of our patients and improvement of their clinical outcomes becomes available. The main goals of HF management are the improvement in quality of life, reducing hospitalizations due to HF decompensation, and cardiovascular mortality, including sudden cardiac death (SCD) [9].

In our case study at the follow-up period of six months, there were no hospitalizations due to HF progression, we

achieved significant structural and functional left ventricular improvements, increased tolerance to physical activity and NYHA class. Also we should mark the disappearance of ventricular tachycardia episodes.

These advantages can be explained by up-regulation of natriuretic peptide (NP) system activity by neprilysin inhibition. It is known that HF progression occurs from imbalance between renin-angiotensin-aldosterone system (RAAS) and NP system [10]. The main idea of clinical benefits of neprilysin inhibition is due to reduced brain natriuretic peptide (BNP) degradation. BNP and N-terminal fragment of the prohormone BNP (NT-proBNP) are secreted in response to mechanical or ischemic myocardial stress with a rapid inducing of natriuresis, diuresis, lowering total peripheral vascular resistance, thus decreasing preload and afterload [11]. Our findings do not conflict with the PARADIGM-HF trial suggesting that ARNI therapy led to reverse cardiac remodeling [7]. There are also similar clinical reports on ARNI therapy in real clinical practice [12, 13]. Interestingly, we have received all mentioned above improvements by achieving maximum tolerable dose of ARNI without achieving the target dose specified in the PARADIGM-HF study [7]. We have found a study in which patients with low systolic blood pressure despite the low mean daily dose of ARNI due to hypotension, obtained significant beneficial cardiac reverse remodeling [14]. Despite dose reduction of sacubitril/valsartan is associated with lower risk of cardiovascular death or hospitalizations due to HF worsening compared with discontinuation of therapy [15] it should not be a reason for insufficient dose titration of ARNI. This example demonstrates the need for an individual pharmacotherapy approach.

Mechanisms reducing the arrhythmic burden in ARNI patients are not studied enough. In the majority of cases SCD has arrhythmic origin linked to myocardial electrical instability [12, 16]. A number of studies [16, 17] have found a correlation between increased levels of BNP and risk of ventricular arrhythmia and have demonstrated that besides reduced LVEF, elevated BNP levels are also significant predictors of SCD. Elevated BNP levels are associated with a worse outcome in patients with HF and decrease in BNP levels means better prognosis from the point of view of malignant ventricular arrhythmias and SCD. NT-proBNP has longer half-life in peripheral blood in comparison with BNP, can also be used as a SCD predictor in HF population, and should be preferred in ARNI treated patients, because is not a substrate for neprilysin [18]. Similarly to these data, observed decline of ventricular tachycardia in our case is associated with significant reduction of NT-proBNP levels.

Recent studies suggested a significant association ARNI therapy with reduction in ventricular tachycardia burden, appropriate ICD shocks and better pacing parameters [19]. In the near future ARNI can become the foundation of optimal medical therapy for HFrEF, making it more effective, so the role of ICD in the ARNI era needs to be reassessed [8].

After recovering from dilated cardiomyopathy, the question of continuing HF therapy has araisen. In the TREAD-HF [20] study, successful withdrawal or reduction of HF therapy was demonstrated only in 50% of patients after six months follow-up and no significant predictors of recurrence were identified. Since these observations were obtained in patients without sacubitril/valsartan treatment, further researchers are needed to investigate this question. Until robust predictors of relapse are identified or until the efficacy of ARNI therapy for HF recurrence is assessed, HF should be continued and requires lifelong therapy [15].

Despite the positive aspects of ARNI therapy, it is not widely implemented in routine clinical practice. There are several reasons, first of all we can name the economic level, the other is lack of awareness about clear practical guidance [15]. Strong hypotensive effect, importance of dose titration, washing period ACE inhibitor treatment, gives doctors a warning before prescribing this treatment in outpatient care [21]. In this work we highlighted the key moments of implementing sacubitril/valsartan in routine clinical practice.

CONCLUSIONS

The main indication for angiotensin receptor blocker/neprilysin inhibitors therapy is heart failure decompensation with a progressive decrease in left ventricular ejection fraction (< 40%) and low NYHA functional class (II-IV).

Dose reduction of sacubitril/valsartan is better compared with refusal to appoint of therapy, but titration to the maximum tolerated dose of ARNI is necessary to achieve the most pronounced clinical effect and need an individual pharmacotherapy approach.

Sacubitril/valsartan therapy did not only improve left ventricular systolic function, but also reduced the frequency of ventricular rhythm disturbances;

In this case, sacubitril/valsartan therapy allowed to avoid or delay cardioverter defibrillator implantation for the primary prevention of sudden cardiac death (Class I);

After the achievement of clinical and functional improvement, sacubitril/valsartan therapy should be continued and requires constant intake.

ADDITIONAL INFORMATION

Funding. The study had no external funding.

Patient's consent. The patient voluntarily signed an informed consent to the publication of personal medical information in an impersonal form.

Conflict of interest. The authors declare no evident or potential conflict of interest related to the current article.

REFERENCES

1. McKenna WJ, Maron BJ, Thiene G. Classification, epidemiology, and global burden of cardiomyopathies. *Circ Res.* 2017;121(7): 722–730. DOI: 10.1161/CIRCRESAHA.117.309711

2. Schultheiss HP, Fairweather D, Caforio ALP, et al. Dilated cardiomyopathy. *Nat Rev Dis Primers*. 2019;5(1):32. DOI: 10.1038/s41572-019-0084-1

3. Braunwald E. Cardiomyopathies: an overview. *Circ Res.* 2017;121(7):711–721. DOI: 10.1161/CIRCRESAHA.117.311812

4. Bakalakos A, Ritsatos K, Anastasakis A. Current perspectives on the diagnosis and management of dilated cardiomyopathy Beyond heart failure: a Cardiomyopathy Clinic Doctor's point of view. H*ellenic J Cardiol.* 2018;59(5):254–261. DOI: 10.1016/j.hjc.2018.05.008

5. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail.* 2016;18(8):891–975. DOI: 10.1002/ejhf.592

6. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC / AHA / HFSA Focused Update of the 2013 ACCF / AHAGuideline for the Management of Heart Failure: A Report of theAmerican College of Cardiology / American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation.* 2017;136(6):e137–161. DOI: 10.1161/CIR.0000000000000509

7. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med.* 2014;371(11):993–1004. DOI: 10.1056/NEJMoa1409077

8. Kaur N, Pruthvi CR, Rohit M. Will introduction of ARNI reduce the need of device therapy in heart failure with reduced ejection fraction? *Egypt Heart J.* 2021;73(1):26. DOI: 10.1186/s43044-021-00152-x

9. Schwinger RHG. Pathophysiology of heart failure. *Cardiovasc Diagn Ther.* 2021;11(1):263–276. DOI: 10.21037/cdt-20-302

10. Docherty KF, Vaduganathan M, Solomon SD, McMurray JJV. Sacubitril/Valsartan: Neprilysin Inhibition 5 years after PARADIGM-HF. *JACC Heart Fail.* 2020;8(10):800–810. DOI: 10.1016/j.jchf.2020.06.020

11. D'Alessandra Y, Chiesa M, Carena MC, et al. Differential role of circulating microRNAs to track progression and pre-symptomatic stage of chronic heart failure: a pilot study. *Biomedicines*. 2020;8(12):597. DOI: 10.3390/biomedicines8120597

12. Corrado E, Saladino A, Morgante G, et al. Reverse remodeling and arrhythmic burden reduction in a patient with an implantable cardioverter defibrillator treated with sacubitril/valsartan: Case report. *Clin Case Rep.* 2020;8(8):1349–1352. DOI: 10.1002/ccr3.2655

13. Cameli M, Pastore MC, Pagliaro A, et al. Sacubitril/Valsartan in an elderly patient with heart failure: a case report. *Cardiology.* 2017;138(suppl 1):3–6. DOI: 10.1159/000484867

14. Hu J, Wu Y, Zhou X, et al. Beneficial effects of Sacubitril/Valsartan at low doses in an Asian real-world heart failure population. *J Cardiovasc Pharmacol.* 2020;76(4):445–451. DOI: 10.1097/FJC.0000000000000873

15. Sauer AJ, Cole R, Jensen BC, et al. Practical guidance on the use of sacubitril/valsartan for heart failure. *Heart Fail Rev*. 2019;24(2):167–176. DOI: 10.1007/s10741-018-9757-1

16. Golukhova EZ, Gromova O, Grigoryan M, et al. Noninvasive predictors of malignant arrhythmias. *Cardiology.* 2016;135:36–42. DOI: 10.1159/000445881

17. Balla C, Vitali F, Brieda A, et al. Predictors of cardiac arrhythmic events in non coronary artery disease patients. *BMC Cardiovasc Disord.* 2019;19(1):104. DOI: 10.1186/s12872-019-1083-6

18. Lepojarvi ES, Huikuri HV, Piira OP, et al. Biomarkers as predictors of sudden cardiac death in coronary artery disease patients with preserved left ventricular function (ARTEMIS study). *PLoS ONE.* 2018;13(9):e0203363. DOI: 10.1371/journal.pone.0203363

19. De Diego C, González-Torres L, Núñez JM, et al. Effects of angiotensin-neprilysin inhibition compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices. *Heart Rhythm*. 2018;15(3):395–402. DOI: 10.1016/j.hrthm.2017.11.012

20. Halliday BP, Wassall R, Lota AS, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. *Lancet.* 2019;393(10166):61–73. DOI: 10.1016/S0140-6736(18)32484-X

21. Grant ADM, Chew DS, Howlett JG, Miller RJH. Cost-effectiveness of earlier transition to angiotensin receptor neprilysin inhibitor in patients with heart failure and reduced ejection fraction. *CJC Open.* 2020;2(6):447–453. DOI: 10.1016/j.cjco.2020.05.009

СПИСОК ЛИТЕРАТУРЫ

1. McKenna W.J., Maron B.J., Thiene G. Classification, Epidemiology, and Global Burden of Cardiomyopathies // Circ. Res. 2017. Vol. 121, No. 7. P. 722–730. DOI: 10.1161/CIRCRESAHA.117.309711

2. Schultheiss H.P., Fairweather D., Caforio A.L.P. et al. Dilated cardiomyopathy // Nat. Rev. Dis. Primers. 2019. Vol. 5, No. 1. P. 1–32. DOI: 10.1038/s41572-019-0084-1

3. Braunwald E. Cardiomyopathies: an overview // Circ. Res. 2017. Vol. 121, No. 7. P. 711–721. DOI: 10.1161/CIRCRESAHA.117.311812

4. Bakalakos A., Ritsatos K., Anastasakis A. Current perspectives on the diagnosis and management of dilated cardiomyopathy beyond heart failure: a Cardiomyopathy Clinic Doctor's point of view // Hellenic J. Cardiol. 2018. Vol. 59, No. 5. P. 254–261. DOI: 10.1016/j.hjc.2018.05.008

5. Ponikowski P., Voors A.A., Anker S.D. et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC // Eur. J. Heart Fail. 2016. Vol. 18, No. 8. P. 891–975. DOI: 10.1002/ejhf.592

6. Yancy C.W., Jessup M., Bozkurt B. et al. 2017 ACC / AHA / HFSA Focused Update of the 2013 ACCF / AHAGuideline for the Management of Heart Failure: A Report of theAmerican College of Cardiology / American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America // Circulation. 2017. Vol. 136, No. 6. P. 137–161. DOI: 10.1161 / CIR.0000000000000509

7. McMurray J.J., Packer M., Desai A.S. et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure // N. Engl. J. Med. 2014. Vol. 371, No. 11. P. 993–1004. DOI: 10.1056/NEJMoa1409077

8. Kaur N., Pruthvi C.R., Rohit M. Will introduction of ARNI reduce the need of device therapy in heart failure with reduced ejection fraction? // Egypt. Heart J. 2021. Vol. 73, No. 1. P. 1–26. DOI: 10.1186/s43044-021-00152-x

9. Schwinger R.H.G. Pathophysiology of heart failure // Cardiovasc. Diagn. Ther. 2021. Vol. 11, No. 1. P. 263–276. DOI: 10.21037/cdt-20-302

10. Docherty K.F., Vaduganathan M., Solomon S.D., McMurray J.J.V. Sacubitril/Valsartan: Neprilysin Inhibition 5 years after PARADIGM-HF // JACC Heart Fail. 2020. Vol. 8, No. 10. P. 800–810. DOI: 10.1016/j.jchf.2020.06.020

11. D'Alessandra Y., Chiesa M., Carena M.C. et al. Differential role of circulating microRNAs to track progression and pre-symptomatic stage of chronic heart failure: a pilot study // Biomedicines. 2020. Vol. 8, No. 12. P. 597. DOI: 10.3390/biomedicines8120597

12. Corrado E., Saladino A., Morgante G. et al. Reverse remodeling and arrhythmic burden reduction in a patient with an implantable cardioverter defibrillator treated with sacubitril/valsartan: Case report // Clin. Case Rep. 2020. Vol. 8, No. 8. P. 1349–1352. DOI: 10.1002/ccr3.2655

13. Cameli M., Pastore M.C., Pagliaro A. et al. Sacubitril/Valsartan in an elderly patient with heart failure: a case report // Cardiology. 2017. Vol. 138 Suppl 1. P. 3–6. DOI: 10.1159/000484867

14. Hu J., Wu Y., Zhou X. et al. Beneficial Effects of Sacubitril/Valsartan at low doses in an Asian real-world heart failure population // J. Cardiovasc. Pharmacol. 2020. Vol. 76, No. 4. P. 445–451. DOI: 10.1097/FJC.0000000000000873

15. Sauer A.J., Cole R., Jensen B.C. et al. Practical guidance on the use of sacubitril/valsartan for heart failure // Heart Fail. Rev. 2019. Vol. 24, No. 2. P. 167–176. DOI: 10.1007/s10741-018-9757-1

16. Golukhova E.Z., Gromova O., Grigoryan M. et al. Noninvasive predictors of malignant arrhythmias // Cardiology. 2016. Vol. 135, No. 1. P. 36–42. DOI: 10.1159/000445881

17. Balla C., Vitali F., Brieda A. et al. Predictors of cardiac arrhythmic events in non coronary artery disease patients // BMC Cardiovasc. Disord. 2019. Vol. 19, No. 1. P. 104. DOI: 10.1186/s12872-019-1083-6

18. Lepojarvi E.S., Huikuri H.V., Piira O.P. et al. Biomarkers as predictors of sudden cardiac death in coronary artery disease patients with preserved left ventricular function (ARTEMIS study) // PLoS ONE. 2018. Vol. 13, No. 9. P. e0203363. DOI: 10.1371/journal.pone.0203363

19. Diego C., González-Torres L., Núñez J.M. et al. Effects of angiotensin-neprilysin inhibition compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices // Heart Rhythm. 2018. Vol. 15, No. 3. P. 395–402. DOI: 10.1016/j.hrthm.2017.11.012

20. Halliday B.P., Wassall R., Lota A.S. et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial // Lancet. 2019. Vol. 393, No. 10166. P. 61–73. DOI: 10.1016/S0140-6736(18)32484-X

21. Grant A.D.M., Chew D.S., Howlett J.G., Miller R.J.H. Cost-effectiveness of earlier transition to angiotensin receptor neprilysin inhibitor in patients with heart failure and reduced ejection fraction // CJC Open. 2020. Vol. 2, No. 6. P. 447–453. DOI: 10.1016/j.cjco.2020.05.009

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Postabaltive Pericarditis in Patient with a Prior History of Rheumatic Disease: a Case Report

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A 60 year-old male with a previous (40 years ago) history of rheumatic carditis without valve involvement and 5 years history of paroxysmal atrial fibrillation underwent ablation (PV isolation with roof and mitral isthmus lines). The following day patient developed AF episode with severe mid-sternal chest pain with widespread concave ST elevation throughout most of the limb leads (I, II, III, aVL, aVF) and precordial leads (V2-6). Serum troponin I was 87.2 ng/ml with a creatinine concentration of 0.88 mg/dl and hemoglobin level of 15 g/dl. 2D transthoracic echocardiogram excluded wall motion abnormalities, or significant pericardial effusions. Recurrence of acute rheumatic fever was excluded based on revised Jones criteria. Careful analysis of ECG allowed us to recognize the ECG criteria of pericarditis and to avoid unnecessary emergent coronary angiography. Ultimately, the patient was diagnosed with pericarditis. After diagnosis, the patient's presenting symptoms resolved with treatment including sotalol 160 mg per day, nonsteroidal anti-inflammatory agents.

Conclusions: This is the first reported case study of post-cardiac ablation pericarditis in patient with prior history of rheumatic carditis.

Keewords: Postabaltive Pericarditis; paroxysmal atrial fibrillation; ablation; complications of ablation.

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Случай развития перикардита после проведения радиочастотной абляции у пациента с предшествующим ревматическим анамнезом

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Представлен клинический случай развития острого перикардита после проведения радиочастотной абляции (РЧА) пароксизмальной фибрилляции предсердий (ФП) у 60-летнего мужчины с указаниями в анамнезе на перенесенный ранее (40 лет назад) ревматический кардит без поражения клапанов. Пациенту была выполнена РЧА в левом предсердии (изоляция устьев всех легочных вен, линейные воздействия в области свода и митрального перешейка). На следующий день у пациента развился эпизод ФП, сопровождавшийся выраженной болью в области грудины и изменениями на ЭКГ — подъемом сегмента ST в отведениях I, II, III, AVL, aVF и прекордиальных отведений (V2-6). Уровень тропонина I составлял 87,2 нг/мл, креатинина — 0,88 мг/дл, гемоглобина — 15 г/дл. Трансторакальная эхокардиография не выявила наличие значимого выпота в перикардиальной сумке и участков гипо и акинеза миокарда левого желудочка. Рецидив острой ревматической лихорадки был исключен на основании пересмотренных критериев Джонса. Тщательный анализ ЭКГ позволил нам распознать ЭКГ-критерии перикардита и избежать ненужной экстренной коронарной ангиографии. В конечном счете пациенту был установлен диагноз перикардит. Пациенту было проведено лечение нестероидными противовоспалительными препаратами средства, которое привело к эффективному купированию болевого синдрома и разрешению воспалительного процесса в перикарде.

Ключевые слова: перикардит; ревматизм; фибрилляция предсердий; радиочастотная абляция.

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ЭКО•ВЕКТОР

INTRODUCTION

Nowadays catheter ablation of atrial fibrillation (AF) is the most effective rhythm control option. The benefits of their use in clinical practice far outweigh the potential risks associated with the complications. It is noteworthy that in the period from 2005 to 2012 (the so-called period of the development of the ablation technique), the overall incidence of complications linked with intervention was from 3.9 to 6% [1]. In the works published in recent years, there is a significant increase in the percentage of complications (from 10.5 to 16.3%) associated with the interventional treatment of AF [2]. This is due to the fact that in the early 2000s, complications of ablation were defined as conditions that led to irreversible consequences in the patient's clinical status (for example, stroke) or required urgent surgical and/or interventional intervention. Also among the possible explanations for the increase in the proportion of complications is the introduction into clinical practice of clear definitions of what should be considered a complication and their classification, published in 2012 [1]. No less interesting, in our opinion, is the evolution of the structure of complications. In particular, the number of cases of pulmonary venous stenosis has significantly decreased over the past 20 years, which is associated with the current trend towards antral ablation. It is noteworthy that the widespread introduction of the cryoablation method into clinical practice has led to the appearance of such complications that were previously extremely rare. From 2005 to 2018, there was at least a fourfold increase in the number of cases of diaphragmatic nerve paresis [3]. In particular, the data from the register of all catheter interventional interventions performed for AF in Germany in 2014 indicate that this complication occurred in 21 cases (0.4%) during cryoablation and in none when using radiofrequency energy [4].

It is also interesting that inflammatory changes in the pericardium associated with ablation have been registered as complications recently [5]. Moreover, in none of the cases described was there any mention of the patient's previous rheumatism.

CASE REPORT

60 years old male was admitted to our clinic on 03 March 2017 for ablation of symptomatic (EHRA–II) paroxysmal AF. Until 2017, combined antiarrhythmic therapy (sotalol 120 mg/day and allapinine 50 mg/day) allowed for effective control of sinus rhythm (AF paroxysms occurred 2-3 times a year). The patient noticed an increase in the frequency of AF events (2–3 episodes per month) in the last three months. The patient's medical history indicated a diagnosis of rheumatism established at the age of 20 (polyarthritis and rheumatic myocarditis). Subsequent dynamic follow-up by a rheumatologist, as well as repeated echocardiographic studies, did not reveal rheumatic signs of the heart valves. Before ablation we excluded an unstable variant of coronary artery disease, thyroid dysfunction and the activity of the rheumatic process. Patient was treated with anticoagulants (xarelto 20 mg/day) 1 month before the ablation.

On 04.03.17, we performed ablation of AF using the CARTO system, which included antral isolation of all pulmonary veins, lines in the mitral istmus and left atrial roof, as well as modification of the arrhythmia substrate at the posterior wall (Fig. 1). Transthoracic echocardiographic no revealed of pericardial effusion next morning and patient was discharged with recommendations for taking sotalol 80 mg/day, allapinine 25 mg at night and xarelto 20 mg. At discharge, the ECG recorded a sinus rhythm without changes in the ST segment (Fig. 2).

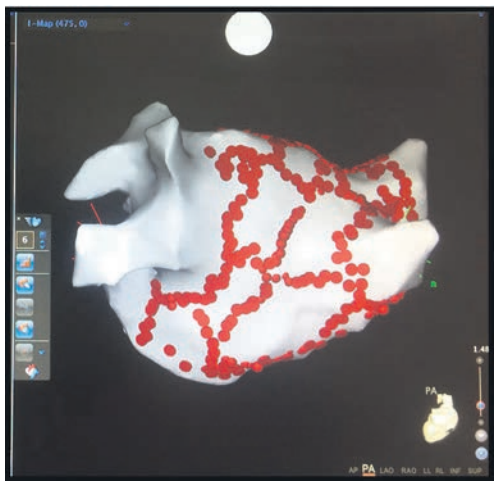

Fig. 1. 3-D reconstruction of the left atrium (posterior view). Brown dots are areas of ablation applications applied along the perimeter of all the pulmonary veins, of the mitral isthmus and the roof of the left atrium, as well as the modification of the substrate of the posterior wall of the left atrium.

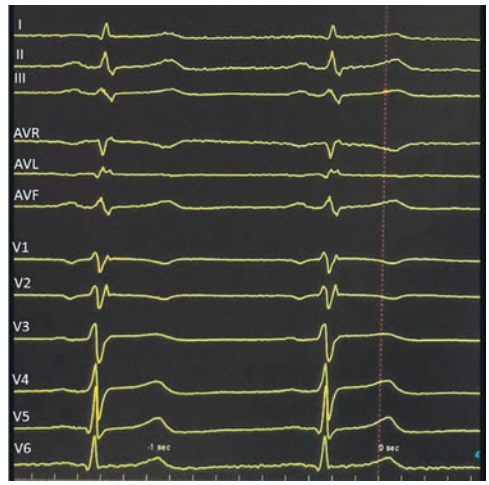

Fig. 2. 12 surface ECG leads recorded at discharge from the hospital on the day after ablation

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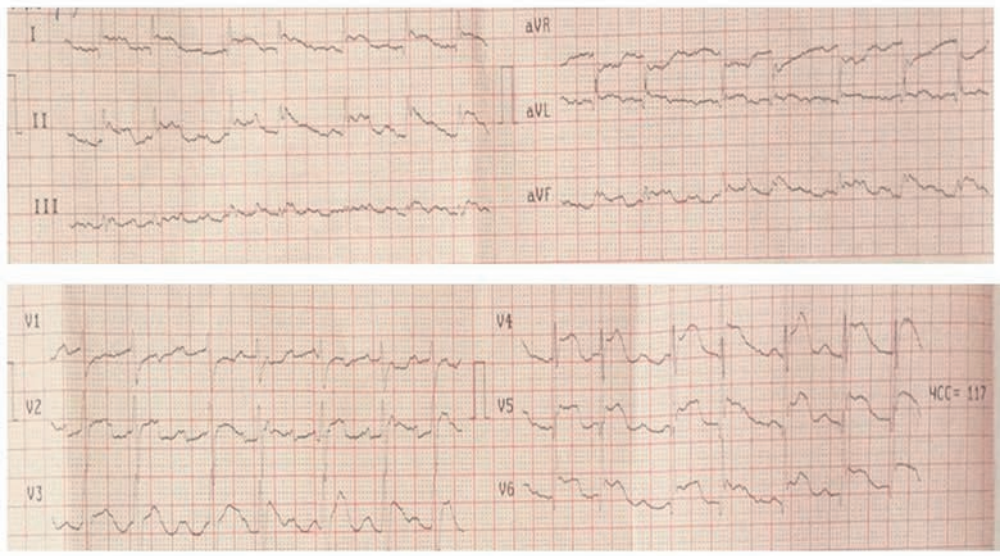

Fig. 3. 12 surface ECG leads registered at the onset of the pericarditis. Atrial fibrillation with a ventricular activation rate of 117 per minute. Note to the diffuse elevation of the ST segment, which is verified in all leads, with the exception of leads III, aVR and V1 without pathological Q waves and a reciprocal decrease in the ST segment. Also there is Spodick sign - a downward direction from the top of the T wave to the atrial fibrillation waves f (see leads I, II, V4-V6).

In the morning of 06 March 2017, the patient had a severe pain in the heart area and palpitations. ECG showed atrial flutter, ST segment elevation in leads I, II, AVL, as well as in the precardial leads (Fig. 3). The patient was admitted to the hospital with suspected acute myocardial infarction. Serum troponin I was 87.2 ng/ml, creatinine level of 0.88 mg/dl and hemoglobin level of 15 g/dl. 2D transthoracic echocardiography excluded wall motion abnormalities, or significant pericardial effusions (150 ml).

According to the results of the examination, the patient revealed exudative pericarditis. Careful ECG analysis allowed us to exclude the diagnosis of acute coronary syndrome. In this regard, it was decided not to perform coronarography.

Against the background of the therapy (xarelto 20 mg, sotalol 120 mg, spironolactone 25 mg, ibuprofen 600 mg, omeprazole 20 mg), the patient's condition improved: the sinus rhythm was restored, the blood pressure was in the range of 100–110/70 mmHg, heart rate 56 per minute. According to repeated transthoracic echocardiography the dynamics showed a decrease in pericardial effusion to 50 ml, the patient was discharged after 10 days. Subsequent clinical 1 and 3 month follow up after ablation did not reveal signs and symptoms of pericarditis or activation of the rheumatic process, although rare episodes of AF remained.

DISCUSSION

Complications of ablation

Today, catheter ablation is the most effective method of controlling sinus rhythm in patients with AF [6, 7].

The half of the patients after ablation of AF have a pericardial reaction [10] with a small amount of fluid in the pericardium which manifest of discomfort in the chest area. As a rule, this symptoms resolve within the natural course of the postoperative period and is not considered as a complication of procedure. It is based on the development of limited pericarditis, which occurs as a result of transmural damage of the atrial myocardium and inflammation of the pericardium. Transthoracic echocardiography may verify a small amount of fluid in the pericardial cavity. This symptom usually resolves within the first few days after ablation without special treatment [1, 6]. Much less often pericarditis requires special treatment. According to the German national registry, which included 33,353 patients who had ablation for AF and/or typical atrial flutter, the diagnosis of pericarditis, which required special treatment, was established from 1.7 to 4% of cases [4]. As a rule, pericarditis can occur acutely (in the first days) after interventional intervention [5] or delayed (in the period from 18 days to 3 months) after RFA (Dressler syndrome) [8]. In most cases, the inflammatory reaction of the pericardium manifests itself in the form of effusive pericarditis, which can be complicated by cardiac tamponade. Isolated cases of constrictive pericarditis and pericarditis after hemotamponade resolution have been described [9]. An analysis of publications on RFA in patients with rheumatism indicates that the frequency of pericarditis does not differ from that in patients with a different etiology of arrhythmic syndrome [5, 8, 9].

Differential diagnosis of acute pericarditis

The onset of acute pericarditis is often manifested by severe pain syndrome in the chest area and gives every reason to assume the possible development of a myocardial infarction with ST-segment elevation. In this regard, conducting a quick and correct differential diagnosis is key to choosing an adequate treatment strategy. In this publication,

we would like to focus the attention on ECG changes that occur in pericarditis, which are different from ECG signs of myocardial infarction with ST segment elevation [10]. A characteristic ECG manifestation of the initial phase of acute pericarditis is diffuse elevation of the ST segment, which is verified in almost all leads, with the exception of leads III, aVR, and V1, and indicates the involvement of the epicardium in the pathological process (subepicardial damage) (see Fig. 3). Another ECG sign of pericarditis is the appearance of similarity of leads I and II (see Fig. 3), whereas in lower myocardial infarction, leads II and III become similar. Attention is drawn to the appearance of the Spodick symptom — a downward direction from the top of the T wave to the P wave, which is often determined in many leads in patients with acute pericarditis. Against the background of sinus rhythm in pericarditis, there is a depression of the PR segment in most leads from the extremities and thoracic leads (a manifestation of atrial damage), with a rise in the PR segment in the AVR lead [11].

In contrast to ST-segment elevation myocardial infarction, acute pericarditis shows no foci of ST-segment changes, no Q-waves, and no reciprocal ST-segment decline.

In some cases, ECG signs of early repolarization syndrome may resemble changes in acute pericarditis (ST segment elevation with downward concavity and positive T teeth). The differential diagnostic criterion that allows us to distinguish these states from each other is the ratio of the ST segment elevation and the T wave amplitude in the V6 lead. If this value is > 0.25, then pericarditis is assumed, and if < 0.25, then early ventricular repolarization is assumed.

CONCLUSION

Despite the tendency to reduce the frequency of complications associated with AF ablation, cardiologists should be wary of relapse of acute pericarditis as a differential diagnosis with rheumatic fever, especially in patients with a history of previous rheumatism.

REFERENCES

1. Hakalahti A, Biancari F, Nielsen JC, Raatikainen MJ. Radiofrequency ablation vs. antiarrhythmic drug therapy as first line treatment of symptomatic atrial fibrillation: systematic review and meta-analysis. *Europace.* 2015;17(3):370–378. DOI: 10.1093/europace/euu376

2. Arbelo E, Brugada J, Blomstrom-Lundqvist C, et al. Contemporary management of patients undergoing atrial fibrillation ablation: in-hospital and 1-year follow-up findings from the ESC-EHRA atrial fibrillation ablation long-term registry. *Eur Heart J.* 2017;38(17):1303–1306. DOI: 10.1093/eurheartj/ehw564

3. Miyazaki S, Tada H. Complications of cryoballoon pulmonary vein isolation. *Arrhythm Electrophysiol Rev*. 2019;8(1):60–64. DOI: 10.15420/aer.2018.72.2

4. Schmidt M, Dorwarth U, Andresen D, et al. German ablation registry: Cryoballoon vs. radiofrequency ablation in paroxysmal atrial fibrillation-One-year outcome data. *Heart Rhythm.* 2016;13(4):836–844. DOI: 10.1016/j.hrthm.2015.12.007

5. Orme J, Eddin M, Loli A. regional pericarditis status post cardiac ablation: a case report. *N Am J Med Sci.* 2014;6(9):481–483. DOI: 10.4103/1947-2714.141653

6. Cappato R, Calkins H, Chen SA, et al. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2010;3(1):32–38. DOI: 10.1161/CIRCEP.109.859116

7. Packer DL, Mark DB, Robb RA, et al. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation. The CABANA Randomized Clinical Trial. *JAMA.* 2019;321(13):1261–1274. DOI: 10.1001/jama.2019.0693

8. Luckie M, Jenkins N, Davidson NC, Chauhan A. Dressler's syndrome following pulmonary vein isolation for atrial fibrillation. *Acute Card Care.* 2008;10(4):234–235. DOI: 10.1080/17482940701843722

9. Troughton RW, Asher CR, Klein AL. Pericarditis. *Lancet.* 2004;363(9410):717–727. DOI: 10.1016/S0140-6736(04)15648-1

10. Surawicz B, Lasseter KC. Electrocardiogram in pericarditis. *Am J Cardiol.* 1970;26(5):471–474. DOI: 10.1016/0002-9149(70)90704-6

11. Spodick DH. Diagnostic electrocardiographic sequences in acute pericarditis: Significance of PR segment and PR vector changes. *Circulation.* 1973;48(3):575–580. DOI: 10.1161/01.cir.48.3.575

СПИСОК ЛИТЕРАТУРЫ

1. Hakalahti A., Biancari F., Nielsen J.C., Raatikainen M.J. Radiofrequency ablation vs. antiarrhythmic drug therapy as first line treatment of symptomatic atrial fibrillation: systematic review and meta-analysis // Europace. 2015. Vol. 17, No. 3. P. 370–378. DOI: 10.1093/europace/euu376

2. Arbelo E., Brugada J., Blomstrom-Lundqvist C. et al. Contemporary management of patients undergoing atrial fibrillation ablation: in-hospital and 1-year follow-up findings from the ESC-EHRA atrial fibrillation ablation long-term registry // Eur. Heart J. 2017. Vol. 38, No. 17. P. 1303–1306. DOI: 10.1093/eurheartj/ehw564

3. Miyazaki S., Tada H. Complications of cryoballoon pulmonary vein isolation // Arrhythm. Electrophysiol. Rev. 2019. Vol. 8, No. 1. P. 60–64. DOI: 10.15420/aer.2018.72.2

4. Schmidt M., Dorwarth U., Andresen D. et al. German ablation registry: Cryoballoon vs. radiofrequency ablation in paroxysmal atrial

fibrillation One-year outcome data // Heart Rhythm. 2016. Vol. 13, No. 4. P. 836–844. DOI: 10.1016/j.hrthm.2015.12.007

5. Orme J., Eddin M., Loli A. regional pericarditis status post cardiac ablation: a case report // N. Am. J. Med. Sci. 2014. Vol. 6, No. 9. P. 481–483. DOI: 10.4103/1947-2714.141653

6. Cappato R., Calkins H., Chen S.A. et al. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation // Circ. Arrhythm. Electrophysiol. 2010. Vol. 3, No. 1. P. 32–38. DOI: 10.1161/CIRCEP.109.859116

7. Packer D.L., Mark D.B., Robb R.A. et al. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation. The CABANA Randomized Clinical Trial // JAMA. 2019. Vol. 321, No. 13. P. 1261–1274. DOI: 10.1001/jama.2019.0693

8. Luckie M., Jenkins N., Davidson N.C., Chauhan A. Dressler's syndrome following pulmonary vein isolation for atrial fibrillation // Acute Card. Care. 2008. Vol. 10, No. 4. P. 234–235. DOI: 10.1080/17482940701843722

9. Troughton R.W., Asher C.R., Klein A.L. Pericarditis // Lancet. 2004. Vol. 363, No. 9410. P. 717–727. DOI: 10.1016/S0140-6736(04)15648-1

10. Surawicz B., Lasseter K.C. Electrocardiogram in pericarditis // Am. J. Cardiol. 1970. Vol. 26, No. 5. P. 471–474. DOI: 10.1016/0002-9149(70)90704-6

11. Spodick D.H. Diagnostic electrocardiographic sequences in acute pericarditis: Significance of PR segment and PR vector changes // Circulation. 1973. Vol. 48, No. 3. P. 575–580. DOI: 10.1161/01.cir.48.3.575

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