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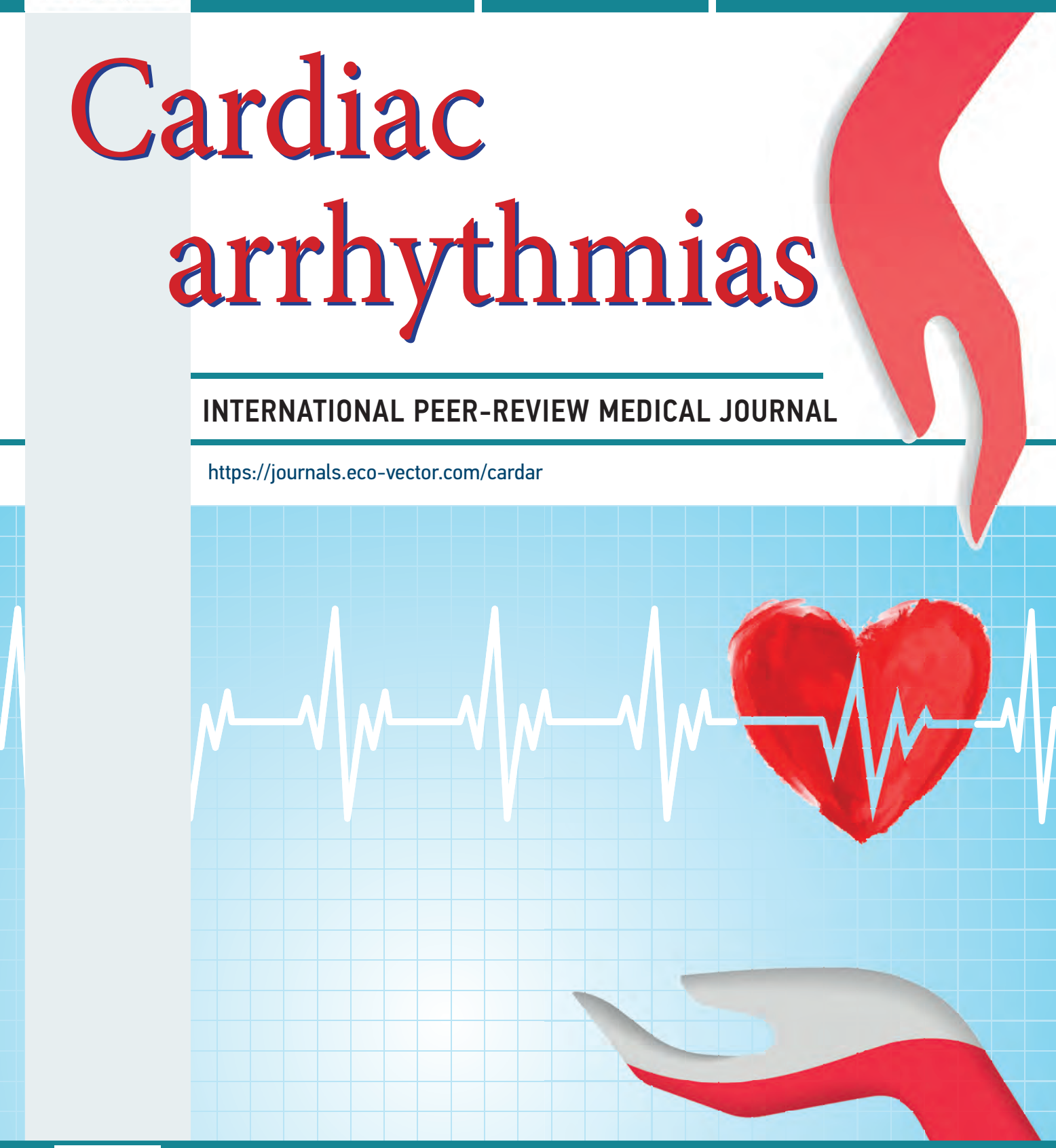

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Review

Access Site Complications by Intracardiac Interventions

Alexander V. Kimkov

St.-Katharinen Hospital GmbH Frechen, Germany

In recent decades, the number of intracardiac procedures using percutaneous puncture access has increased manifold. Despite the acquisition by operators of expertise and standardization of methods, the problem of complications remains relevant.

***AIM*:** to analyze the frequency and nature of complications of percutaneous access in intracardiac interventions. Suggest recommendations to reduce the incidence of complications.

***MATERIALS AND METHODS*:** analysis of data published in international peer-reviewed journals on the topic, as well as the experience of the vascular surgery clinic of St. Katarina's Hospital.

***CONCLUSIONS*:** the frequency and severity of complications depend on the experience of the operator, the size and frequency of changing the instrument, as well as compliance with the rules of preoperative diagnosis and postoperative management of the patient.

***RECOMMENDATIONS*:** standardized preoperative preparation, careful planning of the intervention, analysis of the state of the access vessels, compliance with the rules of vessel puncture and competent performance of postoperative compression in combination with the use of suturing devices according to indications can reduce the frequency and severity of complications.

Keywords: vascular surgery; arrhythmology; access complications; kardiology.

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Обзорная статья

Осложнение места доступа при интракардиальных вмешательствах

А.В. Кимков

Госпиталь св. Катарины, Кёльн-Фрехен, ФРГ

В последние десятилетия многократно возросло количество интракардиальных процедур с использованием чрезкожного пункционного доступа. Несмотря на приобретение операторами экспертизы и стандартизации методов, проблема осложнений остаётся актуальной.

***Цель*:** проанализировать частоту и характер осложнений чрезкожного доступа при интракардиальных вмешательствах. Предложить рекомендации для снижения частоты осложнений.

***Материалы и методы*:** анализ данных, опубликованных в международных рецензируемых журналах по теме, а также опыта клиники сосудистой хирургии госпиталя св. Катарины.

***Выводы*:** частота и тяжесть осложнений зависят от опыта оператора, размера и частоты смены инструмента, а также соблюдения правил предоперационной диагностики и послеоперационного ведения пациента.

***Рекомендации*:** стандартизированная предоперационная подготовка, тщательное планирование вмешательства, анализ состояния сосудов доступа, соблюдение правил пункции сосуда и грамотное выполнение послеоперационной компрессии в сочетании с применением ушивающих устройств по показаниям может снизить частоту и тяжесть осложнений.

Ключевые слова: сосудистая хирургия; аритмология; осложнение доступа; кардиология.

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ЭКО•ВЕКТОР

In 1929, the German urologist W. Forsmann inserted a urinary catheter into his cubital vein and pushed it in a central direction, and then took a radiographic image of his chest in a frontal view. This event was the first proven case of cardiac catheterization [1]. Subsequently, in 1956, he was awarded the Nobel Prize in Medicine. In 1953, the Swedish radiologist Seldinger proposed a vessel puncture technique for subsequent manipulations, named after him [2]. Finally, in the 1990s, Kiemenej and Laarman developed and implemented in clinical practice the technology of transradial percutaneous coronary intervention [3]. Currently, interventional technologies are the basis of many specialties.

In 2018, 220,000 coronary stenting interventions were performed in the Russian Federation, with approximately a 4-fold increase over 10 years. In the USA, 75,000 atrial ablations were performed in 2017 [4]. In all cases, manipulations were performed either through transradial or transfemoral access. Discussions about the advantages of one approach over the other ended after the publication of several studies, especially the RIVAL study [5]. At present, the radial approach is preferred in case of a suitable anatomy and in the absence of specific contraindications.

Despite the vast experience gained, complications of the access site during interventional procedures remain a major problem. In the 1990s, complications occurred in 6% of all patients after coronary interventions; 22%–25% of these cases required blood transfusion, and 21%–38% required surgery [6, 7]. Currently, with the accumulation of experience, the incidence of complications has significantly decreased (up to 1%–2%) [8–11], although it is still a concern given the huge number of interventions. Therefore, the mortality rate in patients who survived such a complication is 7.5% (1.1% without complications), the duration of hospital stay is twice longer, and the cost of inpatient treatment is almost two times higher ($ 9,583 vs. $ 18,350) [12].

The main complications of the access site are hematoma, ischemia of the access site in the limb dependent on the vessel, hemorrhage (including hemodynamically significant), false aneurysm requiring revision, vessel evulsion, and infection. Socioeconomic and psychological problems (staff distraction, psychological trauma to the patient, blocking the patient, and excessive use of resources) should also not be ignored. Factors that increase the risk of complications include female gender, age of 65 and older, body surface area greater than 1.62 m^2, long duration of the procedure, high puncture site with transfemoral access, history of hemorrhagic diathesis, obesity, uncontrolled arterial hypertension, renal failure (creatinine level > 2 mg/d), use of glycoprotein IIB/IIIA inhibitors, and peripheral atherosclerosis [8–14].

Complications of the radial access

Occlusion of the radial artery is the most common complication with appropriate access. It occurs in 2%–18% of all transradial interventions14,15, and its occurrence depends largely on the surgeon's experience, the method of compression and, most importantly, the quality of its application. According to studies, the course of this complication is usually asymptomatic, requiring no special treatment. The pathogenetic process is based on thrombogenesis in areas of the affected intima. Occlusion of the radial artery becomes symptomatic only in case of palmar anastomoses failure or in the presence of ulnar artery occlusion. In this situation, conducting an Allen test before the study will help prevent the development of a serious complication. This test is technically simple and does not require additional resources. In case of occlusion in both arteries, the patient is threatened with a higher risk of ischemia in the region dependent on these vessels and, in case of an unfavorable course, the development of necrosis and the need for amputation. In addition, perioperative injection of 5,000 IU heparin reduces the risk of vessel occlusion (71% vs. 4.3%). Factors that increase the risk of radial artery occlusion include excessive postoperative compression, repeated punctures, and large sluice diameters.

Non-occlusive lesions of the radial artery. This group includes, first, intimal hyperplasia and vascular remodeling. Studies of postoperative intima using intravascular ultrasound scan showed significant intimal hyperplasia with a resulting significant reduction in the diameter of the latter. A small series using optical coherence tomography revealed intimal tears in a significant group of patients (67%) and media dissection (36%). This damage leads to a decrease in the quality of the vessel during its subsequent use as a graft in arterial myocardial revascularization. A retrospective series revealed a decrease in the early patency of such grafts.

Spasm of the radial artery occurs in 5%–10% of all interventions. It rarely leads to serious consequences; however, it can lead to the failure of the procedure. Risk factors include small vessel diameter, female gender, multiple catheter replacements, use of a long sluice, and lack of experience of the operating surgeon. The radial artery has a well-defined tunica media, which is under the control of α-1 adrenoreceptors. For prophylactic purposes, sedation of the patient and local anesthesia can be used to control the effect of circulating endogenous catecholamines. Spasms respond well to treatment. Currently, nitroglycerin, subcutaneous injections of lidocaine, and various vasodilatory cocktails are used. The use of low-profile hydrophilic sluices also contributes to a reduction in the risk of spasm [25, 26]. Ouadhour et al. suggested based on their own research that subcutaneous administration of 0.5 mg isosorbide dinitrate with 1% lidocaine for local anesthesia can improve the radial access function [27].

Vessel perforation is a rare complication, which can lead to serious consequences in the form of loss of access, the need for conversion and, in case of an untimely response, the development of hematoma, compartment syndrome, and ischemia of the dependent area. In an analysis by Calvino-Santos et al., its incidence of less than 1% of cases was reported. Data from a large series showed an incidence of < 0.1% [6]. Moreover, most of these complications occurred in short women with tortuous

vessels of the forearm [30]. Access safety in these patients can be improved by using a long sluice [30] and a guiding catheter [31]. If perforation is detected early, a small-diameter peripheral balloon can be used for angioplasty [32].

Compartment syndrome is a much rare but hazardous complication that requires emergency fasciotomy. Its incidence has been described in large series of cases at 0.004% [33]. The diagnosis is established based on clinical manifestations in the form of a massive tumor of the forearm with symptoms of peripheral ischemia, primarily neurological disorders.

False aneurysm is another rare complication. It occurs in < 0.1% of cases [6] and manifests itself as a penetrating injury to the vessel, which was not recognized in due time. The false aneurysm course is also facilitated by multiple punctures of the vessel and incorrect application of compression of the access site (for example, TR-Band) after the end of the procedure. Diagnosis is made by ultrasound. Conservative (adequate compression, injection of thrombin into the false aneurysm cavity under ultrasound control [34, 35]) or surgical (revision of the access site with hematoma evacuation and suturing) treatment is performed. Ligature of the radial artery is rarely required.

Table 1 presents the most common complications of radial access, their incidence, and methods of prevention and treatment.

Complications of the transfemoral access

Despite the proven advantages of the transradial approach, the transfemoral approach continues to be widely used when indicated or preferred by a particular operating surgeon. The most common complications of this approach are puncture site hematoma, retroperitoneal hematoma, false aneurysm, arteriovenous fistula, and arterial dissection restricting the blood flow. Less complications are infections, thrombosis, and long-term lesions of nerve structures. Incorrect puncture of the vessel plays a huge role in the occurrence of these complications. Many interventional specialists do not have practical surgical experience and often deviate from the recommended puncture technique, considering it an insignificant stage of the intervention.

In addition, the anatomy of the common femoral artery is characterized by low variability expressed in different bifurcation heights. Ultrasound-guided puncture is generally recommended. When performing a puncture under radiological control, a specialist should focus on the femoral head and puncture slightly medially to its center toward the xiphoid process at an angle of 45°. The anatomy of the common femoral artery is schematically presented in Figure 1.

Puncture should not be performed above the inguinal ligament, since in this area, the external iliac artery is oriented in the anteroposterior direction, and the puncture cannula passes parallel to the vessel without providing a puncture. In addition, in case of a high puncture, there is no bone base for performing postoperative compression. In this regard, the risk of bleeding with the formation of a retroperitoneal hematoma increases significantly.

The following factors should be considered risk factors for complications:

- insufficient knowledge of the femoral artery anatomy;
- little experience of the operating surgeon;

Table 1. Complications of transradial access (modified from Kanei)

Complication	Incidence	Risk factors	Prevention and treatment
Occlusion	2%–18%	Overcompression Repeated punctures Large sluice diameter	Anticoagulation Quality hemostasis
Non-occlusive involvement of the radial artery	often		Critical evaluation when used as a graft
Hand ischemia	Very rare	Prolonged cannulation	Pre-procedure assessment of the circulation
Spasm	5%–10%	Small vessel diameter Female gender Multiple catheter replacements Large sluice diameter Insufficient experience	Antispasmodic therapy Sparing manipulation
Perforation	0.1%	Aggressive manipulation Excessive anticoagulation	Timely diagnosis and bandaging
False aneurysm	<0.1%	Multiple punctures Bacterial contamination of the catheter Excessive anticoagulation Large sluice diameter	Compression Thrombin injection Bandaging
Nerve involvement	Extremely rare	Multiple punctures	Neurological therapy
A-B fistula	Extremely rare	Numerous punctures	Surgical correction if necessary
Significant bleeding	0.15%		Correct hemostasis Transfusion Surgical treatment if necessary

- increased BMI;
- female gender;
- refusal of ultrasonic navigation;
- agitated patient.

Hematoma of the puncture site is the most common complication, and it has been reported to occur in 5%–23% of cases by different authors. The hematoma scope varies from slight staining of the skin at the puncture site to a massive tumor requiring surgical treatment and blood transfusion. First, the causes of hematoma include multiple puncture attempts, incorrect or insufficiently long-lasting postoperative compression, and incorrect use of suturing devices. In the vast majority of cases, hematomas do not require special treatment and persist for 1–2 weeks. Follow-up and local therapy with heparin ointment are usually sufficient. If a growing hematoma is detected during the intervention itself, it is possible to use endovascular methods of treatment, such as balloon compression or implantation of a short stent or stent prosthesis. In this case, a contralateral approach is required. If it becomes necessary to implant a stent or a stent graft, it should be taken into account that the puncture site is anterior to the hip joint, that is, it is located in the mobile segment. The implantation of a stent in such a segment poses the risk of implant fracture and, as a consequence, the occurrence of vascular obstruction, limiting blood flow. Sometimes surgical treatment is necessary due to the hematoma size. The CT presentation of such a hematoma is shown in Figure 2. In case of the rapid development of a massive hematoma, necrotic changes in soft tissues are also possible. An example of such a case is presented in Figure 3. A special variant of local hematoma leads to the occurrence of a false aneurysm (0.5%–9%), and emergency surgery is indicated in this case. When performing postoperative compression, the size of the tool used to catheterize the vessel should be considered. The compression force should be approximately 20 mmHg above the systemic systolic pressure. The reference points in Table 2 can be used to determine the compression time.

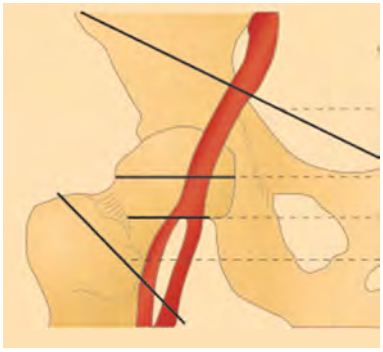


Fig. 1. Topography of the femoral artery (from [36])

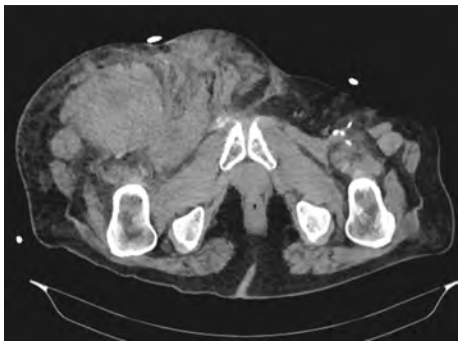
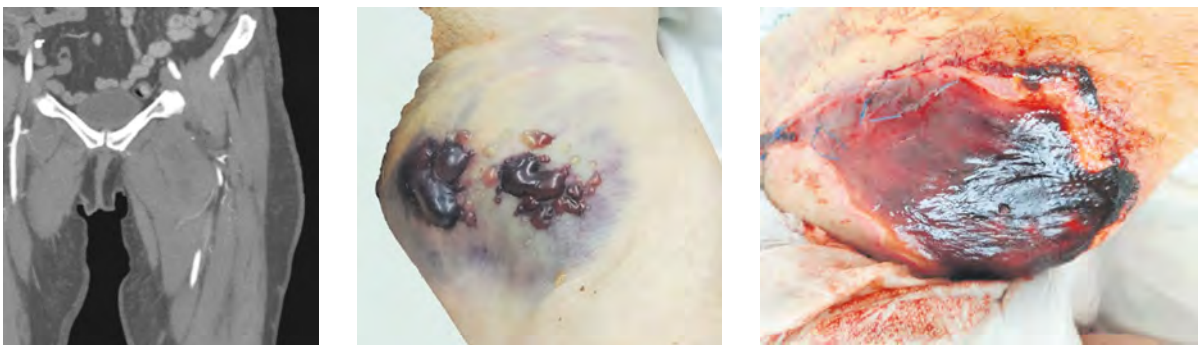


Fig. 2. Massive hematoma in the right inguinal region and thigh after percutaneous coronary intervention (author's case)



a *b* *c*

Fig. 3. Massive puncture site hematoma extending to the proximal femur; *a* — radiological image; *b* — rapid soft tissue necrosis due to hematoma pressure from the inside; *c* — clinical presentation 8 days after hematoma evacuation and revision of the puncture site (author's case)

Table 2. Recommended compression and bed rest times for transfemoral arterial access

Tool	Compression time, min	Bed rest, *h*
Catheter 4F	5	2–4
Sluice 4F Catheter 5F	10–15	6–8
Sluice 5F	15–20	6–8
Sluice 6F	>20	>8

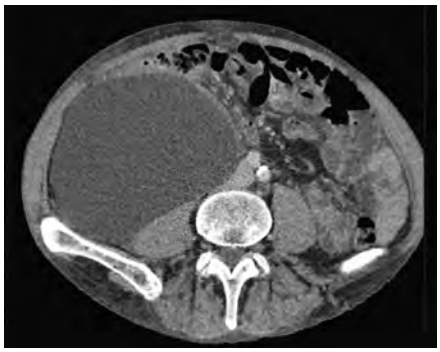


Fig. 4. Giant lymphocele (> 2.5 *L*) after evacuation of a retroperitoneal hematoma (author's case)

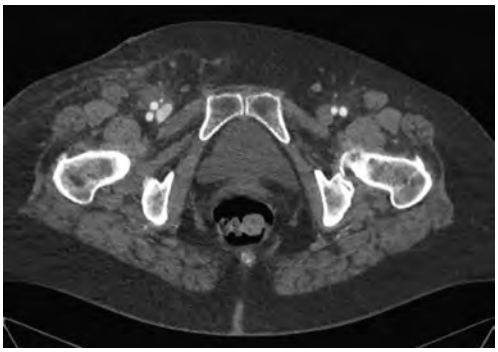


Fig. 5. Post-intervention arteriovenous fistula. The arrow indicates contrasting of the femoral vein (author's case)

When using tools larger than 6 Fr in diameter for arterial access, the use of a suturing device is recommended. In the early postoperative period, strict adherence to bed rest by the patient and control of the puncture site by the department staff are of key importance.

Retroperitoneal hematoma is a rare but serious complication. It has an incidence of 0.8%–0.44%. The occurrence of this pathology is associated primarily with suprainguinal puncture of the external iliac artery. The main danger consists in the delayed manifestation of symptoms, namely hypovolemia, pain in the ipsilateral hypogastrium, and deterioration in the general condition of the patient. Diagnosis is based on physical examination, ultrasound scan, and CT scan with contrast agent. Treatment includes an emergency revision with the imposition of a vascular suture, hematoma evacuation, and drainage in the retroperitoneal space. In some cases, interpolate implantation and blood transfusion are required. Rebleeding or lymphocele occurs in rare cases (Figure 4).

Arteriovenous fistula (0.2%–2.1%) occurs when an artery is accidentally punctured through a vein or when a vein is accidentally punctured through an artery (Figure 5). In most cases, such fistulas close spontaneously within a few weeks. Surgical treatment is indicated in case of signs of overload of the heart compartments.

To take home

- Before puncturing the radial artery, the Allen test should be performed;
- Control the tool position in the vessel lumen;
- Avoid frequent, unnecessary tool changes;
- Perform adequate hemostasis;
- When using suturing devices, follow the instructions for use;
- Perform manual compression properly;
- Encourage patients to stay in bed;
- Control the access site before discharge;
- Share the experience.

ADDITIONAL INFORMATION

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

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Review

Non-Invasive Electrophysiological Markers Associated With Long QT Syndrome

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Long QT syndrome (LQTS) is a life-threatening channelopathy, characterized by permanent or transient QT interval prolongation on the 12-lead electrocardiogram and syncope associated with malignant ventricular *rhythm disturbances, particularly polymorphic ventricular tachycardia also known as torsade de pointes*. Corrected QT (QTc) interval measurement remains the initial source of LQTS diagnosis in any patient, but the «borderline» QTc interval prolongation should induce further investigation. Genetic testing has the greatest value to provide definitive diagnosis in such situations, but it can't be applied to each patient routinely, putting aside that it can often be incomprehensive, costly or unavailable. The present review discusses the most promising non-invasive electrophysiological markers associated with Long QT syndrome, particularly in absence of visible QT interval prolongation and clinical manifestations.

Keywords: long QT syndrome, corrected QT interval, QT interval dispersion, T wave alternans; QT-RR hysteresis, QT interval variability; T-peak – T-end interval.

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Обзорная статья

Неинвазивные электрофизиологические маркеры, ассоциированные с синдромом удлиненного интервала QT

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Синдром удлиненного интервала QT (СУИ QT) — это потенциально жизнеугрожающая каналопатия, сопровождающаяся удлинением интервала QT на 12-канальной ЭКГ, синкопальными состояниями и высоким риском внезапной сердечной смерти вследствие развития полиморфной желудочковой тахикардии типа «пируэт». Удлинение интервала QT свыше 500 мс является общепринятым фактором риска и самостоятельным предиктором развития жизнеугрожающих желудочковых аритмий, однако не менее опасно и «немое», латентное течение СУИ QT, без очевидных клинических проявлений с нормальными или «пограничными» значениями продолжительности интервала QT. Генетическое тестирование имеет наибольшую ценность для постановки окончательного диагноза в таких ситуациях, но его нельзя применять у каждого пациента рутинно, не говоря уже о том, что оно часто может быть неполным, дорогостоящим или недоступным. В настоящем обзоре обсуждаются наиболее перспективные неинвазивные электрофизиологические маркеры, ассоциированные с СУИ QT, особенно при отсутствии видимого удлинения интервала QT и характерных клинических проявлений.

Ключевые слова: синдром удлиненного интервала QT; корригированный интервал QT; дисперсия интервала QT; альтернация зубца T; гистерезис QT-RR; вариабельность интервала QT, интервал T-peak – T-end.

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INTRODUCTION

Long QT syndrome (LQTS) is a life-threatening channelopathy, characterized by permanent or transient QT interval prolongation on the 12-lead electrocardiogram and syncope associated with malignant ventricular rhythm disturbances, particularly polymorphic ventricular tachycardia (PVT) also known as torsade de pointes (TdP) [1, 2]. Excessive QT interval prolongation is predisposed to arrhythmogenesis due to asynchronous repolarization of different areas of the ventricular myocardium and consequently the increase in the general length of repolarization, which induces early afterdepolarizations and spatial dispersion of refractoriness.

LQTS may be either congenital or acquired. To date more than 600 mutations of 17 different genes responsible for a hereditary form of LQTS have been identified (LQT1-17) [3], mostly being associated with the mutations in the genes coding for cardiac ion channels (sodium, potassium and calcium) and their channel interacting proteins. Acquired LQTS is associated with exposure to QT prolonging drugs, electrolyte imbalance (hypokalemia, hypocalcemia, hypomagnesemia), structural cardiac diseases (myocardial infarction, myocarditis, hypertrophic cardiomyopathy), metabolic and endocrine abnormalities or after recent conversion to sinus rhythm in patients with atrial fibrillation [4].

In its most characteristic cases, with obvious QT interval prolongation, stress-induced syncope and family history of sudden cardiac death, the diagnosis of LQTS is quite uncomplicated for cardiologists to suspect. However, in cases of borderline or intermittent QT interval prolongation and in absence of clinical manifestations, a correct diagnosis may be more difficult.

Genetic testing has the greatest value to provide definitive diagnosis in such situations, but it can't be applied to each patient routinely, putting aside that it can often be incomprehensive, costly or simply unavailable. That's why physicians have to perform more accessible additional testing, which provides in turn a great variety of electrophysiological markers, sometimes over- or on the contrary underrated.

The aim of this review was to analyze the features and limitations of the non-invasive electrophysiological markers associated with long QT syndrome and torsades de pointes.

MATERIALS AND METHODS

This review was conducted according to the PRISMA guidelines [5]. Comprehensive research was conducted on PubMed, EMBASE, Google scholar and eLIBRARY databases by using the terms «long QT syndrome», « QT interval dispersion», «T wave alternans», «QT-RR hysteresis», «QT interval variability», «T-peak – T-end interval», «torsades de pointes» and their Russian equivalents for studies published until September 1, 2021. Two authors independently screened titles and abstracts to identify relevant studies in English and Russian. Duplicates were removed. Full texts of the chosen articles were independently assessed by two authors. The search was supplemented by a screening of studies included in recent systematic reviews and meta-analyses.

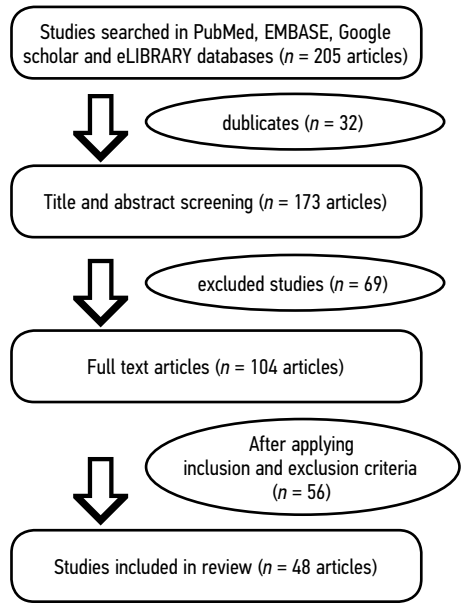


Fig. 1. Flowchart of the studies included in review following PRISMA guidelines

Inclusion criteria were: original studies, reviews and meta-analyses analyzing electrophysiological markers of long QT syndrome and/or torsades de pointes

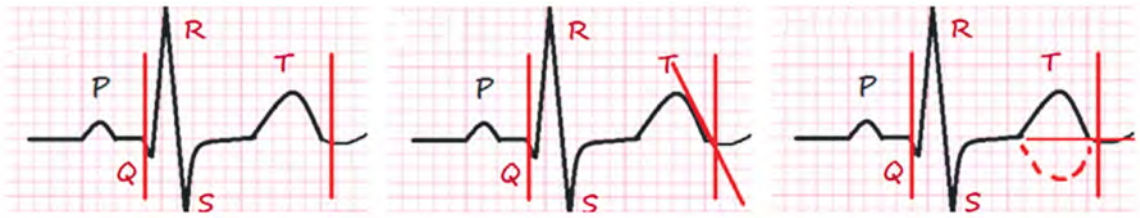
Exclusion criteria were: case reports, studies with less than 10 subjects, studies on pediatric patients, articles in language other than English and Russian (Fig. 1).

RESULTS

1. QT interval

QT interval is defined as the time from the start of the Q wave to the end of the T wave of the 12-lead ECG, which represents depolarization and subsequent repolarization of the ventricular myocardium. On the standard ECG the onset of the QRS complex is usually easily identifiable, in contrast to the end of the T wave, which is affected by its morphology, amplitude and presence of the U wave, which represents Purkinje fibers repolarization [6]. The end of the T wave can be measured manually or automatically with the help of threshold method (fig. 2, *a*), slope method (fig. 2, *b*) and their variations or novel-method proposed by A. Hunt [7]. The latter is based on the axiomatic principle that the T wave end point is the first point of intersection of the T wave with a superimposed inverted image of itself, so the T wave becomes a template which measures itself (Fig. 2, *c*).

It is a common knowledge that QT interval varies in the different leads of the same ECG. Different clinical studies have suggested measuring QT interval only in the limb leads, in all 12 leads, in the lead with the highest T wave, in the aVL lead, where the U wave is usually isoelectric, and in «quasi-orthogonal» I, aVF and V2 leads [1, 2, 4]. Differences



a *b* *c*

Fig. 2. Methods of QT interval measurement: *a* — threshold method; *b* — slope method; *c* — novel-method

in approaches lead to differences in the assessment of the normal QT interval.

According to the AHA/ACCF/HRS Guidelines for the Standardization and Interpretation of Electrocardiogram[8], the QT interval should be measured in all 12 ECG leads, and in further calculations, the lead with the longest QT interval should be used (usually it is V2 or V3 lead). If the duration of the QT interval in this lead exceeds its duration in other leads by more than 40 milliseconds, it should be considered erroneous, and it is proposed to use the QT interval duration measured in one of the standard leads.

QT interval is known to be influenced by age and gender. In young and middle-aged women it is longer than in men. During puberty QT interval in boys shortens due to the effect of testosterone which accelerates potassium flow through the fast potassium channels, while in girls its duration remains unchanged. This difference varies from 12–15 ms in young people, decreases to 6–10 ms in the older age groups and practically levels out in old age [9]. Also QT interval in men has been reported to be longer in winter than in summer, being the longest in October [10].

According to the results of the NHANES study, QT interval values increase in proportion to the age of the patients, reaching maximum values in people over 70 [11]. Since QT interval gender difference decreases in older age groups, it means that increase in QT duration with age is not parallel and seems more expressed in men. Increase in the QT interval with age can be explained by a combination of factors. Aging processes change the myocardium itself with the development of myocardial fibrosis, and also change the ratio of the influence of the sympathetic and parasympathetic nervous system, which can slow down myocardial repolarization. In addition, patients in the older age group take more drugs that can cause QT interval prolongation.

2. Corrected QT interval (QTc)

The most significantly QT interval depends on the heart rate. The first attempt to standardize the QT\RR adaptation was made in 1920 by English physiologist H. Bazett. The formula he proposed a hundred years ago ($QTc = QT/\sqrt{RR}$) is still used by medical professionals all over the world due to its simplicity and reliability. It works more precisely in the range from 60 to 100 beats per minute, but it can give erroneous results both at slower (excessive correction) and higher (insufficient correction) heart rates. A few dozens of other formulae were designed to replace Bazett's formula (among them Fridericia, Mayeda, Kawataki, Youshinaga (for children), Boudoulas, Ashman, Karialainen, Adams, Ljung (for patients with hypokalemia), Schlamowitz, Framingham, Simonson, Akhras & Rickards, Hodges, Kovach, Arrowood, Sarma, Lecocq, Rautahajru, Dmitrienko, e.c.), but none of them proved to be universally reliable [6].

For a long time, it was believed that the dependence of QT interval on the heart rate is linear and obeys the model $QT = \beta + \alpha \times RR$. However, further studies have shown that this relationship is highly individual and can be linear, power, parabolic, logarithmic, exponential or may represent any other subject-specific curvature.

Recently developed by S. Rabkin et al. age and gender-adjusted spline-formula is based on the NHANES (U. S. National Health and Nutrition Examination Survey) population study and was shown to be relatively independent of heart rate and was superior to other formulae, including some other more recently proposed. It was developed on the basis of the flexible regression spline approach which permitted modeling of almost any shape of the QT-RR relationship [6, 12].

It is also important to note that this formula can only be used in patients with sinus rhythm in the absence of left ventricular hypertrophy, intraventricular conduction disorders, ST-segment elevation myocardial infarction, and significant ST-T changes [12, 13].

However, the question remains: which duration of QTc interval can be called excessive. In the original 1985 LQTS diagnostic (Schwartz) criteria any QTc (there and further on QT interval values are calculated with the help of Bazett formula) ⩾ 440 ms was considered prolonged. In the later editions of the same criteria QTc values were ranged from 3 points for QTc ⩾ 480 ms, 2 points for QTc — 460–479 ms (both suggest intermediate probability of LQTS even without any other risk factors) to 1 points for QTc — 450–459 ms in males (low probability) [14].

According to the 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death LQTS is diagnosed in corrected QT ⩾ 480 ms in repeated 12-lead ECGs or ⩾ 460 ms in the presence of unexplained syncope [15].

2009 AHA/ACCF/HRS Recommendations for the Standardization and Interpretation of the Electrocardiogram states that a QTc ⩾ 450 ms in males and ⩾ 460 ms in females is considered prolonged [8]. Several reviews have labeled QTc values within 20 ms of these limits as borderline [16, 17] (see Table 1). But borderline QTc value is not sufficient enough for a diagnosis of LQTS or even possible LQTS.

Table 1. QT corrected (Bazett) interval values stratification

Group	Normal QT, ms	Borderline QT, ms	Prolonged QT, ms
Males	< 430	430–450	> 450
Females	< 450	450–460	> 460
Children ⩽ 15 years and newborns	< 440	440–460	> 460

In the study by DJ Tester et al., 27% of patients with a known LQTS genetic defect had a QTc interval less than 440 ms [18]. On the other hand, the data derived from 79.743 ambulatory subjects has shown that the 99th percentile of QTc distribution is 470 ms for males and 480 ms for females, which means that approximately 10% to 15% of all people have QTc values ⩾ 440 ms and don't have LQTS [19]. That's why if physicians rely only on QTc value, without any additional markers, it may result in premature and incorrect diagnosis.

3. QT interval dispersion

QT interval dispersion (QTd) is measured as the difference between the maximal and minimal QT intervals within a 12-lead ECG. Its measurement is based on the assumption that each ECG lead measures regional repolarization, and consequently dispersion serves as a marker of spatial dispersion of ventricular recovery time. C.P. Day et al. put forward the hypothesis that the risk of life-threatening arrhythmias is directly proportional to the increase in the QTd and not to the prolongation of QT interval itself [6, 20].

Later, it was shown that QT dispersion does not directly reflect the dispersion of recovery time and that it results mainly from variations in the T wave morphology and the errors of QT interval measurement [6]. Moreover, surface ECG is able to estimate only the end of the repolarization, while its onset remains undetected (it is known to be situated near the T wave peak), which makes these data insufficient for correct estimation of the repolarization phase.

Reported normal values of QT interval dispersion vary from 10 to 71 ms, with only significantly high values (more than 100 ms) [21], potentially having practical predicative value in genesis of ventricular arrhythmias. Increase in QT dispersion has been associated with risk of sudden cardiac death in patients with ischemic heart disease [22], diabetes mellitus [23] and peripheral vascular disease [24]. However, the prognostic value of QTd remains controversial in patients after myocardial infarction [25] and in patients with congestive heart failure [26]. In patients with LQTS increased QTd is reported to be associated with high susceptibility to ventricular arrhythmias, and also predicts efficacy of antiadrenergic therapy [27].

4. QT-RR hysteresis

In recent years it has been found that the QT interval duration does not depend solely on the duration of the preceding RR interval or on a small number of preceding RR intervals, but is influenced by a long history of preceding heart rate. This phenomenon has been called QT-RR hysteresis and its increase considered a potential biomarker of arrhythmic risk. It is characterized by longer QT intervals at a given RR interval while heart rates are increasing during exercise and shorter QT intervals at the same RR interval while heart rates are decreasing during recovery. It is calculated as the QT interval difference between exercise and 1 to 2 minutes into recovery at heart rates of approximately 100 b.p.m.

The mechanism of QT-RR hysteresis has been attributed to a lagging QT response to different directional changes in RR interval during exercise and recovery, however later in the studies by D.J. Pelchovitz et al. it has been found that changes in the QT interval duration exercise and recovery are predominantly mediated by autonomic nervous system [28]. The study by A.D. Krahn has shown that increased QT-RR hysteresis is highly specific for LQTS (46 +/-19 ms in not genotyped LQTS patients vs 19 +/- 11 ms in healthy controls 1 minute into recovery) [29]. These observations were confirmed and expanded by J.A. Wong et al., who performed provocative testing of patients with suspected LQTS that consisted of a modified Bruce protocol treadmill exercise test. According to this study, increased QT-RR hysteresis was identified in LQT2 patients only, and not in LQT1 or LQT-negative patients (average 15ms in LQT1 phenotype vs 40 ms in LQT2) [30]. Beta-blockers were reported to reduce QT-RR hysteresis in both subtypes [30-32].

5. Short-term QT interval variability (ST-QTV)

QT interval variability is a measure of the spontaneous fluctuations in the duration of the QT interval during the 24/48 h ambulatory ECG monitoring. In resting conditions QTV results mainly from heart rate variability (HRV) and is dependent on individual-specific QT-RR curvatures. Variation in QT duration at a constant RR interval is caused by beat-to-beat variability of the overall ventricular repolarization, which has been acknowledged as arrhythmic risk marker. Increased short-term QTV has been associated with sudden death in animal experiments and multiple clinical situations, including coronary artery disease, myocardial infarction, ischemic and non-ischemic cardiomyopathy [35]. The QT Variability Index (QTVI) is ratio of normalized QT variability to normalized heart rate variability, and therefore includes an assessment of autonomic nervous system tone. QTVI is defined as $\log10\ [(QTv/QTm^2)/(RRv/RRm^2)]$, where QTv represents the QT interval variance, QTm is the mean QT interval, RRv is the RR interval variance, and RRm is the mean RR interval [6].

Increased ST-QTV has been reported in LQTS patients with different genetic mutations. Groups that included LQTS2 and LQTS3 mutation carriers showed also increased QTVI [33]. In LQTS1 patients ST-QTV changes seem less pronounced and there is no increase in QTVI was found. Moreover, increases in QTV in LQT1 may be seen only after sympathetic stimulation [34]. In patients with drug-induced LQTS, documented TdP was associated with increased QTV in the absence of QT prolongation [35, 36]. ST-QTV was already elevated before drug-administration in these patients, identifying the diminished repolarization reserve, even in absence of visible QT interval prolongation, which proves its ability to unmask latent QT prolongation.

6. T wave morphology

Presence of an abnormal T wave morphology is one of the important ECG features of LQTS. Later investigations of T wave changes were mainly focused on its duration, amplitude and symmetry. Each subtype of congenital LQTS is known to have its own characteristic features. LQT1 patients usually have tall early-onset and broad-based T waves. LQT2 genotype is linked with low amplitude, often bifid, asymmetric or notched T-waves. LQT3 patients tend to have long ST-segment and late narrow and peaked T waves [37]. But these T wave features are often subtle and can be overlooked by a non-expert in the field of channelopathies (Fig. 3).

Novel software-based means of the T wave analysis allow quantitative evaluation of such morphological features as flatness, asymmetry, and notching with the help of principal component analysis. Morphology combination score (MCS) proposed by A. Porta-Sanchez et al. can be calculated automatically from these measures using the equation: MCS = 1.6 × flatness + asymmetry + notch score [38]. The study has shown that MCS was significantly higher in LQTS patients compared with control subjects and in LQTS2 patients compared with LQTS1 patients. Moreover, it also was increased in patients with LQTS and normal QT duration compared with controls, which makes T-wave analysis quite valuable in borderline phenotypes.

7. T-wave alternans

Both congenital and acquired LQTS are associated with T-wave alternans (TWA) — beat-to-beat variations in the amplitude, morphology and polarity of the T waves with each subsequent contraction that reflect the spatiotemporal heterogeneity of ventricular repolarization. In experiments TWA usually occurs at very fast heart rates (200–300 bpm) due to steep slope of action potential duration restitution at short diastolic intervals [39]. But if the repolarization reserve is initially reduced (as it happens in LQTS) TWA manifests at normal heart rates and is often potentiated by bradycardia in presence of early afterdepolarizations.

When the fluctuations in the amplitude of the T-wave are large enough that they can be recorded on a surface electrocardiogram, it is called macrovolt T-wave alternans the important but uncommon marker of arrhythmic susceptibility and precursor of sudden cardiac death. Microvolt TWA are more common, but not visible to the naked eye [37]. They can be detected only on subtle levels with the computerized techniques of Spectral and Modified Moving Average methods. Microvolt TWA has been described in patients with congestive heart failure [38], hypertrophic cardiomyopathy [41] and LQTS [42]. In a study by Takasugi et al. it was found that microvolt TWA has high sensitivity but comparatively low specificity for LQTS and is strongly associated with TdP history [42].

8. T-peak – T-end interval

Tpeak–Tend (Tp-e) interval seems to be another promising marker of arrhythmic risk, which has been reported as an index of transmural dispersion of repolarization. It is defined as the time difference between the peak and the end of the T-wave, and in case of negative or biphasic ones it could be measured on the interval from the nadir to the end of the T-wave. The increased duration of the Tp-e interval may reflect the period when the epicardium is completely repolarized, but the subendocardial layer (M-cells) is still recovering. It forms an electrical substrate for subsequent depolarization, leading to ventricular arrhythmias. The Tp-e to QT interval ratio (Tpe/QT ratio) is less heart rate dependent than Tp-e itself, because it remains constant despite dynamic changes in heart rate.

According to recent studies, an increase in the Tpeak-Tend duration also increases the risk of life-threatening arrhythmias and, consequently, sudden cardiac death, in patients with Brugada syndrome [43, 44], hypertrophic cardiomyopathy [45] and slow coronary flow [46].

There has been reported an association of prolonged Tp-e interval with a high risk for developing TdP in patients with both acquired and congenital long QT syndromes [47].

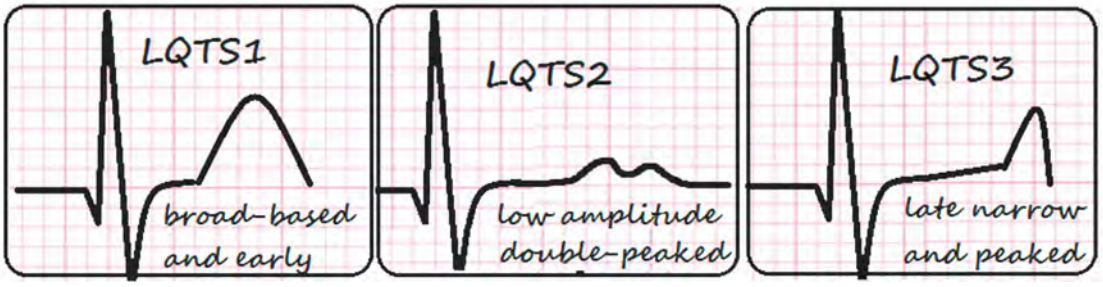


Fig. 3. T-wave morphology in different sybtypes of congenital LQTS

Tp-e interval can also be prolonged in patients with a history of drug-related TdP and serve as a marker of drug-induced abnormal repolarization [48].

But a number of studies showed that the duration of the QT interval and Tp-e are closely related, and prolongation of Tp-e seems a fraction of total QT-interval prolongation [47, 49]. So, Tp-e interval cannot be used to distinguish symptomatic patients with LQTS from asymptomatic and can be used only as additional repolarization marker.

CONCLUSIONS

QTc interval measurement remains the initial source of LQTS diagnosis, but the «borderline» QTc interval duration should be the key to further electrophysiological investigation. Moreover, the formula used to calculate the corrected QT interval should take into account the individual nature of the relationship between the size of the QT interval and heart rate and should be adapted to the gender and age of the patients. At present, the spline QTc formula seems the most suitable for these criteria, but Bazett formula is traditionally used in all international guidelines and scores.

QT interval dispersion doesn't seem an accurate indicator of spatial heterogeneity of ventricular repolarization and cannot be used to quantify its degree, but can be applied to determine the QT interval variability index. Tpeak-Tend interval cannot be applied to distinguish symptomatic patients with LQTS from asymptomatic and can be used only as additional repolarization marker. Nowadays, QT-RR hysteresis and short-term QT interval variability are the most promising electrophysiological markers even in absence of visible QT interval prolongation, which proves their ability to unmask latent QT interval prolongation.

ADDITIONAL INFORMATION

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Research article

Factors of Cardiovascular Risk in Drivers of Locomotive Crews of Railway Transport with Ventricular Arrhythmias

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AIM: This study aimed to assess cardiovascular risk factors in drivers and assistant drivers of railway engine crews with ventricular rhythm disorders.

MATERIALS AND METHODS: The study included 120 patients aged 39 to 61 years (mean age M ± SD: 50.4 ± 4 years), who were distributed into two groups with and without ventricular rhythm disorders. All participants underwent 12-lead daily ECG monitoring with assessment of noninvasive markers of myocardial electrical instability (circadian profile, QT interval, late ventricular potentials, T-wave alternation, rhythm variability). Traditional factors of cardiovascular risk, the employment period in the profession, and the level of personal and situational anxiety on Spielberger's state-trait anxiety inventory (STAI) were evaluated.

RESULTS: In Group 1, in comparison with Group 2, significant differences were revealed in the duration of the PQ interval (during the day and at night) and the indicators of late ventricular potentials (RMS 40 and TotQRSF). When analyzing risk factors, elevated indices of total blood cholesterol were registered in both groups, and the risk on the SCORE scale was at a moderate level. In the group of workers with ventricular rhythm disorders, higher indicators of total blood cholesterol and the frequency of smoking and alcohol consumption were established. In individuals with ventricular rhythm disorders, a significant relationship was detected between the number of registered single monomorphic ventricular extrasystoles and the age of the employee ($r = -0.3$, $p < 0.05$), and blood pressure level ($r = 0.3$, $p < 0.05$), and the relationship between the level of anxiety and the registration of single supraventricular extrasystoles was established ($r = -0.3$, $p < 0.05$). In the Group 2, a significant correlation was revealed between the number of registered single supraventricular extrasystoles and age ($r = 0.2$, $p < 0.05$), the employment period in the profession of a driver ($r = 0.2$, $p < 0.05$), the blood pressure level ($r = 0.2$, $p < 0.05$), and the level of anxiety on the STAI ($r = 0.3$, $p < 0.05$).

CONCLUSIONS: Drivers of railway engine crews with ventricular rhythm disorders are characterized by a higher level of total blood cholesterol and a higher frequency of smoking and alcohol consumption. They have significant changes in the duration of the PQ interval (during the day and at night) and indicators of late ventricular potentials (RMS 40 and TotQRSF) according to Holter monitoring. The relationship of the number of ventricular rhythm disorders with age and the office values of systolic and diastolic blood pressure is noted in drivers of engine crews of railway transport.

Keywords: risk factors for cardiovascular disease; ventricular rhythm disorders; Holter monitoring; ventricular late potentials; workers of engine crews.

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Научная статья

Факторы сердечно-сосудистого риска у работников локомотивных бригад железнодорожного транспорта с желудочковыми нарушениями ритма

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Цель исследования: оценить факторы сердечно-сосудистого риска у машинистов и помощников машинистов локомотивных бригад железнодорожного транспорта с желудочковыми нарушениями ритма.

Материалы и методы. В исследование включено 120 пациентов в возрасте от 39 до 61 года (средний возраст M ± SD: 50,4 ± 4 года), которые были разделены на две группы с желудочковыми нарушениями ритма и без желудочковых нарушений ритма. Всем исследуемым было выполнено 12-канальное суточное мониторирование ЭКГ с оценкой неинвазивных маркеров электрической нестабильности миокарда (циркадный профиль, интервал QT, поздние потенциалы желудочков, альтернация волны Т, вариабельность ритма). Оценивались традиционные факторы сердечно-сосудистого риска, а также стаж работы в профессии и уровень личностной и ситуационной тревожности по шкале Спилберга-Ханина.

Результаты. В первой группе, по сравнению со второй, выявлены значимые различия по длительности интервала PQ (в дневное и ночное время) и по показателям поздних потенциалов желудочков (RMS 40 и TotQRSF) . При анализе факторов риска в двух группах встречались повышенные значения уровня общего холестерина крови, риск по шкале SCORE находился на уровне умеренного. В группе работников с желудочковыми нарушениями ритма установлены более высокие показатели общего холестерина крови, частоты курения и употребления алкоголя. У лиц с желудочковыми нарушениями ритма выявлена значимая связь между количеством зарегистрированных одиночных мономорфных желудочковых экстрсистол с возрастом работника ($r = –0,3$, $p < 0,05$), и уровнем артериального давления ($r = 0,3$, $p < 0,05$), установлена связь уровня тревоги и регистрации одиночных суправентрикулярных экстрасистол ($r = –0,3$, $p < 0,05$). Во второй группе выявлена значимая корреляционная связь между количеством зарегистрированных одиночных суправентрикулярных экстрасистол с возрастом ($r = 0,2$, $p < 0,05$), и стажем труда в профессии машиниста ($r = 0,2$, $p < 0,05$), уровнем АД ($r = 0,2$, $p < 0,05$), и уровнем тревоги по шкале Спилберга-Ханина ($r = 0,3$, $p < 0,05$).

Выводы. Машинисты локомотивных бригад железнодорожного транспорта с желудочковыми нарушениями ритма характеризуются более высоким уровнем общего холестерина крови и более высокой частотой курения и употребления алкоголя. У них отмечаются значимые изменения длительности интервала PQ (в дневное и ночное время) и показателей поздних потенциалов желудочков (RMS 40 и TotQRSF) по данным Холтеровского мониторирования. У машинистов локомотивных бригад железнодорожного транспорта имеется связь количества желудочковых нарушений ритма с возрастом и офисными значениями систолического и диастолического АД.

Ключевые слова: факторы сердечно-сосудистого риска; желудочковые нарушения ритма; Холтеровское мониторирование; поздние потенциалы желудочков; работники локомотивных бригад.

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ЭКО•ВЕКТОР

One of the most urgent problems of modern medicine is the high mortality rate due to cardiovascular diseases (CVD). Due to their high prevalence, mortality from the pathology, and early disability, the medical and social significance of these diseases is very high. The mortality rate due to this CVD reaches 1462 cases per 100,000 population [1]. In most cases, the mechanisms underlying the development of sudden cardiac death (SCD) are ventricular tachycardia (VT) and ventricular fibrillation (VF) [1, 2].

Being an engine crew (EC) driver of railway transport (RT) is one of the professions of high social importance [3]. Issues related to train traffic safety are among the top priorities in RT [4]. However, all design, organizational, regime, and operational measures cannot ensure complete traffic safety, since among other things, it depends on the "reliability" of the human link in the control system [5]. The results of the analysis of the causes of sudden death among drivers and assistant drivers of the EC revealed that death was due to CVD in 80.6% of cases [6]. Due to a combination of negative stress factors, the dietary pattern and physical activity are disturbed, which increases the risk of the circulatory system diseases (CSD) [7, 8]. It is known that out of the total number of deaths that occurred in relation to traffic safety, the proportion of sudden arrhythmias was 2.1%. In addition, according to the literature, ventricular rhythm disorders were recorded in half of the drivers aged 40–49 years [6]. The above data indicate the expediency of investigating cardiovascular risk factors in RT workers, the prevalence and nature of recorded rhythm disorders, as well as noninvasive markers of myocardial electrical instability, as precursors of adverse, including fatal, outcomes.

Aim: The study aimed to evaluate cardiovascular risk factors in RT EC drivers and assistant drivers with ventricular rhythm disorder (VRD).

MATERIALS AND METHODS

The study included 120 male patients aged 39–61 years (mean age M ± SD: 50.4 ± 4 years). The average age of patients was 50 ± 4.2 years in Group 1 and 50.4 ± 3.8 years in Group 2. The patients were distributed into two groups according to the effect of heart rhythm disturbances (HRD) on life prognosis and labor prognosis. Group 1 consisted of patients with all types of HRD, including VRD (single and paired, polymorphic and monomorphic, runs of unstable VT), while Group 2 consisted of EC workers without VRD.

Group 1 consisted of 43 engine drivers and their assistants, which accounted for 36% of the total study population, while Group 2 consisted of 77 EC workers, which accounted for 64% of the study participants.

All employees were examined with regard to the annual commission to determine occupational aptitude. According to the medical documentation, 18 (41%) EC workers with a previously established diagnosis of arterial hypertension (AH) were identified in Group 1, and 45 (58%) patients with AH were identified in Group 2. According to the survey, the participants did not constantly take antihypertensive drugs. ACE inhibitors and beta-blockers were taken symptomatically before the pre-trip medical check-up.

The inclusion criteria for the study were men over 18 years old, RT EC employees (drivers and assistant drivers), and signed an informed consent to participate in the study.

Exclusion criteria were refusal to participate in the study, ischemic heart disease, chronic heart failure, congenital and acquired heart defects, decompensated diabetes mellitus, active inflammatory diseases, mental illness, and oncological diseases.

The study was approved by the local ethics committee.

In accordance with the National Russian recommendations for the use of the 24-h ECG monitoring (24-h ECGM) technique in clinical practice [9], a 12-lead 24-h ECGM was performed using Incart devices in the Result-2 program, with an analysis of traditional indicators, including daytime and nighttime heart rate (HR), average HR per day, circadian index (CI, the ratio of average daytime to average nighttime HR), HRD (presence and number of supraventricular and ventricular extrasystoles and tachycardias), conduction (presence of atrioventricular and sino-atrial blocks), PQ intervals (interval duration during the day and at night), QT intervals (assessment of the value of the corrected QT interval and QT interval dispersion), and parameters of myocardial repolarization (assessment of ST-segment and T-wave displacement). In addition, indicators of heart rate variability were analyzed. Moreover, the presence of T-wave alternation and indicators of late ventricular potentials (LVP) were assessed (TotQRSF as the duration of the filtered QRS complex after averaging, RMS40 as the root mean square value of the tension in the last 40 ms of the QRS complex (RMS40), LAS40 as the low-amplitude signal duration, and below 40 μV).

Risk factors (RF) were studied, such as age, employment period in the EC driver profession, smoking and the degree of nicotine addiction according to the Fagerström test, the frequency and amount of alcohol consumed. The level of personal and situational anxiety on the Spielberger's state-trait anxiety inventory (STAI) was assessed, and the body mass index (BMI), impaired tolerance (IT) to carbohydrates, level of total blood cholesterol, degree of AH, risk on the SCORE scale, and results of bicycle ergometry (BEM) were evaluated.

Statistical analysis of the data was performed using the Statistica 10.0 program. The differences between the groups was assessed using the Mann–Whitney test, the significance level was considered as $p < 0.05$. Continuous variables were presented as mean and standard deviation, and qualitative variables were expressed as absolute number and percentage. The correlations between pairs of quantitative variables were assessed using the non-parametric Spearman coefficient, and the significance level was considered as $p < 0.05$.

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RESULTS AND DISCUSSION

Rhythm disorders in the studied groups were presented as shown in Table 1.

There was no significant difference in the occurrence of supraventricular rhythm disorders between the groups. In both groups, single SVES were recorded in all subjects. In addition, in both groups, patients with paired and group SVES, as well as episodes of unstable SVT were identified. According to studies, supraventricular rhythm disorders in the population were recorded at a frequency of 20%–50%. The increase in the incidence of supraventricular extrasystole in RT EC workers is due to a shift work schedule and the frequent night shifts, which provokes an increase in sympathetic influences and a decrease in parasympathetic control over the heart rhythm. In patients with AH, an insufficient decrease in BP at night, associated with a specific work schedule, also induces supraventricular rhythm disorders [10].

In Group 1, compared with Group 2, significant differences were revealed in the duration of the PQ interval (during the day and at night) and in terms of LVP (RMS 40 and TotQRSF).

Table 2 presents the differences in the studied parameters according to the 24-h ECGM data between the two groups.

The RT EC workers in Group 1 had ventricular rhythm disorders of high grades according to the Rayn classification, which may indicate a myocardial restructuring and the appearance of an arrhythmogenic substrate. The short episodes of ventricular tachycardia in patients represent an unfavorable factor associated with a significant risk of SCD [11]. In addition, in Group 1, this also can be evidenced by changes in the LVP parameters,

Table 1. Rhythm disorders in RT EC workers.

Cardiac rhythm disorders	Group 1 (*n* = 43)	Group 2 (*n* = 77)
Single SVES, *n* (%)	43(100)	77(100)
Single SVES, *n* (%)	16(37)	28(36)
Group SVES, *n* (%)	11(25)	14(18)
SVT, *n* (%)	4(10)	5(6)
Single monomorphic VES, *n* (%)	15(34)	-
Single polymorphic VES, *n* (%)	26(60)	-
Paired monomorphic VES, *n* (%)	3(7)	-
Paired polymorphic VES, *n* (%)	4(8)	-
MVT, *n* (%)	2(3)	-

Note: SVES — single supraventricular extrasystoles, SVT — supraventricular tachycardia, VES — ventricular extrasystoles, MVT — monomorphic ventricular tachycardia.

Table 2. Indicators of 24-h ECGM among RT EC workers.

Indicator	Group 1 (*n* = 43)	Group 2 (*n* = 77)
HR during the day, beats/min	75 ± 8	75 ± 8
HR at night, beats/min	62 ± 7	61 ± 7
CI, c.u.	1.21 ± 0.1	1.2 ± 0.1
Corrected QT, ms	404.6 ± 13	406 ± 16
QT dispersion, ms	14 ± 8	14 ± 9
PQ day, ms	162.3 ± 26*	170 ± 24
PQ night, ms	173 ± 30*	180 ± 26
TotQRSFcp, ms	93.4 ± 11.8*	87 ± 5
RMS 40 max uV	55.9 ± 39*	115 ± 48
T-wave alternation, people (%)	32 (74)	55(71)

Note: *$p < 0.05$; HR — heart rate; CI — circadian index; TotQRSF, RMS 40 — indicators of the ventricular late potentials.

Table 3. Parameters of cardiovascular risk in RT EC workers.

Parameter	Group 1 (*n* = 43)	Group 2 (*n* = 77)
BP, *n* (%)	20(46)	42(54)
SCORE, %	2.6 ± 1.7	2.2 ± 1.1
Level of total cholesterol, mmol/l	5.4 ± 1*	5.1 ± 0.8
SBP, mmHg	125 ± 8	123 ± 8
DBP, mmHg	80 ± 5	78 ± 6
Employment period, years	26 ± 9	25 ± 9
Level of anxiety, points	11.6 ± 7	13 ± 6
Smoking, n (%)	30 (70)	35 (45)
Pack/years index, c.u.	15 ± 12*	9 ± 12
Level of nicotine addiction, points	2.4 ± 2.2*	1.5 ± 2
Alcohol consumption, *n* (%)	42 (97)	63 (81)
Level of alcohol consumption, points	3.9 ± 2*	2.8 ± 2
Glucose IT, *n* (%)	8 (19)	12 (16)
BMI, kg/m^2	28 ± 4*	27.3 ± 4
Age, years	20(46)	42(54)

Note: *p < 0.05; SBP — systolic blood pressure; DBP — diastolic blood pressure; IT — impaired tolerance; BMI — body mass index.

as a noninvasive criterion for possible arrhythmogenic processes and confirmation of a more heterogeneous process of ventricular myocardial repolarization [12]. The PQ interval in both groups was within the normal range; however, in the group of EC workers with VRD, the PQ interval revealed was significantly shorter than in the group of workers without VRD. This phenomenon is probably because the atrioventricular (AV) node receives innervation from the sympathetic and parasympathetic nervous systems and is sensitive to circulating catecholamines. Sympathetic stimulation, in turn, shortens AV conduction, while parasympathetic stimulation leads to the opposite effects [13].

All the patients examined had a negative BEM test. Rhythm disorders were not recorded during the exercise.

RT EC workers are characterized by the presence of traditional cardiovascular risk factors (Table 3). Analysis of RF in both groups was performed by reviewing the medical records (the presence of AH, calculation of the 10-year risk of death on the SCORE scale, total blood cholesterol, working BP level, employment period and age, anxiety level, presence of bad habits such as smoking and alcohol consumption, BMI, and presence of IT to glucose). The analysis of RF in both groups revealed elevated levels of total blood cholesterol, and the risk according to the SCORE scale was at the moderate level. In the group of EC workers with VDR, most of subjects surveyed smoked and drank alcohol. Significant differences between the two groups were revealed in terms of total blood cholesterol, the frequency of smoking as determined by the pack/year index and the Fagerström Test for Nicotine Dependence, and the degree of alcohol consumption calculated using the AUDIT scale. Significantly higher rates of total blood cholesterol, frequency of smoking and alcohol consumption, and degree of nicotine dependence were revealed in the group of railway workers with VRD. Identification of these RFs can exacerbate the course of VRD and accelerate the development of fatal complications [14].

A correlation analysis revealed a significant relationship between the number of registered single monomorphic VESs and the age of the EC workers in Group 1 (r = –0.3, p < 0.05), as well as SBP (r = 0.3, p < 0.05) and DBP (r = 0.3, p < 0.05). In addition, a relationship was revealed between the level of anxiety on the Spielberger's STAI and the occurrence of single SVES (r = –0.3; p < 0.05).

In Group 2, a significant correlation was revealed between the number of registered single SVES and age (r = 0.2; p < 0.05), employment period in the profession of an RT EC driver (r = 0.2; p < 0.05), BP level (r = 0.2; p < 0.05), and anxiety level according to the Spielberger's STAI (r = 0.3; p < 0.05).

The study revealed a high prevalence of rhythm disorders and CVD RF, mainly related to the lifestyle and working conditions of the profession of an EC driver. The data obtained may be of practical value in preventive interventions for EC workers.

CONCLUSIONS

1. Drivers of RT engine crews with ventricular rhythm disorders are characterized by a higher level of total blood cholesterol, and a higher frequency of smoking and alcohol consumption.

2. The number of ventricular rhythm disorders is associated with age and office values of systolic and diastolic BP among drivers of RT engine crews, while the number of supraventricular extrasystoles is associated not only with age and BP level, but also with employment period in the profession and the level of anxiety.

3. Drivers of railway engine crews with ventricular rhythm disorders have significant changes in the duration of the PQ interval (during the day and at night) and indicators of LVP (RMS 40 and TotQRSF) according to Holter monitoring, which may be significant when examining this cohort.

ADDITIONAL INFORMATION

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Research article

Disease-Modifying Therapy of Chronic Heart Failure on the Background of Heart Rhythm and Conductivity Disorders (Clinical Case)

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The article presents a clinical case of the development and progression of chronic heart failure (CHF) in a patient with postinfarction cardiosclerosis after implantation of a permanent pacemaker due to binodal dysfunction. The progression of CHF was exacerbated by the patient's transition to a permanent form of atrial fibrillation. Complex therapy for CHF, including cardiac resynchronization therapy, drug therapy with valsartan + sacubitril, empagliflozin, eplerenone, metoprolol succinate (quadrotherapy) led to a complete recovery of the ejection fraction (EF) of the left ventricle. After the patient stopped taking one of the components of quadrotherapy (valsartan + sacubitril), there was a tendency to decrease in EF. The clinical case emphasizes the importance of the timely transformation of traditional permanent pacing into cardiac resynchronization therapy and the appointment of complex modern drug therapy for CHF. When an improvement or restoration of EF is achieved, it is advisable to continue the therapy against which the improvement was obtained in order to avoid the negative consequences that are possible when the components of the quadrotherapy are cancelled.

Keywords: schronic heart failure; atrial fibrillation; permanent pacing; cardiac resynchronization therapy; valsartan + sacubitril; rivaroxaban.

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Научная статья

Болезнь-модифицирующая терапия при хронической сердечной недостаточности на фоне нарушений ритма сердца и проводимости (клинический случай)

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В статье представлен клинический случай развития и прогрессирования хронической сердечной недостаточности (ХСН) у пациента с постинфарктным кардиосклерозом после имплантации постоянного электрокардиостимулятора по поводу бинодальной слабости. Переход пациента на постоянную форму фибрилляции предсердий усугубил прогрессирование ХСН. Комплексная терапия ХСН, включающая сердечную ресинхронизирующую терапию, медикаментозную терапию валсартаном+сакубитрил, эмпаглифлозином, эплереноном, метопролола сукцинатом (квадротерапия) привела к полному восстановлению фракции выброса (ФВ) левого желудочка. После прекращения пациентом приема одного из компонентов квадротерапии (валсартана+сакубитрил) наметилась тенденция к снижению ФВ. Клинический случай подчеркивает важность своевременного преобразования традиционной постоянной электрокардиостимуляции в сердечную ресинхронизирующую терапию и назначения комплексной современной медикаментозной терапии ХСН. При достижении улучшения или восстановлении ФВ целесообразно продолжить терапию, на фоне которой получено улучшение, чтобы избежать негативных последствий, возможных при отмене

Ключевые слова: хроническая сердечная недостаточность; фибрилляция предсердий; постоянная электрокардиостимуляция; сердечная ресинхронизирующая терапия; валсартан+сакубитрил; ривароксабан.

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ЭКО•ВЕКТОР

INTRODUCTION

The incidence of chronic heart failure (CHF) in European countries reaches 1–2% in the adult population [1]. In Russia, according to epidemiological studies, the prevalence of CHF in the general population is 7% [2]. CHF is a syndrome resulting from many diseases and conditions accompanied by myocardial damage. One of the most common causes of CHF is coronary heart disease, primarily myocardial damage during acute myocardial infarction. Cardiac arrhythmias and conduction disturbances can also contribute to the development of CHF. Atrial fibrillation (AF), especially its permanent form, is associated with the onset and progression of CHF. Violation of the physiological sequence of electrical activation of the left ventricle (LV) myocardium against the background of a complete blockade of the left branch of the bundle of His or against the background of constant pacing of the apex of the right ventricle (RV) can lead to CHF. When CHF symptoms appear and LV EF decreases against the background of traditional permament RV apical pacing, the implanted device should be upgraded to a resynchronizing device in a timely manner [1, 2].

Among the causes of CHF that are not related to cardiovascular diseases, type 2 diabetes mellitus occupies a special place. First of all, against the background of type 2 diabetes mellitus, coronary artery disease (CAD) develops and progresses. In addition, diabetes mellitus, even in the absence of CAD, can be complicated by diabetic cardiomyopathy, leading not only to CHF with preserved EF, but also to CHF with low EF [2, 3].

Modern complex drug therapy for CHF with reduced EF stops the processes of negative heart remodeling, favorably affects the prognosis, leads to an increase and even normalization of EF [4].

CLINICAL CASE

Patient S., 68, came to the clinic due to the deterioration of exercise tolerance, the appearance of shortness of breath. At the age of 51 (2001) he suffered a myocardial infarction in the basin of the anterior interventricular artery. During hospitalization for myocardial infarction, type 2 diabetes mellitus was diagnosed. Myocardial infarction led to an asymptomatic decrease in LV EF to 42%. A year after myocardial infarction, coronary bypass grafting was performed due to multivessel coronary disease and the presence of asymptomatic LV dysfunction: mammary bypass to the anterior interventricular artery, autoarterial coronary bypass grafting (grafts from the radial artery to the 1st and 2nd diagonal arteries). The patient regularly took ramipril, metoprolol succinate, atorvastatin, acetylsalicylic acid, glimepiride. Against the background of the therapy, indicators of the components of the lipid spectrum and glycemia were achieved the target level. After complete revascularization against the background of optimal, relevant for that time, therapy, EF returned to normal and reached 59% according to Echocardiography (ECHOCG) data from 2009 (Table 1). The patient felt good before 2010. In 2010, at the age of 60, there were arrhythmia. 22.574 monomorphic ventricular extrasystoles per day,

Table 1. Dynamics of echocardiographic parameters

Year	EF (%)	End-diastolic volume index EDVI (ml/m^2)	Left atrial volume index LAVI (ml/m^2)	Mitral regurgitation
2001 (Acute Myocardial Infarction)	42	No data	No data	Absent
2002 year – complete revascularization + optimal medication				
2009	59	No data	No data	Absent
2010	58	No data	No data	Absent
2012 year – permanent conventional pacing due to binodal dysfunction 2013 year – permanent form of AF				
2017	49	86	40	1st degree
2018	47	81	49	1st degree
2019 August	33	85	No data	2nd degree
2019 September	25	97	54	3rd degree
Therapy with valsartan + sacubitril, empagliflozin in addition to β-adrenergic blocker and AMPR was started, CRT-D implantation				
2020 September	60	54	No data	Absent
2021 – stopped taking valsartan + sacubitril				
2021 December	40	73	No data	1st degree

Note: AF — atrial fibrillation; AMR — mineralocorticoid receptor antagonist; CRT-D — cardiac resynchronization therapy- defibrillator; EF — ejection fraction

37 episodes of non-sustained ventricular tachycardia were registered during 24-hour ECG monitoring (Fig. 1).

Coronary angiografy was performed to rule out coronary shuntes stenosis as the cause of ventricular arrhythmias: the shuntes were patent, and no hemodynamically significant stenoses were detected outside the bypass areas of the coronary arteries. An echocardiographic (ECHO) examination revealed cicatricial changes in the myocardium of the left ventricle (LV), with a lesion area of 31% and a local contractility index of 1.6, LV diastolic dysfunction, dilatation of the left atrium (LA), LV EF 58%. Due to the lack of indications for implantation of a cardioverter-defibrillator, a catheter procedure was performed for ventricular arrhythmias. A year later, in 2011, the patient developed paroxysmal AF against the background of binodal dysfunction that had developed by that time. Instead of acetylsalicylic acid, anticoagulant therapy was prescribed (warfarin under the control of INR with a transition to rivaroxaban 20 mg per day). Due to binodal dysfunction, complicated not only by AF, but also by syncope, in 2012 a permanent dual-chamber pacemaker (PM) was implanted. During 24-hour ECG monitoring after PM implantation it was observed an alternation of A-V sequential pacing with ventricular pacing after atrial tracking, a decrease in the number of ventricular extrasystoles to 100 per day (as compared to the year 2010), episodes of unstable ventricular tachycardia to two per day (Fig. 2). As expected, the catheter procedure for ventricular arrhythmias associated with postinfarction cardiosclerosis gave a "cosmetic effect", reducing, but not completely eliminating ventricular arrhythmias. Amiodarone was added to therapy.

A year later, in 2013, despite taking amiodarone, AF got a permanent form. One of the reasons for the AF transition to a permanent form was a high percentage (90%) of right ventricular stimulation against the background of subtotal atrioventricular (AV) blockade. Amiodarone was cancelled.

During the next scheduled ECHOCG examination in 2017, there was a decrease in EF to 49%, mild LV dilatation with an end-diastolic volume index (EDVI) of 86 ml/m^2, a slight increase in LA with an LA volume index (LAVI) of 40 ml/m^2 [5].

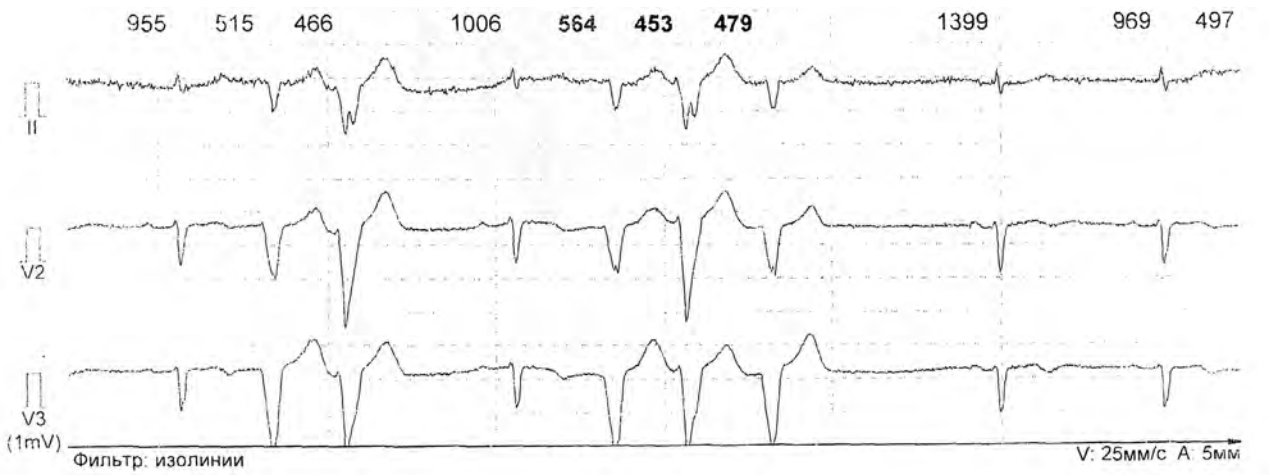

Fig. 1. Fragment of ECG monitoring. Explanation in the text

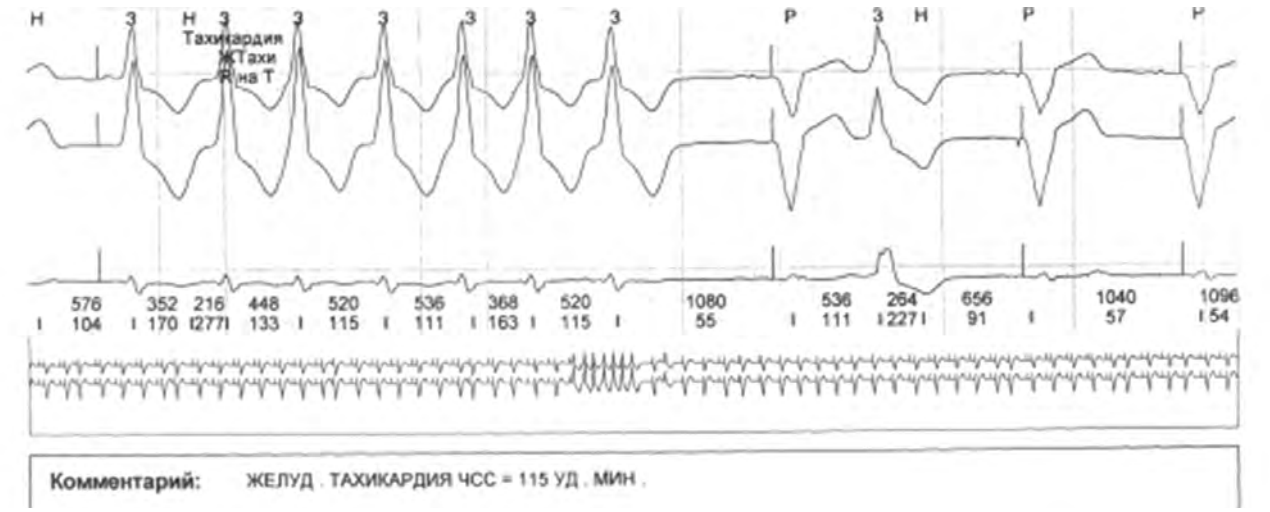

Fig. 2. Fragment of ECG monitoring after permanent pacemaker implantation. Explanation in the text

Secondary mitral regurgitation of 1 degree was also revealed. Due to the absence of complaints, the previous therapy was continued. When observed in dynamics in 2018, a decrease in EF to 47%, an increase in the LAVI to 49 ml/m^2, ECDO (81 ml/m^2) were revealed. Complaints were absent, correction of therapy was not carried out. In 2019, the patient felt a deterioration in exercise tolerance. An ECHOCG study performed in August 2019 revealed a decrease in EF to 33%, an increase in EDVI (85 ml/m^2), secondary mitral regurgitation of the 2nd degree. Correction of therapy was not carried out again.

In September 2019, the patient was admitted to our clinic for examination and selection of therapy. Clinical examination showed: satisfactory condition, no peripheral edema, height 180 cm, weight 85 kg, body mass index 26.2 kg/m^2, blood pressure 110/70 mmHg., heart rate and pulse 60 beats per 1 minute, rhythmical (PM rhythm). Borders of relative cardiac dullness: left — along the left mid-clavicular line, upper — 2nd intercostal space, right — along the right edge of the sternum. Auscultatory findings: 1st tone is muffled at the apex, the 3rd tone, a musical blowing systolic murmur at the apex. On percussion of the lungs there was pulmonary sound, on auscultation there was vesicular breathing, no wheezing. The liver is not enlarged. An ECHO study revealed a decrease in EF up to 25%, a global longitudinal strain of the left ventricular myocardium went down up to — 5.7%, an increase in EDVI up to 97 ml/m^2 (significant deviation), and an LAVI up to 54 ml/m^2 (sharp deviation) [5]. LV diastolic dysfunction of the 2nd degree was registered: the speed of movement of the lateral segment of the mitral annulus (Em) was 7 cm/sec (normal value ⩾ 10 cm/sec), the speed of movement of the septal segment was 4 cm/sec (normal value ⩾ 7 cm/sec), ratio E/Em reached off 13.6 (E is the peak velocity of the transmitral blood flow in the phase of rapid filling of the left ventricle, normal value ⩽ 13), tricuspid regurgitation was absent [6]. The volume of mitral regurgitation was 34 ml, the area of the effective regurgitation orifice was 0.25 cm^2, which corresponded to a severe degree of secondary mitral regurgitation [7]. The function of the RV was not impaired. Dyssynchrony of mechanical movement of the LV myocardium with a maximum delay in movement of the myocardium against the background of permament right ventricular stimulation outside the zone of scar tissue was found: in the area of the interventricular septum, mainly its inferior parts, the inferior wall, the posteriolateral and anterolateral walls at the basal and mid levels (Fig. 3).

When programming PM there was a permanent form of AF, pacing in the VVIR mode for 100% of the time despite taking metoprolol succinate in the dose of 50 mg per day. It diagnosed chronic heart failure (CHF) with reduced EF. During the 6-minute walk test, the patient walked 417 m, which corresponded to the II functional class of CHF. To exclude coronary shunts stenosis as the cause of a significant decrease in EF, coronary shuntography was performed. It demonstrated the following: the right type of coronary blood supply; main left coronary artery showed no stenosis; anterior interventricular artery had an occlusion at the border of the proximal and middle third, filled from a functioning shunt of the left internal mammary artery; 1st diagonal branch was occluded at the mouth, filled in a retrograde way from the basin of the right coronary artery, the shunt is not visualized; 2nd diagonal branch was occluded at the mouth, filled from a functioning shunt;

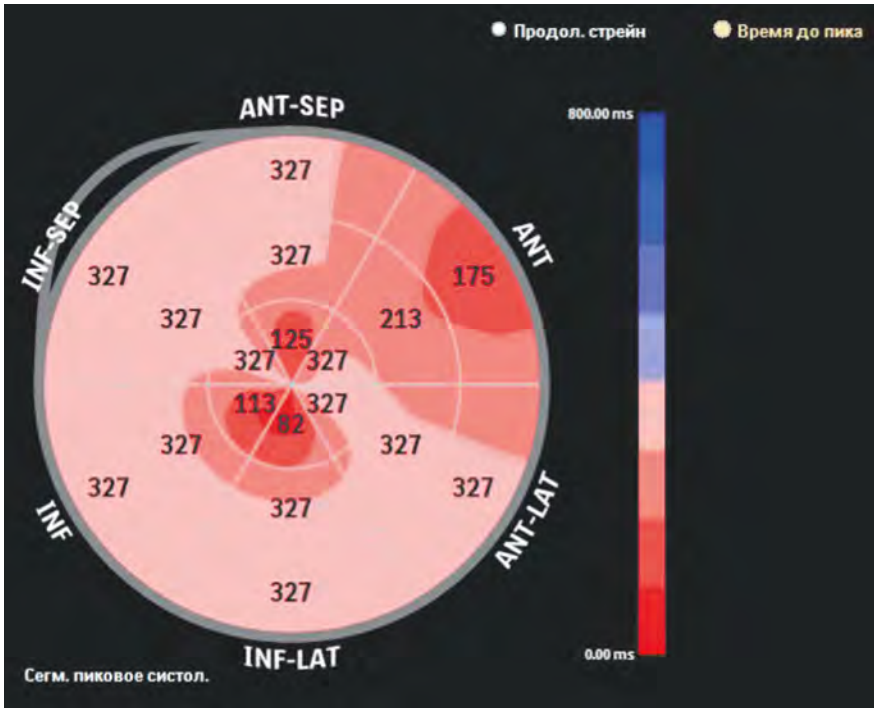

Fig. 3. Assessment of myocardial dyssynchrony. Explanation in the text

circumflex branch had no significant stenosis; 1st marginal branch was moderately altered in the proximal third with 70–75% stenosis (fractional flow reserve — FFR > 0.8), the periphery is satisfactory, 2nd marginal branch was less than 1.5 mm in diameter, diffusely changed from the mouth, the periphery is poor; the right coronary artery had no significant stenoses.

Thus, it was not possible to link the decrease in EF with the progressive pathology of the coronary arteries. The decrease in EF was associated with LV mechanical dyssynchrony that developed against the background of permament pacing of the right ventricular apex and retrograde propagation of electrical excitation to the LV. The transition of the patient to a permanent form of AF with the loss in this connection of mechanical atrial systole, which compensated for the violations of diastolic function that had taken place, also contributed to a decrease in EF. According to national and European recommendations for the diagnosis and treatment of CHF, patients with LV EF ⩽ 35%, in whom the course of heart failure worsens against the background of a traditionally implanted PM with a significant proportion of right ventricular pacing (despite optimal drug therapy) should consider the possibility of "updating" the implanted device to the resynchronizing one [1, 2]. The patient underwent PM replacement with a cardiac resynchronization therapy-defibrillator (CRT-D). The drug therapy was adjusted. Ramipril was changed to valsartan + sacubitril after a 36 hour break from ramipril. Due to the low dose of ramipril and the patient's tendency to hypotension, the starting dose of valsartan + sacubitril was 50 mg 2 times a day, followed by a slow dose titration to 200 mg 2 times a day. Glimepiride was replaced by empagliflozin at a dose of 10 mg daily. Eplerenone 25 mg per day was added to therapy, followed by dose incrising thtoughout a month to 50 mg per day under the control of potassium and serum creatinine. The glomerular filtration rate (GFR) was determined using the CKD-EPI formula. The resulting result was 46 ml/min/1.73 m^2, which corresponded to stage 3a chronic kidney disease (CKD). To assess the correctness of the dose of rivaroxaban, creatinine clearance (CC) was calculated using the Cockcroft-Gault formula without standardization to body surface area (it was this formula that was used in randomized clinical trials comparing direct oral anticoagulants with warfarin in AF). The resulting result was 55 ml/min. The dose of rivaroxaban remained the same — 20 mg per day, dose adjustment to 15 mg per day is required only with a creatinine clearance of 15–49 ml/min.

Against the background of complex therapy for CHF, including cardiac resynchronization therapy, drug quadrotherapy (valsartan + sacubitril, empagliflozin, eplerenone, beta-blocker), a year later, by September 2020, EF increased to 60%, EDVI decreased to 54 ml/m^2, LV diastolic function performance improved: velocity of movement of the lateral segment of the mitral valve anulus (10 cm/sec), of the septal segment (11 cm/sec), E/Em ratio (7.1). Mitral regurgitation was not determined. The symptoms of CHF disappeared. Since the implantation of the CRT-D, there have been no cardioverter-defibrillator shocks. When programming a resynchronization device with a cardioversion-defibrillation function, it was found that the proportion of biventricular stimulation was 90%. During the period from the moment of CRT-D implantation until December 2020, only one episode of non-sustained ventricular tachycardia was recorded, which lasted 3 seconds and spontaneously stopped. In the spring of 2021, due to low blood pressure (down to 80/60 mmHg), the patient stopped taking valsartan + sacubitril. At the next ECHO examination after discontinuation of valsartan + sacubitril in December 2021, an asymptomatic decrease in EF to 40%, an increase in EDVI to 73 ml/m^2, mitral regurgitation of the 1st degree reappeared. The patient was warned about the need to take all recommended drugs and resume titration of the dose of valsartan + sacubitril with systolic blood pressure (SBP) ⩾ 100 mm Hg to optimal well-tolerated (according to the PARADIGM HF study design) [8]. During the period of titration of the dose of valsatran + sacubitril, temporary discontinuation of the drug is recommended only when the SBP decreases < 95 mmHg with the resumption of titration when the SBP stabilizes at the level of ⩾ 100 mmHg. In addition, the dose of metoprolol succinate was increased to 75 mg with further titration to an optimal well-tolerated dose in order to better control AV conduction and achieve at least 95% biventricular pacing.

DISCUSSION

One of the most important aspects of the prevention, development and progression of CHF in patients with structural heart disease is the timely correction of rhythm and conduction disturbances. In particular, a catheter procedure for AF is recommended to eliminate LV dysfunction in AF in patients with a high likelihood of CHF being associated with a tachyarrhythmia, regardless of the presence or absence of symptoms [9, 10]. In the described clinical case, performing a catheter procedure to restore sinus rhythm was problematic due to a long history of permanent AF (about 7 years) and severe LA dilatation (LA volume 111 ml, LAVI 54 ml/m^2).

In 2012, the patient was implanted with a conventional two-chamber PM due to common indications (the presence of binodal dysfunction complicated by syncopal conditions). Due to the AV blockade that took place, the percentage of right ventricular pacing was high. There was a clear relationship between the fall in EF and permament right ventricular pacing. In accordance with national and European recommendations, the patient underwent a replacement

of a conventional pacing with a CRT-D [2, 10]. Against the background of the initial AV blockade, metoprolol succinate therapy provided control of AV conduction of supraventricular impulses and 90% biventricular stimulation. If it is not possible to control AV conduction with medication and the total duration of biventricular stimulation is less than 90–95%, the procedure of catheter modification of the AV node is resorted to [10].

Cardiac resynchronization therapy should be accompanied by optimal medical therapy. At the time of contacting our clinic, the patient had functional class II CHF with an unfavorable prognosis due to a sharp decrease in EF and needed effective life-saving therapy. Currently, two new classes of drugs, along with β-blockers and mineralocorticoid receptor antagonists (MRAs), are successfully used to treat CHF with reduced EF. These are, first of all, angiotensin II of type 1 receptors and neprilysin inhibitors, represented by valsartan + sacubitril. In the randomized controlled registration clinical trial PARADIGM HF, the addition of valsartan + sacubitril to optimal medical therapy for CHF with reduced EF reduced the relative risk of achieving the combined primary endpoint (death due to cardiovascular causes or first hospitalization due to heart failure) by 20% compared with enalapril, a well-studied drug for CHF [11]. During therapy with valsartan + sacubitril, the relative risk of individual components of the primary endpoint was statistically significantly reduced: the risk of cardiovascular death went down by 20%, the risk of first hospitalization due to heart failure decreased by 21%. In addition, a statistically significant reduction of 16% in the relative risk of such an important secondary endpoint as death from all causes was obtained. A statistically significant 20% reduction in the relative risk of sudden cardiac death deserves special attention [12]. Accumulated experience of real clinical practice confirms the results of the randomized controlled registration clinical trial PARADIGM HF [13, 14, 15].

Sodium-glucose co-transporter type 2 inhibitors (iSGLT2) represent the second innovative class of drugs for the treatment of CHF with reduced EF. Only two representatives of iSGLT2 (dapagliflozin and empagliflozin) successfully completed randomized controlled registration clinical trials on the basis of which the following indication was registered: treatment of CHF with reduced EF independent of etiology (both against the background of diabetes mellitus and in patients without diabetes) [16, 17] .

In combination with β-blockers and MRAs, the angiotensin II of type 1 receptors and neprilysin inhibitors and SGLT2 form a disease-modifying quadrotherapy [4]. In our patient, on the background of disease-modifying quadrotherapy, there was a complete recovery of EF and a positive, reverse remodeling of the heart chambers. Positive LV remodeling led to the disappearance of secondary mitral regurgitation. In a randomized clinical trial of D-H. Kang et al demonstrated pharmacological correction of the degree of functional mitral regurgitation with valsartan + sacubitril [13]. The disappearance of mitral regurgitation against the background of complex therapy for CHF in our patient confirms the results of the study by D-H. Kang et al.

Disease-modifying therapy contributs to a decrease in the number of ventricular arrhythmias. From December 2020 to November 2021, the built-in CRT-D monitoring features recorded only one episode of nonsustained ventricular tachycardia in the patient. In a study by C. de Diego et al. in patients suffering from CHF with reduced EF and implanted cardioverter-defibrillators without resynchronization function in patients with an initially narrow QRS complex or CRT/CRT-D in patients with a wide QRS, therapy with valsartan + sacubitril in combination with β-blockers and MRAs resulted in a statistically significant reduction in the number of non-sustained and sustained ventricular tachycardias compared with conventional therapy with angiotensin-converting enzyme inhibitors/angiotensin II receptor type 1 antagonists, β-blockers, and MRAs [14].

Our case demonstrated the positive effect of disease-modifying quadrotherapy. At the same time, it is obvious that not all patients suffering from CHF with reduced EF can use quadrotherapy, primarily due to the fact that the side effect in the form of hypotension is given by all four drugs included in it. Disease-modifying therapy for the treatment of CHF still requires the development of schemes and algorithms for the use of drugs [18].

Another issue requires discussion: the issue of anticoagulant therapy and the choice of a specific drug. In this case, in a patient with a polymorbid pathology, including coronary artery disease, rivaroxaban turned out to be the optimal drug with a unique evidence base to protect a patient with AF not only from stroke, but also from acute coronary events [19]. When prescribing an anticoagulant to a patient with CKD, GFR and CC should be carefully monitored and a drug without a negative effect on renal function should be preferred. A more favorable effect of rivaroxaban on renal function compared to warfarin has been demonstrated both in registration randomized controlled clinical trial and in studies performed in real clinical practice [20].

CONCLUSIONS

The case we presented illustrates the negative remodeling effect of traditional long-term pacing of the right ventricular apex in combination with a permanent form of AF in a patient with postinfarction cardiosclerosis. Complex therapy for CHF, including cardiac resynchronization therapy, drug therapy with valsartan + sacubitril with dose titration to optimal, empagliflozin, eplerenone, metoprolol succinate, made it possible to stop the processes of negative remodeling and to restore myocardial contractility. The clinical case emphasizes

the importance of converting traditional permanent pacing into cardiac resynchronization therapy in the development of CHF with reduced EF, as well as the advisability of continuing drug therapy after improvement and even recovery of EF. A negative effect on EF of the withdrawal of such an important component of quadrotherapy as sacubitril + valsartan was demonstrated.

ADDITIONAL INFORMATION

Conflict of interest. There is no conflict of interest.

Consent and anonymity of the patient. The patient provided consent for anonymous use and publication of his medical data.

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Research article

Catheter ablation of sustained idiopathic right ventricular outflow tract tachycardia in a pregnant patient without fluoroscopy

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In 2020, our department has performed 739 operations on nonpregnant patients. Additionally, 545 highly successful nonfluoroscopic catheter ablation of cardiac arrhythmias were routinely performed using a three-dimensional navigation system, including 47 patients with idiopathic ventricular tachycardia (VT) from the right ventricular outflow tract (RVOT).

A 38-year-old female patient with a structurally normal heart was admitted to our hospital in 10–11 weeks of her third pregnancy because she sustained recurrent 166 regular heartbeats per minute, wide QRS-complex tachycardia with left bundle branch morphology, and frequent premature ventricular contractions on Holter monitoring with complaints of presyncope and dyspnea. Standard antiarrhythmic drugs failed to control tachycardia. This case report presents our initial successful experience of the rescue zero-fluoroscopy catheter ablation of sustained poorly tolerated idiopathic RVOT tachycardia in a pregnant patient. Our result suggests that this technique may be considered in the few rare cases in which drug-resistant, sustained frequent VT is accompanied by hemodynamic compromise with fluoroscopy contraindication.

AIM: Diagnostic algorithm of idiopathic sustained drug-resistant, poorly tolerated VT and the possibility of radiofrequency catheter ablation in the most vulnerable first trimester of pregnancy without fluoroscopy were presented in our case report.

Keywords: safety; catheter ablation of arrhythmia; pregnancy; electro-anatomical mapping; non-fluoroscopy imaging.

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УДК 61

Научная статья

Катетерная абляция устойчивой идиопатической желудочковой тахикардии из выходного тракта правого желудочка у беременной женщины без использования рентгеноскопии

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Цель. Представлен случай диагностического алгоритма у пациентки с пароксизмальной устойчивой идиопатической желудочковой тахикардией с гемодинамическим компромиссом, рефрактерной к антиаритмической терапии, и возможностей радиочастотной абляции (РЧА) без рентгеноскопии в наиболее уязвимом первом триместре беременности.

Материалы и методы. В 2020 году в нашем отделении выполнено 739 операций у небеременных пациентов. 545 весьма успешных нефлюороскопических РЧА по поводу аритмий проведены с использованием 3-х мерной навигационной системы, в их числе 47 пациентов с идиопатическими желудочковыми тахикардиям (ЖТ) из выходного отдела правого желудочка (ВТПЖ).

В нашу больницу госпитализирована 38-летняя женщина на 10-11-й неделе третьей беременности со структурно нормальным сердцем и устойчивой рецидивирующей тахикардией с широкими QRS-комплексами, частыми ЖЭ при холтеровском мониторинге, с жалобами на пресинкопе и одышку. Тахикардия была рефрактерна к антиаритмическим препаратам. Нами представлен наш первый, успешный опыт нефлюороскопической РЧА устойчивой идиопатической тахикардии с клиническими проявлениями из ВТПЖ у беременной пациентки.

Результаты. Наш случай говорит о том, что методика может быть применима в тех редких случаях, когда имеет место аритмия с гемодинамическим компромиссом, рефрактерная к антиаритмическим препаратам, и рентгеноскопия противопоказана.

Выводы. Представлен случай возможного диагностического алгоритма у пациентки с пароксизмальной устойчивой идиопатической желудочковой тахикардией с гемодинамическим компромиссом, рефрактерной к антиаритмической терапии, и возможностей радиочастотной абляции без рентгеноскопии в наиболее уязвимом первом триместре беременности.

Ключевые слова: безопасность; катетерная абляция аритмии; беременность; электро-анатомическое картирование; нефлюороскопическое картирование.

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ЭКО•ВЕКТОР

INTRODUCTION

Physiological, hemodynamic, hormonal, and metabolic changes occur during pregnancy [1–2] and may induce maternal arrhythmia, regardless of any preexisting heart pathology. Usually, this has a benign prognosis. However, drug-resistant arrhythmia with hemodynamic compromise rarely occurs and may require precise management, considering that maternal and fetal safety should be paramount. The radiofrequency catheter ablation (RFCA) of arrhythmia with zero-fluoroscopy is a rescue approach in the severe tachyarrhythmia treatment in pregnant women, when it is without other existing alternatives [3].

CASE REPORT

Our department has performed 739 operations on nonpregnant patients in 2020. Additionally, 545 highly successful nonfluoroscopic catheter ablation of cardiac arrhythmias were routinely performed using a three-dimensional navigation system, including 47 patients with idiopathic ventricular tachycardia (VT) from the right ventricular outflow tract (RVOT).

A 38-year-old female patient in 10–11 weeks of her third pregnancy was admitted to our hospital, due to sustained recurrent 166 regular heartbeats per minute, wide QRS-complex tachycardia with left bundle branch block (LBBB) morphology, and frequent premature ventricular contractions (PVCs) on Holter monitoring (Fig. 1) with complaints of presyncope and dyspnea. She had two uncomplicated vaginal deliveries and two healthy children.

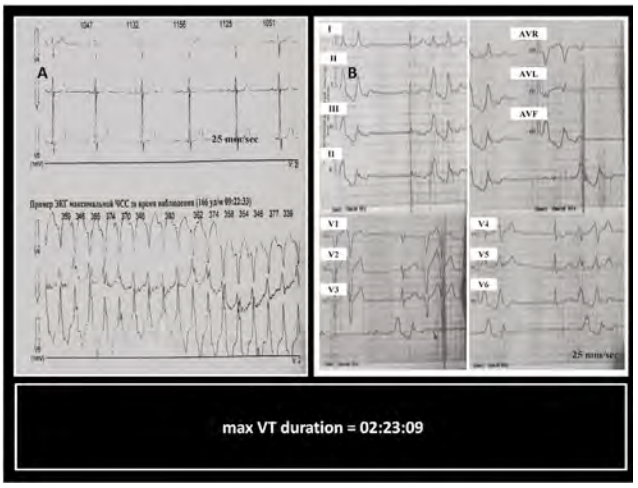

Fig. 1 (A). Holter monitoring: sustained 166 regular heartbeats per minute wide QRS-complex tachycardia with LBBB morphology was introduced (B). 12-lead ECG: coupled PVCs are shown in all leads

The patient had been suffering from irregular heartbeats for 5 years but had never been referred to a cardiologist. Her condition worsened 3 months ago due to recurrent presyncope. Her blood pressure was normal and there was no family history of sudden cardiac death.

A pregnancy termination was scheduled by the local outpatient obstetrician and physician due to arrhythmia.

A blood and urine analysis did not indicate thyroid and electrolyte disturbances and the myocardial injury markers

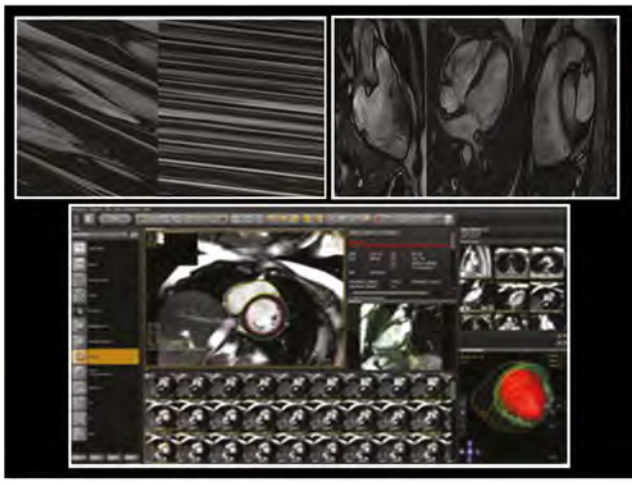

Fig. 2. MRI without gadolinium-based contrast: regional RV akinesia, dyskinesia, or dyssynchronous RV contraction were not determined. The RV was not dilated. The ratio of the RV end-diastolic volume to BSA was 75 mL/m2. The RV ejection fraction was not reduced (51%). The results of the cardiac MRI did not concur with the Padua criteria for diagnostic arrhythmogenic cardiomyopathy 2020

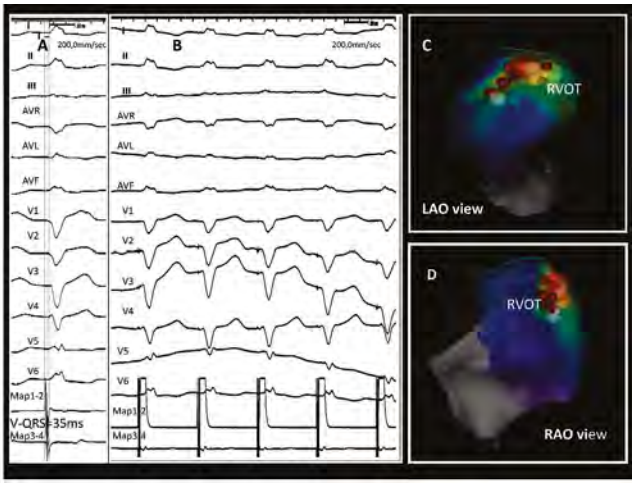

Fig. 3. Serial images of pace- and electroanatomical and activation mapping that guided successful RFCA recurrent VT, originating from the RVOT. (A) Only PVCs with a morphology similar to VT morphology were recorded during the procedure. Ventricular preexcitation recorded on Map 1–2 = 35 ms during spontaneous PVC. (B). Pace-mapping RV. A similar QRS-complex morphology both during pacing (Panel B) and spontaneous PVC (Panel A) is shown. Simultaneous intracardiac recordings are presented in Panels C and D, the earlier ventricular activation was recorded at the RVOT in the septal area, and a successful RF application at 35 W was conducted in the specific area of interest.

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were not increased. RV morphological PVCs were registered on 12-lead electrocardiography (ECG) (Fig. 1). However, the ECG was normal, as well as the echocardiography and cardiac magnetic resonance imaging (MRI) without gadolinium-based contrast (Fig. 2).

Standard antiarrhythmic drugs failed to control tachycardia. Thus, propafenone is advised as a B category and b-blocker Sotalol as a C category by the United States Food and Drug Administration [3].

Echocardiogram and cardiac MRI without gadolinium contrast were notable for preserved left and right ventricular structure and function. The LBBB morphology with tall R waves in inferior leads of the wide complex tachycardia and frequent PVCs was highly suggestive of VT originating from the outflow tract region. The findings were suggestive of a benign prognosis; however, its presence during pregnancy significantly increased the risk of maternal mortality or severe morbidity following the World Health Organization classification of cardiovascular maternal risk [3].

A multidisciplinary team approach was used in patient management. However, not all cardiac arrhythmias can be conservatively treated in pregnancy. She suffered from sustained drug-resistant and poorly tolerated VT with a high risk of recurrence. Therefore, we recommended catheter ablation of the arrhythmia (RFCA) without fluoroscopic exposure during the procedure. Informed consent was obtained after a detailed discussion of procedure risks and benefits. Antiarrhythmic medications were discontinued for at least 5 half-lives before the procedure.

The procedure was guided by the nonfluoroscopy electroanatomical mapping system CARTO 3 SYSTEM VERSION 6 (Johnson & Johnson Medical Devices), and intracardiac echocardiography (ICE) imaging was performed using a Sequoia ultrasound system (Acuson Corporation, Siemens Medical Solutions USA, Inc.) with an AcuNav diagnostic ultrasound catheter. A transfemoral approach was used.

An electrophysiological study was conducted during the initial stage of the operation to exclude supraventricular tachycardia (SVT) with a bundle branch block and VT induction. The arrhythmogenic zone (RVOT, septal part) was determined by electroanatomical, activating- and pace-mapping RV (Fig. 3).

A single irrigated RF application at 35 W was conducted with a Thermocool Smarttouch catheter in the area of interest. The contact force was >5 g. The ectopy, similar to the clinical VT, was noted during ablation, and arrhythmia was suppressed after 60 s.

The operation time was 38 min, and it was performed with local anesthesia to avoid maternal hypotension and low placental perfusion. Fetal cardiotocography was used for intraprocedural fetal monitoring.

Surveillance levels during delivery among women with arrhythmias were estimated and an action plan was formulated [3]. The woman in question gave birth to the infant by vaginal delivery with epidural anesthesia to full term. The infant's condition was fair (bodyweight of 2.420 The patient was discharged in a stable condition 3 days later. The postoperative followup at 6 and 12 months did not indicate any pathological myocardial activity.

DISCUSSION

Herein, we examine the issues relating to pregnancy due to clinical situation underestimation, antiarrhythmic drug prescription limitations [3], which would lead to pregnancy termination, complicated by idiopathic, sustain, recurrent, drug-resistant, and poorly tolerated VT from the RVOT. Our initial successful experience of a rescue RFCA of arrhythmia with zero-fluoroscopy in pregnant women is presented.

The prognosis and treatment strategies of VT substantially differ, and a correct diagnosis was important. Similar to other clinicians, we were dealing with a situation of limited diagnostic capabilities in the first trimester of pregnancy, due to the potential fetal risk.

MRI without gadolinium-based contrast is advised as IIa (C), indicating whether other noninvasive, diagnostic measures are insufficient in providing a definitive diagnosis in the latest European Society of Cardiology (ESC) guidelines [3]. Novel MRI sequences, as well as endomyocardial biopsy, may assist in achieving a correct diagnosis [4]. The safety of MRI rendered it the only applicable method after echocardiography, as a means of excluding structural heart diseases, such as arrhythmogenic cardiomyopathy (ACM), sarcoidosis, and other common cardiomyopathies in this case.

In accordance with the Padua criteria for ACM diagnosis, our case showed only one minor ECG criterion (sustained VT of RV outflow configuration, LBBB with inferior axis [positive QRS in leads II, III, and aVF, and negative QRS in lead aVL]), which was insufficient for any diagnosis. Therefore, genotyping is indicated to identify a pathogenic or likely pathogenic mutation in a proband with consistent phenotypic disease features [5] according to the expert recommendations for genetic testing in ACM, and genetic testing was not recommended in patients with only a single minor criterion.

Idiopathic RVOT was determined as a likely diagnosis in the case of our patient [5-7]. Idiopathic RVOT is the most frequent VT type during pregnancy, and antiarrhythmic drug therapy is the first stage of treatment for acute and longterm management of this condition to avoid medication prescription, which could potentially be harmful to the fetus. Maternal arrhythmia can be transient, well-tolerated during delivery, and disappear after childbirth [3].

Managing idiopathic sustained VT, in this case, was a challenge due to its hemodynamic instability and drug resistance. We could follow the latest ESC guidelines [3] for the immediate electrical cardioversion for both sustained unstable and stable VT as I (C) indication if arrhythmia was not continuously recurrent in this case.

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The ESC recognized catheter ablation with electroanatomical mapping systems in sustained drug-refractory and poorly tolerated VT as II b (C) level of indication in its latest guidelines. Potential risks to the mother and fetus from catheter ablation during pregnancy include anesthesia-related risk, pacing-induced maternal tachycardia, and radiation exposure [3]. However, this was determined as the only remaining fundamental solution, considering its ability to eliminate the arrhythmogenic zone in our event.

Meng-meng Li et al. have reported that ~28 pregnant patients without structural heart pathology underwent successful RFCA with zero-fluoroscopy, as their arrhythmia was drug-resistant and hemodynamically significant. SVT was determined in 15 cases, PVS in 10, and VT in 3 [8].

Chen et al. have demonstrated 2 cases of successful zero-fluoroscopy catheter ablation of severe drug-resistant arrhythmia guided by the Ensite NavX system during pregnancy, including one healthy woman with PVCs and VT in the third trimester of pregnancy. They also conducted a literature review of cases of pregnant women with SVT who underwent zero-fluoroscopy ablation. All women and fetuses were in good condition and had an uneventful postoperative course after the procedure. Recurrence of arrhythmia and complications related to the procedure were not reported [9].

Herein, we demonstrated our initial, clinical experience of rescue RFCA of idiopathic, sustained, recurrent poorly tolerated VT from RVOT, with zero-fluoroscopy in the most vulnerable first trimester of pregnancy as a safe and effective procedure, resulting in the survival of the mother and fetus, when executed by an experienced operator.

Unfortunately, very few cases of RFCA with zero-fluoroscopy of sustained poorly tolerated VT in pregnant women without heart pathology are recorded in the database, which would enable clinicians to make a risk-benefit ratio reassessment of this procedure in cases of pregnancy, complicated by VT. Currently, this technique may be considered in the few rare cases in which drug-resistant sustained frequent VT is accompanied by hemodynamic compromise with fluoroscopy contraindication.

ADDITIONAL INFORMATION

Conflict of interest. The authors declare no conflict of interest.

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Editorial

Corrigendum to "Late Electrode Sepsis: Clinical Features, Diagnostics and Management. Clinical Cases". DOI: 10.17816/cardar71367

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There is an error occurred in the published article “Late Electrode Sepsis: Clinical Features, Diagnostics and Management. Clinical Cases” by Vera Yu. Zimina, Gevorg R. Airapetian, Yuri N. Grishkin, Sergey A. Sayganov. Due to a technical error on author’s part and without any malicious intent, the names of the authors who were directly involved in writing the article and made a great contribution to the work were lost. The full-text of the article begins with an introduction previously partially included in the abstract of this article. The error does not change the essence of the data presented in the article, does not violate their perception by readers or interpretation.

Authors confirm the accuracy of the information provided in this letter about the composition of the team of authors, and that the contribution of each member of the authors team indicated in this letter is sufficient to be recognized as an author in accordance with the recommendations of the ICMJE.

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

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Наш авторский коллектив статьи «Поздний электродный сепсис: особенности клинического течения, диагностики и ведения. Клинические случаи» в составе Зиминой В. Ю., Айрапетяна Г. Р., Гришкина Ю. Н., Сайганова С. А. обнаружил ошибку в опубликованной статье: случайным образом, в силу технической ошибки с нашей стороны и без какого-либо злого умысла были утеряны фамилии авторов, принимавших непосредственное участие в написании статьи и внесших большой вклад в работу. Ошибка произошла по вине всего авторского коллектива, но не изменяет сути изложенных в статье данных, не нарушает их восприятие читателями или интерпретацию.

Наш авторский коллектив подтверждает достоверность указанных в настоящем письме сведений о составе авторского коллектива, и то, что вклад каждого из указанных в настоящем письме членов авторского коллектива достаточен для признания его автором в соответствии с рекомендациями ICMJE.

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

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