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CONTENTS

СОДЕРЖАНИЕ

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Review

Epicardial Adipose Tissue and Cardiac Arrhythmias

Sergey G. Kanorskii

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Obesity is associated with an increased risk of atrial and ventricular arrhythmias, including life-threatening ones. Epicardial adipose tissue (EAT) is located deep under the visceral pericardium (epicardium) and is therefore in direct contact with the underlying myocardium. In pathological conditions, EAT undergoes a phenotypic transition from a "neighbor" with protective properties to a substrate that secretes many substances that change the electrophysiology of cardiomyocytes by modulating ion currents that disrupt intercellular electrical connections and stimulate fibrosis. An excess of EAT can cause atrial and ventricular conduction disturbances, which are already evident with standard electrocardiography, predispose to the occurrence of the re-entry phenomenon and cardiac arrhythmias. Among the mechanisms of arrhythmogenesis under the influence of EAT, modulation of ion channels and gap junctions, fibrous remodeling and fatty infiltration are more often considered. However, most of these mechanisms have been studied in experimental studies and cannot easily be extrapolated to humans. There is convincing evidence of a direct relationship between EAT volume and the severity of atrial fibrillation, as well as the clinical benefit obtained from weight loss in patients with this arrhythmia. It is likely that the benefits of weight loss may extend to ventricular arrhythmias.

Keywords: obesity; epicardial adipose tissue; cardiac arrhythmias; inflammation.

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Обзорная статья

Эпикардиальная жировая ткань и аритмии сердца

С.Г. Канорский

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Ожирение связано с повышенным риском предсердных и желудочковых аритмий, в том числе угрожающих жизни. Эпикардиальная жировая ткань (ЭЖТ) локализуется глубоко под висцеральным перикардом (эпикардом) и, следовательно, находится в непосредственном контакте с нижележащим миокардом. При патологических состояниях ЭЖТ претерпевает фенотипический переход от «соседа» с защитными свойствами к субстрату, секретирующему множество веществ, которые изменяют электрофизиологию кардиомиоцитов путем модуляции ионных токов, нарушающих межклеточные электрические связи пациентов стимулирующих фиброз. Избыток ЭЖТ способен вызывать нарушения предсердной и желудочковой проводимости, которые очевидны уже при стандартной электрокардиографии, предрасполагать к возникновению феномена re-entry и аритмиям сердца. Среди механизмов аритмогенеза под влиянием ЭЖТ чаще рассматриваются модуляция ионных каналов и щелевых контактов, фиброзное ремоделирование и жировая инфильтрация. Однако большинство этих механизмов изучены в экспериментальных исследованиях и не могут быть легко экстраполированы на человека. Убедительно доказана прямая связь между объемом ЭЖТ и тяжестью течения фибрилляции предсердий, а также клиническая выгода, получаемая при снижении массы тела у пациентов с этой аритмией. Вполне вероятно, что польза от потери веса может распространяться и на желудочковые аритмии.

Ключевые слова: ожирение; эпикардиальная жировая ткань; аритмии сердца; воспаление.

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BACKGROUND

The prevalence of obesity and the number of associated diseases are increasing worldwide [1, 2]. More than 650 million obese people on our planet (body mass index (BMI) ⩾ 30 kg/m^2) [3], according to the World Health Organization, are associated with an increased risk of type 2 diabetes mellitus, cardiovascular and oncological diseases, chronic kidney disease, pathology of the musculoskeletal system, and infections, resulting in a 1.3-fold increase in the probability of early death compared with people with normal weight [4]. In the human body, white, brown, and beige adipose tissues are extensive, and they perform important physiological functions [5]. BMI higher than 25 kg/m^2 is associated with a higher risk of sudden cardiac death [6] and atrial fibrillation (AF) [7]. In addition, high BMI and obesity correlate with QTc prolongation and QRS complex duration [8], which are independent risk factors for cardiac arrhythmias. Therefore, obesity may be significant in causing life-threatening cardiac arrhythmias.

Visceral adipose tissue tends to accumulate in the abdominal cavity around the internal organs and the heart [9]. BMI and the volume of visceral, including epicardial adipose tissue (EAT), have a significant relationship [10]. Due to its proximity to the heart, EAT is considered to have a potential proarrhythmic effect [11]. The volume of EAT is directly related to the occurrence, duration, and recurrence of AF [12]. In addition, the EAT volume on free ventricle walls correlates with the incidence of ventricular extrasystole [13], and the volume of fat surrounding the parietal pericardium and EAT is directly related with the development of ventricular tachyarrhythmia in patients with cardiac failure [14]. Despite an increasing number of publications on the effect of EAT on the risk of cardiac arrhythmias, its electrophysiological mechanisms are still unspecified.

This study aimed to summarize the literature data on the proposed mechanisms of EAT arrhythmogenicity to determine guidelines for its correction in clinical practice. In the furtherance of this aim, a search and analysis of literary sources in English and Russian languages were performed in the MEDLINE/PubMed database for the keywords “epicardial adipose tissue”, “epicardial fat”, “electrophysiological remodeling”, “cardiac arrhythmias”, as well as in the eLIBRARY database for keywords “epicardial adipose tissue” and “cardiac arrhythmias”. The filters “clinical trial”, “meta-analysis”, “randomized controlled trial”, “review”, “systematic review”, and “10 yr” were used. For inclusion in the review, studies of any design, presenting modern outlooks of the relationship between EAT and cardiac arrhythmias, were considered. When choosing publications, full-text articles in peer-reviewed journals with a high impact factor were preferable. After screening 260 literature sources, 124 of the most significant full-text articles were selected and analyzed, and 91 most cited ones of them were included in the review.

Epicardial adipose tissue: From physiology to pathology

There are three types of adipose tissue: white, brown, and beige. White adipose tissue is extensive throughout the body in the form of subcutaneous or visceral fat. Its main function is an energy storage site, and adipocytes consist of individual lipid droplets of triglycerides, which impart the characteristic yellow color to the tissue, with minimal space for mitochondria [15]. In addition, white adipose tissue secretes a number of hormones, cytokines, complement, and growth factors with both endocrine and paracrine activity that affect adjacent and distant tissues [16]. In relation to white adipose tissue, brown adipose tissue dissipates energy through thermogenesis and is found in the cervical, supraclavicular, axillary, paravertebral, mediastinal regions, and upper abdomen, and is antagonistic [15, 17]. Based on its function, brown adipose tissue is characterized by an abundance of mitochondria, which imparts a brown tint to adipocytes, and triglycerides are stored there in the form of small vacuoles. Brown adipose tissue also has a denser network of vascular microcirculation and sympathetic innervation due to a greater need for oxygen and the need to respond to thermogenesis [15]. Beige adipose tissue is an intermediate phenotype that has the functions of white and brown adipose tissues; it regulates energy balance and thermogenesis [18].

EAT represents a depot of white visceral fat that uniquely exhibits the characteristics of beige adipose tissue. Due to the absence of a fascial boundary, EAT is localized deep under the visceral pericardium (epicardium) and thus in direct contact with the underlying myocardium. EAT is mainly localized along the atrioventricular and interventricular sulci, circumflex artery, and left anterior descending coronary artery, around the atria, and is located in the right ventricle, as well as free wall and apex of the left ventricle [19]. EAT can cover up to 80% of the heart surface and reach 20% of the entire cardiac mass.

EAT protects the myocardium and coronary arteries from mechanical influences because of its elasticity and compressibility. Unlike other fat depots, EAT has an extraordinarily high rate of lipogenesis and lipolysis, functions as a local energy store of free fatty acids (FFAs) and a buffer against the lipotoxic effects of their excess [5, 20]. EAT also functions as an endocrine organ that secretes a number of adipokines [21], is a source of catecholamine biosynthesis, including noradrenaline [22], modulates the proliferation and contractility of vascular wall smooth muscle, and has antiapoptotic and antioxidant effects [5, 20].

The release of FFA from EAT adipocytes into plasma can take place locally and be a rapidly mobilized source of energy supply to the heart given the proximity between EAT and cardiomyocytes. Although mitochondrial FFA oxidation represents 60%–90% of the metabolic substrate of cardiomyocytes, lipid overload is toxic [23]. If the absorption of FFA by cardiomyocytes exceeds the oxidative capacity

of mitochondria, toxic lipids accumulate, which leads to mitochondrial and endoplasmic reticulum dysfunction, dysregulation of calcium movement, and increased production of reactive oxygen species [24]. The resulting calcium overload of the cytosol and spontaneous calcium release are significant in arrhythmogenesis through late post-depolarization and trigger activity [25]. Reactive oxygen species induce early post-depolarization, facilitate the onset of ventricular arrhythmias in rats, and alter the electrical connection between cardiomyocytes, leading potentially to conduction delay and increased risk of arrhythmias [26].

FFAs can be stored in the form of myocardial cytosolic lipid droplets [24], which can serve as an energy reservoir and prevent lipotoxicity. They can also be used to perform lipid signaling functions and to construct membranes [27]. However, this might result in an excessive production of reactive oxygen species and contribute to arrhythmia when the capacity of lipid droplets in cells is exhausted or their function is impaired [28].

The anatomical proximity of EAT to the myocardium and their common blood supply from the coronary arteries have induced scientific interest and promoted research with accumulating evidence of the paracrine role of EAT in the development of cardiovascular diseases.

Inflammation and products of secretion of epicardial adipose tissue

EAT undergoes a phenotypic transition from a "neighbor" with protective properties to an inflammatory substrate in pathological conditions. For example, a higher pro-inflammatory activity of EAT was noted in patients with coronary heart disease than in people without it [29]. Matrix ribonucleic acid expression is activated. Levels of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and monocytic chemotactic protein-1 are increased, while the formation of anti-inflammatory adiponectin is suppressed [30]. In type 2 diabetes mellitus, there was also a shift toward pro-inflammatory secretome (i.e., all secretion products) of EAT, as well as decreased levels of adiponectin, and increased cell expression of Monocyte Chemotactic Protein 1 and CD68+ compared with people without diabetes [31]. Pharmacotherapy of coronary heart disease and type 2 diabetes mellitus has been shown to contribute to the regression of the inflammatory phenotype of EAT, a less inflammatory profile of its secretome [32, 33].

The cause-and-effect relationships of the processes documented remain controversial despite the evidence for the transition of EAT to a pro-inflammatory state in cardiometabolic disorders and its reversibility with pharmacotherapy. EAT is known to significantly differ from subcutaneous adipose tissue in its pronounced pro-inflammatory profile, in particular higher concentrations of matrix ribonucleic acid, levels of IL-1b, IL-6 and TNF-α, leptin, resistin, CD45, macrophages, mast cells and T lymphocytes, and so forth, as well as a drastically reduced level of adiponectin [34]. Meanwhile, the inflammatory nature of EAT has a genetic basis, being detected in overweight and obese people, regardless of the presence of cardiovascular diseases [35].

Obesity, epicardial adipose tissue, and risk of cardiac arrhythmias

Obesity is characterized by excessive fat deposition and represents a chronic, mild, systemic pro-inflammatory condition. Hypertrophy of adipocytes with an increase in the volume of adipose tissue creates a hypoxic environment and induces genetic mutations, which leads to an increase in levels of pro-inflammatory mediators and a decrease in anti-inflammatory mediators, respectively [36]. Obesity is associated with an increased risk of atrial and ventricular arrhythmias [37], similar to another pathology that is characterized by a pro-inflammatory condition. For example, compared with people with normal BMI values (18.5–24.9 kg/m^2), the risk of AF can be increased by 65% in people with a BMI higher than 30 kg/m^2, corresponding to a 4% increased risk for each unit of BMI gain. This predisposition to AF may be due to electrophysiological remodeling caused by an increase in atrial volume, conduction disorders, and an increase in the expression of profibrotic mediators that contribute to the formation of an arrhythmogenic substrate [38]. Such changes are reversible with weight loss, as shown in a model of obese sheep, where a 30% weight loss reduced atrial pressure and fibrosis, while also improving conductivity by means of increase in connexin expression [39]. In addition to systemic obesity, it was revealed that electrical and structural remodeling is modulated by localized obesity, resulting in the most pronounced pathological changes in areas adjacent to EAT, which was associated with arrhythmogenesis [38].

Taking into consideration that EAT is a metabolically active depot in direct contact with the myocardium, several variants of its connection with arrhythmogenesis are suggested. G. Thanassoulis et al. [40] demonstrated in the Framingham Heart study that the risk of AF increased with an increase in pericardial fat volume. The mass of epicardial fat, determined using computed tomography, was significantly higher in patients with paroxysmal AF compared with examined patients with sinus rhythm [41]. The volume of pericardial fat correlates with the severity of AF; in persistent AF, it is significantly higher than in paroxysmal AF [42]. According to a meta-analysis of 63 observational studies involving 352.275 participants, an increase in EAT volume was associated with a predominantly increased risk of persistent AF rather than paroxysmal AF. In addition, EAT volume was a better predictor of AF risk than other indicators of obesity, such as BMI, body surface area, waist circumference, waist-to-hip ratio, as well as intrathoracic fat and abdominal fat volumes [43]. EAT is an independent predictor of AF recurrence after catheter ablation [44]. In patients with recurrent AF, EAT volume and serum C-reactive protein levels are directly correlated, suggesting

inflammation as a mediator between EAT and arrhythmic risk [45]. These data confirm that adipose tissue, being in direct contact with the myocardium, contributes to the development of the arrhythmia substrate, possibly through paracrine mechanisms.

There is inconsistent data linking EAT volume to ventricular arrhythmias. Thus, EAT thickness has been reported to correlate directly with the frequency of ventricular extrasystoles [46] and is a prognostic factor for significant prolongation of the QT interval (> 450 ms), the risk of ventricular tachycardia or ventricular fibrillation in heart failure, and relapse of ventricular tachycardia after ablation [8, 47, 48]. However, other authors have not noted a relationship between EAT volume and QTc interval duration [49] and have reported that EAT thickness correlates better with increased PR interval [50] and P wave length, but not with QT variance [51].

Electrophysiological changes induced by epicardial adipose tissue

Traditionally, abnormal generation and abnormal conduction of an electrical impulse are considered as mechanisms of cardiac arrhythmias. Abnormalities in the generation of impulses are due to pacemaker and trigger activity, with the latter depending on the action potential duration (APD) or an increase in the concentration of Ca^{2+} ions in the cytosol due to exit from the sarcoplasmic reticulum. Impulse conduction abnormalities can result in anatomically or functionally determined re-entry cardiac arrhythmias. The basis for unidirectional block and re-entry is provided by the spatial heterogeneity of repolarization timing. The standard surface electrocardiogram contains information about APD, automatic behavior, and delay in conduction and, therefore, can provide mechanistic information about arrhythmogenesis in the most accessible way.

An increase in the P wave duration on the electrocardiogram indicates atrial conduction delay. The volume of EAT correlates positively with the P wave duration and atrial conduction delay [52]. At the same time, in patients with morbid obesity, the increase in the P wave duration indicates at least partially the atrial dilatation [53]. The P wave dispersion is determined as the difference between the maximum and minimum duration in several superficial leads of the electrocardiogram. It serves as a marker for anatomical remodeling and heterogeneous distribution of atrial activation. In healthy individuals, P wave dispersion is associated with EAT thickness [54]. The degree of infiltration of the interatrial septum with adipose tissue is independently related to the number of P wave fragmentations (a marker of heterogeneous conduction) in patients with paroxysmal AF and people at risk of developing this arrhythmia [55]. Overall, this demonstrates an association between infiltration of interatrial septum with adipose tissue and atrial conduction delay and discontinuity.

The P-R interval is the total time required to conduct impulses through the right atrium, atrio-ventricular node, bundle of His, and its branches. After adjusting for the effects of variables, EAT volume correlates linearly with longer P-R interval [52]. It has been revealed that in examined patients with the highest EAT volume, the P-R interval duration is 10–16 ms longer than in people with the lowest EAT volume [56]. According to observational studies, an association between P-R interval prolongation and increased incidence of AF, heart failure, and mortality [57]. Since the P-R interval includes conduction through various structures, it is not clear whether EAT affects the conduction velocity in each of them or whether there is an area of its preferential effect.

An increase in the duration of the QRS complex may be caused by myocardial hypertrophy or a delay in intraventricular conduction. A study with the participation of 3,087 healthy subjects revealed that EAT volume was directly related to longer QRS complex duration after adjusting for several variables [56]. In addition, the presence of a fragmented QRS complex was associated with an increase in the volume of EAT both in healthy people and in patients with arterial hypertension [58, 59]. Inhomogeneous anisotropic ventricular conduction may be the root cause of ventricular re-entry arrhythmias.

The QT interval, which indicates the time required for ventricular depolarization and repolarization, is usually corrected (corrected QT interval, QTc) using the H.C. Bazett's equation taking into account heart rate. Significant prolongation of the QTc interval can cause ventricular tachyarrhythmias, such as torsades de pointes [60]. There have only been a few studies on the relationship between EAT volume and QT interval and its variance, and their results are unpersuasive [52, 54]. Therefore, the relationship between EAT and ventricular repolarization remains unclear.

The heterogeneity of ventricular repolarization is shown by changes in the shape or duration of the T wave. A longer time interval between the peak and the end of the T wave indicates the repolarization heterogeneity, is a predictor of the risk of sudden cardiac death and death from all causes [61]. In an observational study, this interval increased in subjects with higher EAT volumes. In this study, high EAT volume was associated with increased QT interval dispersion, which indicated increased repolarization heterogeneity [62], as well as the risk of ventricular re-entry arrhythmias and sudden cardiac death.

Possible mechanisms of arrhythmogenesis under the influence of epicardial adipose tissue on the heart

Ion-channel modulation

Local and systemic inflammation can induce a proarrhythmic substrate in the heart by modulating ion channels mediated by cytokines IL-1b, TNF-α, and IL-6, which are actively secreted by EAT [63]. As a result, an increase in the current of Ca^{2+} ions with a decrease in their concentration in the sarcoplasmic reticulum, a decrease in the current of K^+ ions lengthen the APD, increase the tendency

to spontaneous diastolic depolarization and trigger activity, as well as a functional block of conduction [64]. However, most of the evidence for cytokine-mediated modulation of ion channels was obtained in experiments in mice. Although the currents of Na^+ and K^+ ions that promote rapid depolarization (phase 0) and the resting membrane potential (phase 4) are similar in mice and humans, the current of Ca^{2+} ions in mice is much weaker, which leads to the almost complete absence of the plateau phase (phase 2) [65], and repolarization is differently regulated by currents of K^+ ions. This means that the effect of EAT on the function of ion channels that has been established in experiments cannot be extrapolated to humans. FFAs secreted by EAT are also capable of exerting an arrhythmogenic effect on the myocardium through direct modulation of APD and predisposing to late post-depolarizations. However, reports on the direction of such an effect are contradictory [34, 66]. Cytokines and FFAs derived from EAT prolong APD, facilitate re-entry and late post-depolarizations, probably contributing to the spatial heterogeneity of repolarization, but these concepts require further confirmation.

Gap junction modulation

Specialized cell surface structures, known as gap junctions, guarantee the direct transfer of ions and small molecules between adjacent cells. Gap junctions between myocardial cells also provide the electrical impulse required for the heart muscle contraction. They consist of two semi-canals, or connexons, each formed by six ion-channel proteins called connexins. Connexin-40 (K40), Connexin-43 (K43), and Connexin-45 (K45) are most abundant in the human heart, revealed in the gap junctions of the atria, ventricles, and specialized conductive tissue. A relationship has been established between reduced connexin expression and a tendency to atrial or ventricular arrhythmias [67]. In obesity, the level of K43 in the atria decreases, which may predispose to AF [68]. In an experiment with obese sheep, it was found that weight loss of 30% was associated with an increased expression of K43 and a simultaneous improvement in conductivity with a decrease in its heterogeneity, a decrease in vulnerability to AF [39]. BMI correlates with EAT volume [69], while weight gain and an increase in EAT volume with a high-calorie diet were associated with suppression of K43 production, a decrease in impulse conduction velocity, and greater inducibility of ventricular arrhythmias [70].

The cytokines IL-6 and TNF-α secreted by EAT are able to widen gap junctions by suppressing the formation of K40 and K43, which leads to slow conduction and an increased risk of re-entry [71, 72]. At the same time, it was revealed that the width of the gaps between adjacent cardiomyocytes is greater in AF patients [73].

Fibrotic tissue remodeling

Fibrotic tissue remodeling in the myocardium creates a substrate for re-entry, forming tortuous conduction pathways and simultaneously delaying macroscopic myocardial conduction. A number of authors have demonstrated that atrial fibrosis increases with the progression of obesity, and the increasing volume of EAT is associated with an increase in the secretion of profibrotic cytokines (IL-1b, IL-6, TNF-α, and monocytic chemotactic protein-1) responsible for local inflammation, collagen deposition, and fibrosis (structural remodeling) [74, 75]. Local concentrations of matrix metalloproteinases-2, metalloproteinases-7, and metalloproteinases-9 are directly correlated with the level of atrial collagen and fibrosis [75], the former being directly related to the volume of EAT and the severity of AF [76]. Connective tissue growth factor and activin A are more actively expressed by EAT in AF patients compared with people with sinus rhythm, closely correlated with fibrosis and atrial remodeling [77].

Adipose infiltration

Along with the paracrine effects of EAT, infiltration of epicardial adipocytes into the myocardium can separate myocardial fibers, resulting in slow conduction or block, contributing to re-entry arrhythmias. This process does not differ from the fibroadipose infiltration noted in hereditary cardiomyopathies [78]. A global decrease in conduction velocity, greater electrogram fractionation, and a decrease in voltage were observed in obese individuals as EAT volume and atrial fat infiltration increased, which were more dependent on EAT volume than on global indices of obesity, such as BMI. These changes were more pronounced in areas adjacent to epicardial fat depots, suggesting their role in the development of the AF substrate [38]. Vulnerability to AF due to epicardial adipose filtration has been demonstrated in obese dogs with or without frequent atrial pacing to induce AF. It is noteworthy that epicardial adipose infiltration was detected after frequent atrial pacing to induce AF even in non-obese animals and correlated with interstitial fibrosis [79]. Lower negative resting membrane potential, lower action potential amplitude, and longer repolarization time due to disturbance of potassium and calcium transmembrane currents in cardiomyocytes, associated with EAT, may explain the predisposition to arrhythmias due to fatty infiltration [80].

Decrease in weight and volume of epicardial adipose tissue for the control of cardiac arrhythmias in humans

Given the evidence for the role of EAT as a source of secretome with a proarrhythmic effect, it is hypothesized that its regression can reduce the risk of arrhythmia. It has been established that the volume of EAT decreases with weight loss achieved through lifestyle modification or surgical intervention. The Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research registry demonstrated an association between weight loss and EAT volume among participants who achieved body weight loss by more than 5% [81]. However, a decrease in body weight by less than 5% was not accompanied by significant changes in EAT volume [82]. Specific weight loss programs using low-calorie diets in obese patients have demonstrated a similar

pattern of EAT changes [83, 84]. As a result, a 6-month diet with an energy value of 900 kcal/day induced a decrease in body weight by an average of 20% and a decrease in EAT thickness by 32% [83]. Restriction of caloric intake to 1,547 kcal/day for 12 weeks was sufficient for the regression of visceral abdominal obesity, a significant (by 11.0%) decrease in body weight, and a decrease in EAT thickness (by 17.2%). In obese individuals, aerobic exercise lasting an hour achieving 60%–70% of the maximum heart rate three times per week for 12 weeks resulted in a decrease in EAT thickness by 9% [84]. It was established that weight loss after bariatric surgery reduced the volume of EAT by an average of 24%, although the effect varied depending on the method of intervention (only 14.6% after creation of Roux-en-Y gastric bypass and only 5.3% after sleeve gastrectomy) [85].

A decrease in the tendency toward cardiac arrhythmias as a result of weight loss has been established. In a randomized controlled trial, caloric restriction and low-intensity physical exercises led to greater weight loss than lifestyle recommendations with a 15-month follow-up (14.3 kg vs. 3.6 kg). It is noteworthy that patients who restricted calorie intake and exercised had a lower burden and severity of AF symptoms than in the control group [86]. A decrease in the burden of arrhythmia has been reported with follow-up for up to 2 yr after catheter ablation of AF. For example, aggressive correction of cardiometabolic risk factors was associated with arrhythmia-free survival rate in 32.9% and 87% of patients with a history of single and repeated ablations, respectively, compared with 9.7% and 17.8% of patients who received standard treatment [87].

In the LEGACY study, in patients with a baseline BMI of 27 kg/m^2 or higher, the relationship between weight loss and arrhythmia-free survival during a 5-yr follow-up of AF patients was noted. Compared with loss of less than 10% of body weight, loss of more than 10% of body weight was associated with a six-fold higher probability of arrhythmia-free survival. Patients who consistently and gradually lost weight experience the greatest improvement, while body weight fluctuations of more than 5% after lifestyle changes created a 2-fold higher risk of AF [88]. In order to assess the progression and possibility of reversal of AF with sustained weight loss, a group of the LEGACY project patients was further examined in the REVERSE-AF project. It turned out that in 88% of patients with weight loss of more than 10%, persistent AF transformed into paroxysmal AF, compared with 49% and 26% in groups that achieved weight loss of 3%–9% and less than 3%, respectively [89]. Given that EAT volume regresses with weight loss, lifestyle modification is a noninvasive and inexpensive intervention that enables to control cardiac arrhythmias.

Although there is convincing evidence for the benefit of weight loss in AF patients, it is not clear whether patients with ventricular arrhythmias will receive similar benefits. A meta-analysis involving 7,197 patients demonstrated QT interval prolongation and greater QT variance in overweight and obese patients compared with normal weight individuals, but these values decreased on average by 25.77 ms and 13.47 ms, respectively, with weight loss [90]. Given that the QT interval and QT variance are indices of risk for ventricular arrhythmia [91], the benefit of weight loss may probably extend to ventricular arrhythmias, although this remains to be established.

ADDITIONAL INFORMATION

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Rewiew

Endocardial Electrophysiological Study in Clinical Practice in Patients with Bradysystole and Conduction Rhythm Disorders: a review

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The article demonstrates modern diagnostic capabilities of endocardial electrophysiological examination in cardiological patients with bradysystole and conduction disturbances that allow adequate assessment of the clinical situation. We made an attempt to systematize current indications for an electrophysiological study in this category of patients based on the analysis of several current recommendations.

Keywords: endocardial electrophysiological research; conduction disorders; weakness of the sinus node; atrioventricular block; distal blockade; two-beam blockade.

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Обзорная статья

Эндокардиальное электрофизиологическое исследование в клинической практике у пациентов с брадисистолией и нарушениями ритма проводимости (обзор)

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В статье продемонстрированы современные диагностические возможности эндокардиального электрофизиологического исследования у пациентов кардиологического профиля с брадисистолией и нарушениями проводимости, позволяющими адекватно оценить клиническую ситуацию. Нами была сделана попытка систематизировать текущие показания к проведению электрофизиологического исследования у этой категории пациентов на основании анализа нескольких текущих рекомендаций.

Ключевые слова: эндокардиальное электрофизиологическое исследование; нарушения проводимости; слабость синусового узла; атриовентрикулярная блокада; дистальная блокада; двухпучковая блокада.

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ЭКО•ВЕКТОР

The widespread implementation of endocardial electrophysiological studies (endoEPS) in clinical practice has made it possible to examine the pathophysiological mechanisms of the development of cardiac arrhythmias and contribute to the emergence of new technologies and highly effective treatment methods [1–3].

Nowadays, endoEPS is a routine in interventional treatment, such as radiofrequency ablation, and evaluation of its results in patients with paroxysmal supraventricular and ventricular tachyarrhythmias [4, 5].

Recent evidence revealed that endoEPS with the implementation of a programmed ventricular pacing protocol for the induction of ventricular arrhythmias is a highly sensitive and highly specific tool for the stratification of sudden cardiac death risk in certain patients, specifically those with a history of acute myocardial infarction with preserved or moderately reduced left ventricular ejection fraction and patients with hypertrophic cardiomyopathy [6–8].

EndoEPS may be of great importance in patients with brady–asystolic disorders. Their pathogenesis is based on two main causes or a combination thereof, namely, an impairment of the automatic function of the sinus node and/or a disorder of the conduction of electrical impulses at various levels of the cardiac conduction system. Adequate implementation of the endoEPS protocol and the correct interpretation of the results are extremely important for the selection of the treatment approach for these patients.

This paper summarizes data on the role of endoEPS in patients with bradyarrhythmias and presents current indications for its execution.

Sinus node dysfunction

Bradysystolic rhythm and conduction disorders are most commonly caused by diseases and/or conditions characterized by the dysfunction of the sinoatrial node (SAN). Electrocardiogram (ECG) signs of SAN dysfunction are as follows:

- Pronounced sinus bradycardia with a heart rate of < 50 per 1 min during wakefulness.
- Sinus arrest, which is a permanent impairment of the formation of the sinus rhythm (in contrast to sinus pauses, which are the result of a transient impairment of an impulse formation in the SAN and last for 2–3 s). Unfortunately, there is no clearer differentiation between these conditions.
- SA blockade.
- Bradycardia–tachycardia syndrome (Short–Rubinstein syndrome) represented by a combination of sinus bradycardia and paroxysms of both supraventricular and ventricular tachyarrhythmias [9, 10].
- Chronotropic incompetence.

Transient and irreversible disorders of SAN function should be distinguished. The former is a result of autonomic regulation disorders (parasympathicotonia syndrome) following exposure to chemical agents (most often medications), and electrolyte disorders and can emerge in acute myocardial ischemia or inflammatory myocardial diseases.

Various diseases can cause irreversible changes in SAN function, such as coronary heart diseases, post-inflammatory changes in the myocardium, mechanical damage to the SAN during heart surgery, and amyloidosis. Idiopathic SAN dysfunction may be caused by sclerodegenerative processes in the conduction system of the heart, decreasing the number of specialized SAN cells and their replacement with fibrous and adipose tissues [9].

If SAN dysfunction is accompanied by clinical symptoms, such as syncope, presyncope, angina pectoris, hypotension, and increase in signs of cardiac failure, this situation is usually called sick sinus syndrome (SSS).

Determining the leading pathogenetic mechanism is extremely important for the development of SSS and determining prognosis and treatment. A specific electrocardiographic type of SAN dysfunction has certain clinical signs and diagnostic and prognostic criteria. If the disease is accompanied by clinical symptoms, as a rule, implantation of a permanent electric cardiac pacemaker (ECP) is necessary.

The endoEPS specificity in diagnosing SAN dysfunction is high, with 75%–95%, whereas its sensitivity is only 50% [11–14]. An increase in procedural sensitivity is achieved when a drug autonomous blockade is employed within the protocol (0.0175 mg/kg of metoprolol or 0.02 mg/kg of propranolol + + 0.04 mg/kg of atropine all administered intravenously) [15, 16].

The main parameters used to characterize the sinus node function during endoEPS are the sinus node recovery time (SNRT) and corrected sinus node recovery time (cSNRT) (Fig. 1). Asynchronous ECP with a frequency exceeding the spontaneous rhythm by 10% is performed for 60 s to determine the above parameters from the upper lateral parts of the right atrium. After the cessation of stimulation, the duration of the post-stimulation pause is measured, i.e., the interval from the last extrastimulus to the complex following it, illustrating spontaneous activation in the upper lateral parts of the right atrium, caused by SAN depolarization (normal value, < 1500 ms). The cSNRT is calculated from the difference between the duration of the post-stimulation pause and the average length of the sinus rhythm cycle (CL) before the start of the ECP (normal value, < 500–550 ms). The ratio of SNRT to the CL should normally be < 1.5 (in percentage terms, < 150%) [17–20]. The evaluation of the sinoatrial conduction time (SACT) (normal value, < 120 ms) according to the Strauss and Narula method is also necessary [17–20].

Currently, endoEPS is rarely performed in patients suspected of SSS because the results of noninvasive research methods (i.e., ECG and Holter monitoring of ECG) are quite sufficient to establish a diagnosis. Table 1 presents the indications for endoEPS in patients with SAN dysfunction.

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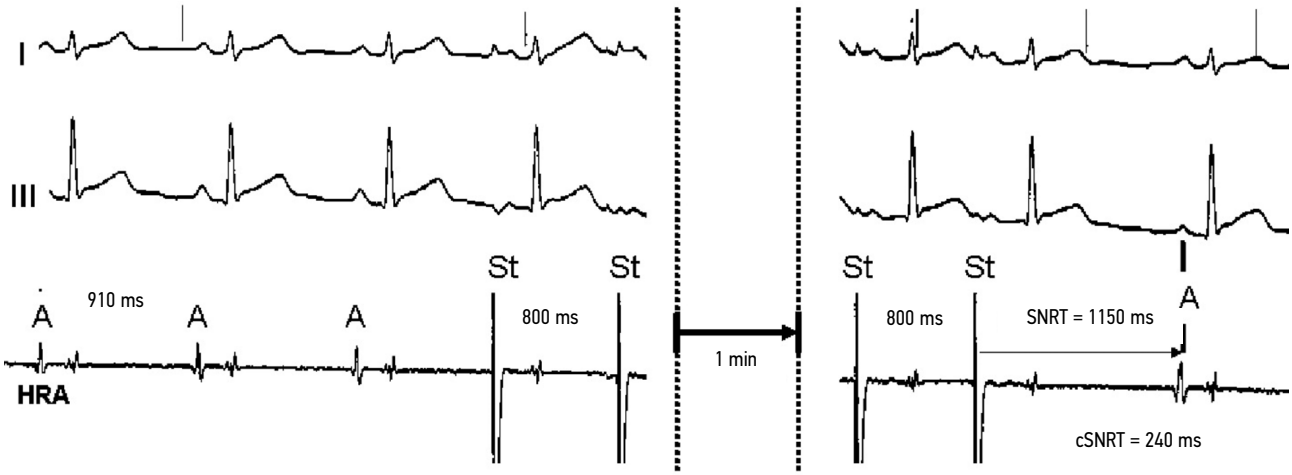

Fig. 1. Determination of SNRT and cSNRT during endoEPS. The leads I and III of the body-surface ECG and intracardiac recording channel from the upper lateral segments of the right atrium are presented from top to bottom. Against the sinus rhythm, there is the A–A interval of 910 ms (left part). After an asynchronous atrial ECP with a cycle length of 800 ms for 1 min, the SNRT is determined as the interval between the last stimulation artifact (St) and the first EG spike on the HRA channel, which is 1150 ms (right part). To calculate the cSNRT, the difference between the SNRT value (1150 ms) and the spontaneous cycle length before the start of the ECP (910 ms) is determined, which is 240 ms in our example

Table 1. Indications for endoEPS in patients with SAN dysfunction [5].

Indication class	Indications	Reference
Class I	Patients in whom a direct relationship between the documented bradycardia and clinical symptoms could not be established using noninvasive diagnostic methods.	[21]
Class II	1. To determine the mechanism of SAN dysfunction (organic pathology, dysfunction of the autonomic nervous system, and effect of drugs) for the selection of the treatment approach in patients with sinus bradyarrhythmias detected on ECG.	[21]
	2. To assess the possibility of induction of other arrhythmias as a potential cause of clinical symptoms in patients with documented SAN dysfunction (e.g., ventricular or supraventricular arrhythmias).	[21]
Class III	1. Routine endoEPS protocol before ECP implantation in patients with documented asystole ⩾3 s, in whom an association between symptoms and clinical bradyarrhythmia was established.	[22, 23]
	2. Routine endoEPS protocol before ECP implantation in patients with documented asystole ⩾6 s.	[22, 23]
	3. Asymptomatic patients with sinus bradyarrhythmias or sinus pauses registered only during sleep, including sleep apnea.	[21]

AV conduction disorders

Atrioventricular (AV) blockade is a disorder of the conduction of excitation from the atria to the ventricles. Therapeutic and diagnostic measures are needed in patients with impaired AV conduction, such as clinical symptoms due to the blockade of conduction and localization of the conduction blockade.

During endoEPS, the impulse conduction function is evaluated by measuring the intervals between spikes indicating the cardiac electrical activity in various parts of the myocardium. Simultaneous registration of the 12 leads of the body-surface ECG and EG (from the region of the upper lateral parts of the right atrium, atrioventricular bundle, venous coronary sinus, and right ventricle apex) based on the measurement of intervals enables the assessment of the sinus impulse conduction to various segments of the heart.

Table 2 presents the reference values of the main intervals and their electrophysiological value [9, 10].

Determining the localization of AV conduction disorders is essential. Generally, atrioventricular conduction disorders that have arisen in the proximal parts of the AV connection (suprahisian blockade) are usually not a threat to patients because the replacement rhythm of the "second-order" pacemakers located in the AV connection will provide a heart rate within 50–60 beats/min. Moreover, the block that occurs in the His–Purkinje system (intra- and infrahisian block) is considered life-threatening because "third-order" pacemakers located in the fibers of the His–Purkinje system can provide a heart rate of no more than 20–40 beats/min [9, 10].

Table 2. Main electrophysiological intervals.

Interval	Denotation	Reference values
AHRA–AHIS	Right atrial conduction time	⩽ 50 ms
P–AHIS	Conduction time from the SAN to the AV connection	20–50 ms
A–H	Activation time between the atria and the atrioventricular bundle. This interval indicates the rate of conduction along the compact part of the AV connection	50–140 ms
Atrioventricular bundle EG (H)	Atrioventricular bundle conduction time	⩽ 25 ms
H–V	Conduction time on the His–Purkinje system	30–55 ms
P–Q	Conduction time from the SAN to the ventricles. The duration of this interval is determined by three components: P–Q = (P–AHIS) + (A–H) + (H–V)	120–200 ms
QRS	Ventricular myocardial activation time	⩽ 90 ms

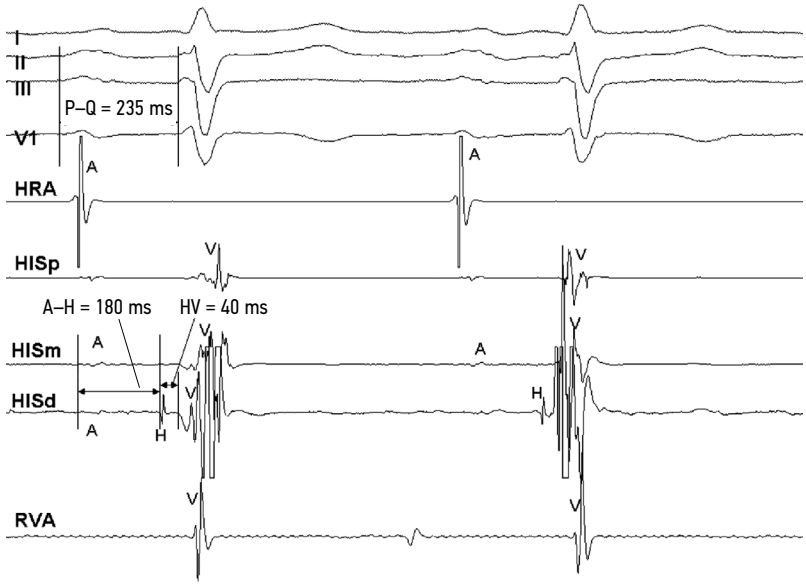

Fig. 2. Degree 1 AV block (proximal or suprahisian). The leads I, II, III, and V_1 of the body-surface ECG, intracardiac endograms from the upper lateral segments of the right atrium (HRA), atrioventricular bundle region (HISp, HISm, and HISd), and right ventricular apex (RVA), recorded against the sinus rhythm, are presented from top to bottom. According to the body-surface ECG, degree 1 AV block is diagnosed (P–Q interval of 235 ms). An analysis of the intervals obtained during the registration of intracardiac EG reveals that AV conduction impairments occur in the proximal parts of the AV connection (A–H interval of 180 ms), whereas no conduction disorders are registered in the distal parts of the AV connection (H–V interval of 40 ms)

Proximal (suprahisian) AV block. The most common mechanism for the development of proximal AV block is an increase in decremental impulse conduction in the AV node. Conduction disorders in the AV node (suprahisian block) often occur in the acute stage of myocardial infarction and active phase of the inflammatory process of the myocardium, when patients are taking drugs such as cardiac glycosides, beta-blockers, calcium antagonists, and antiarrhythmic drugs. Since the blood supply to the AV connection originates from the territory of the right coronary artery, acute coronary syndrome resulting from impaired coronary blood flow in this artery is often complicated by proximal AV block. When coronary blood flow is restored, conduction in the AV connection often resumes. However, a hemodynamically significant symptomatic bradycardia following proximal (suprahisian) AV conduction disturbances requires implantation of temporary ventricular ECP.

Distal (intra- and infrahisian) AV block. Ischemia and myocardial infarction resulting from impaired blood flow in the left anterior descending artery, which supplies blood to the His–Purkinje system, often cause a transient distal block. In addition, any inflammatory process in the myocardium may be accompanied by inflammation in the distal parts of the cardiac conduction system.

However, unlike proximal AV conduction disorders, the distal block is most believed to be often a manifestation of a chronic and progressive pathological process.

The level of AV conduction disturbance cannot be determined based on the ECG analysis, and only the registration of intracardiac EG from the atrioventricular bundle region during endoEPS can finally answer this question. If P–Q interval elongation on the body-surface ECG occurs due to an increase in the A–H interval, then it is referred to suprahisian blockade (Fig. 2). With infrahisian

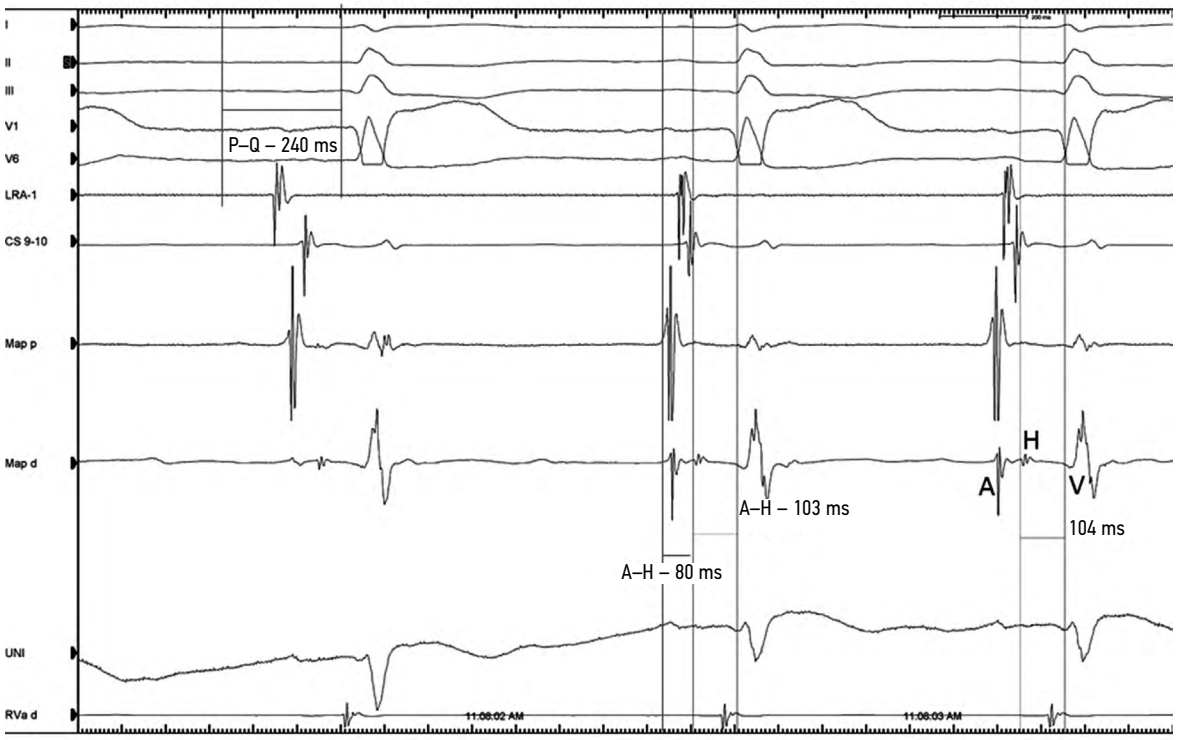

Fig. 3. Distal degree 1 (infrahisian) block and complete left bundle branch block. Leads I, II, III and V_1 of the body-surface ECG, intracardiac endograms from the upper lateral segments of the right atrium (LRA), proximal parts of the coronary sinus (CSp), mapping electrode positioned in the area of the atrioventricular bundle (MAPp and MAPd), recorded against the sinus rhythm, are presented from top to bottom. According to the body-surface ECG, degree 1 AV block (P–Q interval of 230 ms) and left bundle branch block are diagnosed. An analysis of the intervals obtained during the registration of intracardiac EG indicates that AV conduction disorders occur in the distal parts of the AV connection (V–H interval of 103 ms), whereas no conduction impairment is noted in the proximal parts of the AV connection (A–H interval of 80 ms).

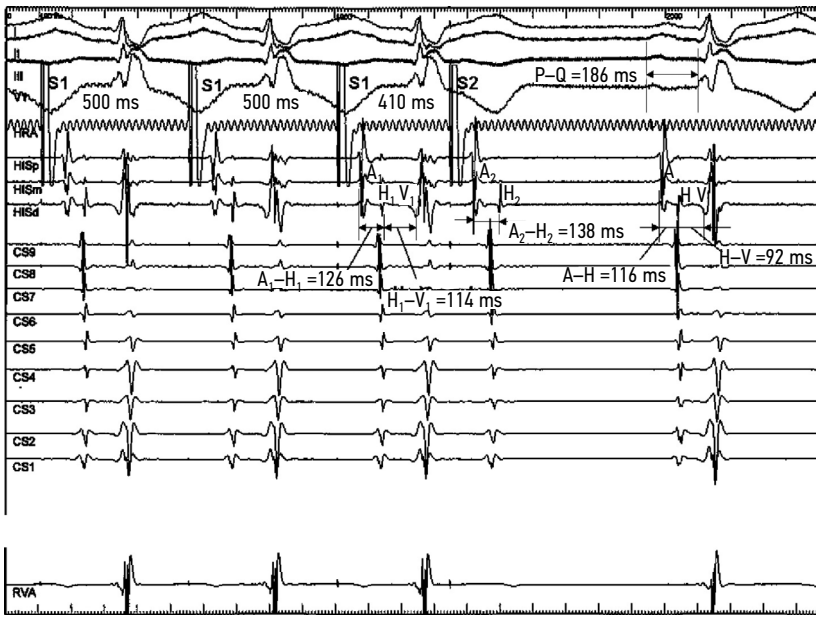

Fig. 4. Distal block with programmed stimulation. Leads I, II, III, and V_1 of the body-surface ECG, intracardiac endograms from the upper lateral parts of the right atrium (HRA), area of the atrioventricular bundle (HISp, HISm, and HISd), coronary sinus (from the proximal pair (CS_9) to the distal part (CS)), and right ventricular apex (RVA) are presented from top to bottom. Against the sinus rhythm, the P–Q interval is 186 ms, there are signs of right bundle branch block, and signs of infrahisian disorders in AV conduction are detected (H–V interval of 92 ms) (complex in the right part of the figure). During the programmed atrial ECP with a base cycle length of 500 ms and the introduction of S2 with a programmed extra stimulus delay of 410 ms, an atrioventricular conduction block is verified in the distal parts of the conduction system of the heart (after the A_2 spike, the H_2 spike is verified without the subsequent appearance of the V_2 spike characterizing myocardial depolarization of ventricles)

Table 3. Indications for endoEPS in patients with AV conduction disorders [5]

Indication class	Indications	Reference
Class I	No	
Class II	1. In patients with degree 2 AV block, Mobitz I, and in patients with type 2:1 degree 2 AV block, an endoEPS protocol is justified to determine the localization level of the blockade (distal or proximal).	[24]
	2. Patients suspected of transient AV block, endoEPS may be considered.	[25]
	3. Patients with extrasystoles from the AV connection, simulating degrees 2 and 3 AV block on the ECG (so-called pseudo AV block).	[21]
Class III	1. Before ECP implantation in patients with complete AV block, high-grade AV block, and degree 2 AV block, Mobitz II.	[22]
	2. Isolated degree 1 AV block in the absence of bundle branch block.	
	3. Asymptomatic patients with AV block that may be associated with increased vagal tone (e.g., nocturnal degree 2 AV block and Mobitz I.	[21]

Table 4. Indications for endoEPS in patients with disorders of His bundle branch conduction and intraventricular conduction [5]

Indication class	Indications	Reference
Class I	Patients with unexplained syncope and bifascicular block.	[22, 31]
Class II	1. Asymptomatic patients with bifascicular block, who are being considered for pharmacological therapy that may cause cardiac conduction abnormalities or AV block.	[21]
	2. A complete endoEPS protocol (evaluation of sinus node function, programmed atrial and ventricular stimulation, and carotid sinus massage) is mandatory for the correct diagnostics of the cause of syncope in patients with a bifascicular block.	[32–35]
Class III	1. Before ECP implantation in patients with complete AV block, high-grade AV block, and degree 2 AV block, Mobitz II.	
	2. Isolated degree 1 AV block in the absence of bundle branch block.	
	3. Asymptomatic patients with AV block that may be associated with increased vagal tone (e.g., nocturnal degree 2 AV block, Mobitz I).	

blockade, AV conduction impairment occurs following an increase in the duration of the H–V interval (Fig. 3).

Generally, endo-EPS is not required in the selection of the approach for the treatment of patients with obvious AV conduction disorders. However, in some cases, the patient may have clinical symptoms associated with conduction disorders, which do not correspond to the changes verified on the body-surface ECG, including during long-term ECG monitoring. In this situation, endoEPS becomes the defining diagnostic procedure.

The value of antegrade effective refractory period in the His–Purkinje system exceeding 400 ms is the next sign of latent AV conduction disorders (Fig. 4). Most electrophysiologists believe that this conduction disorder reflects a far advanced pathological process in the distal parts of the cardiac conduction system and requires a permanent ECP.

The indications for endoEPS in patients with AV conduction disorders are presented in Table 3.

Conduction disorders along the bundle branches and intraventricular conduction impairments

Bundle branch and His–Purkinje conduction disorders tend to progress with subsequent risk of developing complete AV block. In this regard, the endoEPS protocol aims to identify the category of patients with a high risk of this scenario and subsequently making a decision on the need for ECP implantation.

The endoEPS protocol primarily evaluates the conduction function in the remaining fibers of the conduction system based on H–V interval assessment. In patients with a bifascicular block, an H–V interval of 33–55 ms indicates normal conduction through the structures of the conduction system, whereas its increase to ⩾ 55 ms implies conduction disorders in the remaining structures of the conduction system of the heart. After 4 years of follow-up with an initial H–V interval < 70 ms, the probability of a complete AV block is ⩽ 4%. If the H–V interval ranges from 70 to 100 ms, then complete AV block develops in 12% of the patients. At an H–V interval of > 100 ms, the probability of a complete AV block is 24% [26]. Currently, ECP implantation is indicated in patients with syncope and bifascicular block with an H–V interval of ⩾ 70 ms [26].

Table 4 presents the indications for endoEPS in patients with conduction disorders along the His bundle branch and intraventricular conduction.

In addition to determining the initial H–V interval during the endoEP protocol, pharmacological testing is performed using class IA antiarrhythmic drugs (ajmaline, disopyramide, or novocainamide) or class IC drugs (flecainide).

Table 5. Algorithm for the use of pharmacological testing (novocainamide) during endoEPS in patients with impaired conduction along the bundle branches and impaired intraventricular conduction [5]

H–V interval	Pharmacological testing	Reference
Symptomatic patients (history of syncope)		
H–V = 35–55 ms	Pharmacological testing can be useful	[40]
H–V = 55–69 ms	Pharmacological testing can be useful	[40]
H–V ⩾ 70 ms	ECP implantation without pharmacological testing	[26]
Asymptomatic patients (no syncope and endoEP was performed for other reasons)		
H–V = 35–55 ms	Without further pharmacological testing	
H–V = 55–69 ms	Without further pharmacological testing	
H–V = 70–100 ms	Further follow-up	[26]
H–V > 100 ms	ECP implantation without pharmacological testing	[26]

Table 6. Indications for endoEPS in patients with conduction disorders after TAVR [5]

Indication class	Indications	Reference
Class I	No	
Class II	1. Recently developed bifascicular block (permanent ECP implantation is indicated if the H–V interval is ⩾65 ms).	[42]
	2. Bifascicular block before TAVR (implantation of a permanent ECP is indicated if the H–V interval after TAVR increases by ⩾13 ms).	[43]
Class III	Patients who develop complete AV block after TAVR (ECP implantation is indicated).	

A significant prolongation of the H–V interval or development of a high-degree AV block during a pharmacological test may predict the development of complete AV block and is the basis for deciding on ECP implantation [27–30]. Pharmacological testing is generally used in patients with syncope and bifascicular block if the baseline H–V interval is < 70 ms or transient (paroxysmal) high-degree/complete AV block is the suspected cause of syncope [36–39].

The diagnostic value of the endoEPS protocol using pharmacological testing in relation to the risk of complete AV block is ⩾80% [22]. However, a negative endoEPS result does not exclude the presence of transient (paroxysmal) high-grade AV block, ventricular and supraventricular tachyarrhythmias, carotid sinus syndrome, and SSS as possible causes of syncope. Thus, the implementation of a full endoEPS protocol, including the evaluation of the sinus node function and the implementation of programmed stimulation of the atria and ventricles, is mandatory in these patients.

Table 5 presents an algorithm for the use of pharmacological testing (novocainamide) during endoEPS in patients with impaired conduction along the bundle branches and impaired intraventricular conduction.

Conduction disorders after transcatheter aortic valve replacement (TAVR)

After TAVR, hemodynamically significant AV conduction disorders requiring ECP implantation develop in approximately 20% of the patients [41]. In some cases, the bifascicular block is registered in some patients after TAVR, which requires clinical interpretation regarding the need for ECP implantation.

Since TAVR is a relatively new treatment method, prospective follow-up data for these patients with respect to the clinical course of emerging conduction disorders is limited. At present, questions remain regarding the need for ECP implantation in the event of an isolated bifascicular block or the emergence of bradycardia (without complete AV block) in patients with permanent atrial fibrillation). In this regard, endoEPS in cases of ECG signs of conduction impairment after TAVR appears to be of decisive importance when choosing further treatment approach.

After TAVR, an H–V interval of > 65 ms and an increase in the H–V interval by 13 ms compared with baseline values (before TAVR) have a high predictive value in relation to the development of complete AV block [42, 43].

Table 6 presents the indications for endoEPS in patients with conduction disorders after TAVR.

CONCLUSIONS

EndoEPI is a unique diagnostic method that enables identifying and determining the mechanisms of arrhythmias in patients with wide range of cardiological conditions. In some patients with symptoms of bradyarrhythmias and/or conduction disorders, endoEPS is the only diagnostic tool used to identify the hidden mechanisms of their occurrence, verify their transient nature, and determine the degree of their malignancy. Ultimately, the results of assessing the function

of SAN automatism and conduction in the structures of the conduction system of the heart, obtained during endoEPS, in some cases can be decisive for an adequate clinical assessment of patients, risk stratification of sudden cardiac death, and selection of the optimal approach for further treatment.

ADDITIONAL INFORMATION

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

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Research article

Correction of Potentially Modifiable Components of Metabolic Syndrome for the Primary Prevention of Atrial Fibrillation in Comorbid Patients with Premature Atrial Complexes

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AIM: The study aimed to evaluate the influence of the correction of potentially modifiable risk factors for the development of atrial fibrillation (AF) as primary prevention of AF in patients with metabolic syndrome (MS) and premature atrial complexes (PAC).

MATERIALS AND METHODS: We monitored 856 MS patients with PAC, aged 58–72 (mean age, 66.4 ± 0.7) years, in the north-western region of the Russian Federation. A 5-year risk of AF was calculated in all patients after the examination by determining the potential prognostic time range for Af development and its index of probable occurrence ($R_{CHARGE-AF}$) using the CHARGE-AF model. The correction of potentially modifiable MS components and risk factors for AF development (smoking cessation, elimination of physical inactivity, etc.) until their target values were achieved was offered to all patients. The follow-up endpoint was the preservation of sinus rhythm or AF registration.

RESULTS: All patients with MS were distributed into three groups. Group I consisted of 557 (65.07%) patients with incomplete correction of risk factors, and group II included 93 (10.86%) who achieved the target values of all potentially modifiable factors for AF development. The control group included the remaining patients without quantitative and qualitative changes in the dynamics AF predictors. No significant differences were found between the groups in terms of sex, age, concomitant diseases, and risk factors for AF. The achievement of the target values of the main MS components, including body mass index and/or waist circumference, correlated with the performance of regular aerobic exercises (odds ratio [OR] = 8.9), adherence to a diet (OR = 7.5), duration of MS diagnosis < 20 years before the start of correction (OR = 12.8), and intake of a glucagon-like peptide-1 receptor agonist (Liraglutide) (OR = 5.4).

In the control group, group I, and group II, AF development did not differ significantly and was registered in 192 (93.20%), 491 (88.15%), and 79 (84.95%) patients ($p > 0.05$), respectively.

CONCLUSIONS: In MS patients with PAC and a high 5-year risk of AF, the correction of potentially modifiable risk factors for AF development, as its primary prevention, is ineffective. The determination of the $R_{CHARGE-AF}$ index in MS patients with PAC in dynamics indicates the efficiency of the correction of potentially modifiable risk factors for AF development, but it does not determine the degree of the risk of its occurrence.

The authors declare no conflict of interest.

Keywords: primary prevention of atrial fibrillation; correction of potentially modifiable components of the metabolic syndrome.

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УДК 61

Научная статья

Роль коррекции потенциально модифицируемых компонентов метаболического синдрома для первичной профилактики фибрилляции предсердий у коморбидных больных с преждевременными предсердными комплексами

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Цель исследования — оценить влияние коррекции потенциально модифицируемых факторов риска развития фибрилляции предсердий (ФП) в качестве первичной профилактики этой аритмии у пациентов метаболическим синдромом (МС) с внеочередными предсердными комплексами (ВПК).

Материал и методы. Наблюдалось 856 больных МС с ВПК Северо-Западного региона РФ в возрасте от 58 до 72 лет (в среднем 66,4 ± 0,7 года). У всех пациентов после обследования был рассчитан пятилетний риск развития ФП путем определения потенциально-прогностического временного диапазона ее развития и индекса вероятного возникновения этой аритмии ($R_{CHARGE-AF}$), используя модель CHARGE-AF. Всем больным предлагалась коррекция потенциально модифицируемых компонентов МС и факторов риска развития ФП (отказ от табакокурения, устранение гиподинамии и т.д.) до достижения их целевых значений. Конечной точкой наблюдения считали сохранение синусового ритма или регистрация ФП.

Результаты. Все больные МС были распределены на три группы. I группу составили 557 (65,07 %) пациентов с неполной коррекцией, во II группу вошли 93 (10,86 %) — с достигнутыми целевыми значениями всех потенциально модифицируемых факторов формирования ФП. Остальные пациенты без количественного и качественного изменения в динамике наблюдения предикторов развития этой аритмии были включены в контрольную группу. По полу, возрасту, сопутствующим заболеваниям, факторам риска развития ФП достоверного различия между группами выявлено не было. Достижение целевых значений основных компонентов МС, включая индекс массы тела и/или окружность талии, коррелировало с выполнением регулярных аэробных физических нагрузок [отношение шансов (ОШ) = 8,9], соблюдением диеты (ОШ = 7,5), продолжительностью регистрации МС менее 20 лет до начала коррекции (ОШ = 12,8), использованием агониста рецептора глюкагоноподобного пептида-1 (лираглутида) (ОШ = 5,4).

В контрольной, I и II группах развитие ФП достоверно не различалось и наблюдалось у 192 (93,20 %), 491 (88,15 %) и 79 (84,95 %) пациентов ($p > 0,05$) соответственно.

Заключение. У больных МС с ВПК и высоким пятилетним риском развития ФП коррекция потенциально модифицируемых факторов риска развития ФП, используемая в качестве ее первичной профилактики, неэффективна. Определение индекса $R_{CHARGE-AF}$ у больных МС с ВПК в динамике отражает эффективность коррекции потенциально модифицируемых факторов риска развития ФП, но он не определяет степень риска ее развития.

Ключевые слова: первичная профилактика фибрилляции предсердий; коррекция потенциально модифицируемых компонентов метаболического синдрома.

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ЭКО•ВЕКТОР

BACKGROUND

The combination of metabolic syndrome (MS) components, such as abdominal obesity, arterial hypertension, diabetes mellitus, and dyslipidemia, determines the potential cardiometabolic risk for the occurrence of various cardiovascular diseases, including atrial fibrillation (AF) [1–5]. The effect of the correction of potentially modifiable MS components has been studied quite well in patients with existing AF (paroxysmal and persistent), and in relation to the development of primary AF, retrospective assessments of the change in the risk of its occurrence, depending on the achievement of target values, such as the body mass index (BMI), have been conducted [1, 2, 5–8].

Hypothetically, the correction of potentially modifiable MS components and other risk factors for AF development in patients with premature atrial complexes (PAC) will result in a decrease in the primary occurrence of AF in high-risk cases. However, no prospective studies have investigated the correction of potentially modifiable risk factors for AF development as primary prevention of AF in MS patients with PAC.

This study aimed to evaluate the effect of the correction of potentially modifiable risk factors for AF development, as primary AF prevention, in MS patients with PAC.

MATERIALS AND METHODS

We monitored 856 MS patients with PAC, aged 58–72 (mean age, 66.4 ± 0.7) years, in the north-western region of the Russian Federation (St. Petersburg, Leningrad region, etc.). There were 398 (46.50%) men and 458 (55.50%) women ($p > 0.05$).

The criteria for inclusion in the study were determined in all patients after clinical, laboratory, and echocardiographic examinations, daily electrocardiogram (ECG), monitoring registration of a signal-averaged ECG, etc. The methods and instruments used for determining the contractility and dysfunction of the left ventricle, volume of cardiac chambers, duration of FiP-P, Pd, prognostic index (PI) for AF development by analyzing PAC, criteria for diagnosing MS, physical inactivity, heart failure grade (6-minute walk test), and mean arterial pressure (BP) are presented in previous studies [7, 9–11].

Based on the analysis of atrial ectopias, PI was calculated as follows: PI = (A ÷ B) × (C ÷ N), where A and B are the duration of FiP-P and Pd determined from signal-averaged atrial ECG data and 24-h ECG monitoring, respectively (ms), C is the linear deviation of the corrected coupling interval in more than 20 premature atrial contractions, and N is the number of extra supraventricular complexes used for the study, expressed as their number per hour [10, 11]. To avoid false-positive results of PI determination when calculating it, the corrected pre-ectopic interval of PAC was analyzed in at least 20 supraventricular ectopias [10, 11].

PI was used because the detection of atrial ectopia determines the potential risk of primary AF in patients with MS given its uncertain implementation in time [3–5, 7]. The total number of extrasystoles, for example, per day of monitoring does not reflect the risk degree of this arrhythmia [3–5, 7].

The 5-year risk for AF was determined when the FiP-P was ⩾135 ms with the FiP-P/Pd ratio of ⩽ 2.5 units [9, 10], followed by PI assessment during follow-up and calculation of the potentially predictive time range for AF development (PTRAF) [12]. Before determining PTRAF, PI was recorded 2–3 times with an interval of 1–3 months. If the PI value decreased in comparison with the initial data, the PTRAF (months) was calculated according to the previously proposed equation [12] $PTRAF = [PI_1 – 0.01] ÷ [PI_1 – (PI_2, PI_3, \text{etc.})] × I$, where PI_1 is the PI values after study 1; PI_2, PI_3, etc., are values of PI_2, PI_3, respectively, at studies 2, 3, and subsequent studies; 0.01 is the PI value at which spontaneous attacks of AF are registered [11, 12]; and I is the interval (months) between study 1 and subsequent (2–3, etc.) studies [12]. The accuracy of determining PTRAF was approximately 86% [10, 12].

The CHARGE-AF model [13] in patients followed up was used to determine the potential risk index for AF occurrence ($R_{CHARGE-AF}$) according to the following equation:

$$R_{CHARGE-AF} = 1 – 0.9718412736^{\exp[(\Sigma(K_1,K_2,K_3,K_4,K_5,K_6,K_7,K_8,K_9,K_{10},K_{11}) – 12.5815600]},$$

where $R_{CHARGE-AF}$ is the index of the potential risk of AF occurrence according to the CHARGE-AF system (units);
K_1 is the (age in years ÷ 5) × 0.5083;
K_2 is ethnicity (Caucasian/White: 1 × 0.46491);
K_3 is the (height in centimeters ÷ 10) × 0.2478;
K_4 is the (weight of the patient in kg ÷ 15) × 0.1155;
K_5 is the (systolic BP in mm Hg ÷ 20) × × 0.1972;
K_6 is the (diastolic BP in mm Hg ÷ 10) × 0.1013;
K_7 is current tobacco smoking (1 × 0.35931);
K_8 is the intake of antihypertensive drugs (1 × 0.34889);
K_9 is diabetes mellitus (1 × 0.2 to my knowledge, references 3666);
K_{10} is chronic heart failure (grades I–IV × 0.70127);
K_{11} is history of myocardial infarction (1 × 0.49659) [13]. A high 5-year risk of AF was considered at $R_{CHARGE-AF}$ values of ⩾ 0.72 units [13].

The inclusion criteria were as follow: sinus rhythm, detection of PAC ⩾100 of supraventricular extrasystoles per day of monitoring [8, 10, 11], chronic heart failure of grades I–II according to the New York Heart Association, absence of AF registration during at least 4–5 procedures of 1–3-day ECG monitoring at least one time per 1–2 weeks for 2–3 months, preserved left ventricular ejection fraction (LVEF) ⩾ 50% [10, 11], determination of 5-year PTRAF using PI [12], values of $R_{CHARGE-AF}$ of ⩾ 0.72 units [13], and informed consent to the examination and treatment [10, 11]. The exclusion criteria were as follows: myocarditis, cardiomyopathies, and other pathologies [10, 11].

Hypertension was diagnosed in 715 (83.53%) patients, diabetes mellitus in 528 (61.68%), chronic obstructive pulmonary disease in 196 (22.90%), a history of myocardial

infarction in 89 (10.40%), smoking in 524 (61.21%), and physical inactivity in 694 (81.07%).

The correction of MS components and other risk factors for AF was offered to all patients, such as smoking cessation, elimination of physical inactivity, etc. The target values for the correction of MS components included a decrease in BMI < 25 kg/m^2 and/or waist circumference of 80 cm and 94 cm or lower in women and men, respectively; BP of 130/80 mm Hg or lower; total cholesterol and triglyceride levels in the blood plasma of 5.2 mmol/L and 1.7 mmol/L or lower, respectively; plasma low-density lipoprotein cholesterol level of 3.0 mmol/L or lower; fasting blood glucose level of 5.8 mmol/L or lower; and increase in plasma high-density lipoprotein cholesterol level to 1.0 mmol/L or higher in men and to 1.2 mmol/L or higher in women [3–7, 14]. To correct MS components such as BMI and/or waist circumference, diet, regular aerobic exercises (lasting ⩾ 150 min per week), and smoking cessation were recommended, whereas antihypertensive drugs (indapamide, telmisartan, valsartan, etc.) and hypoglycemic and hypolipidemic agents (diet, metformin, empagliflozin, liraglutide, statins, etc.) were used to normalize BP, glucose levels, and blood lipids [6–8, 14]. Antiarrhythmic therapy was not used to eliminate PAC.

The efficiency of the correction of potentially modifiable MS components and risk factors for AF development was evaluated (points) using the equation K × D, where K is equal to "0" and "1" in the absence of correction and incomplete correction (not reaching the values of the "health passport" [6–8, 14], respectively, "2" is upon reaching the target values of the predictors of AF (units); and D is the duration of the corrected risk factors after their modification (months)).

Patients were followed up for 1–5 years. AF registration or maintenance of sinus rhythm was the endpoint of this study. Anticoagulants (dabigatran, rivaroxaban, etc.) were prescribed if AF occurs [1, 2]. All studies were conducted in sinus rhythm at least once every 1–2 months. The values of BMI, waist circumference, BP, and fasting blood glucose were recorded by medical staff. Patients performed daily pulse control independently at least two times a day, using, as a rule, automatic blood pressure monitors. If an irregular pulse was detected, an ECG was recorded on a smartphone or when visiting a family doctor's office, polyclinic, etc. [1, 6, 7, 15–17]. When AF (paroxysmal or persistent) appeared, the studies were performed after the relief of the first attack, and in the case of pharmacological cardioversion, these were performed after 5–7 half-lives of the antiarrhythmic drugs used to eliminate AF.

For statistical processing of the data, the mean values and their error ($M \pm m$), mean-square deviation (σ), 95% confidence interval of the mean values, Student's *t*-test, and X^2 test were used, and $p < 0.05$ was taken as a significant difference in the indicators. The normality of distribution of the quantitative indicators was assessed using the Kolmogorov–Smirnov test, and according to the ± 3σ rule (Gaussian distribution), Pearson's linear pairwise correlation and Spearman's rank correlation (for non-parametric indicators) (*r*) were used. Moreover, the comparison of two binary variables was evaluated by multivariate logistic regression with the determination of the odds ratio (OR). Statistica version 11.0 software was used.

The study was performed in accordance with Good Clinical Practice and the principles of the Declaration of Helsinki.

RESULTS

After inclusion in the study, PTRAF ranged from 6 to 12 months in 284 (33.18%) patients with MS, from 1 to 3 years in 255 (29.79%) patients, and from 4 to 5 years in the rest of the patients. Depending on the main MS component (BMI and/or waist circumference) modification, all patients were distributed into three groups, where group I consisted of 557 (65.07%) patients with an incomplete correction (1 point), and group II included 93 (10.86%) patients with achieved target values (2 points) of BMI and/or waist circumference. The control group included the remaining patients without correction (0 points) or with incomplete correction (1 point) of these components for no more than 2–3 months.

Upon study enrollment, a significantly shorter duration of MS registration before the start of correction was revealed in group II than in group I and control group (Table 1). Significant differences in other studied parameters (Tables 1, 2), as well as in sex, age, frequency of detection of hypertension, diabetes mellitus, chronic obstructive pulmonary disease, myocardial infarction, smoking, and physical inactivity, were not revealed between groups I and II and when compared with the control group.

In groups I and II (in group II to a greater extent), a significant decrease in BMI and/or waist circumference was found when compared with the control group, and the efficiency of correction of other indicators in these groups was comparable, approaching the target indicators (Table 3). The achievement of target values of BMI and/or waist circumference correlated with regular aerobic exercise (OR = 10.9), adherence to a diet (OR = 8.5), duration of MS registration < 20 years before correction (OR = 12.8), and intake of a glucagon-like peptide-1 receptor agonist (Liraglutide) (OR = 5.4).

After the examination, recurrent AF (paroxysmal and persistent) was registered in 192 (93.20%), 491 (88.15%), and 79 (84.95%) patients of the control group, group I, and group II, respectively ($p > 0.05$) (Fig. 1). Lethal outcomes, myocardial infarction, stroke, or other complications did not occur during follow-up.

In the control group, by the end of the predicted period of AF development or when it occurred, a significant decrease in LVEF, E/A ratio, mean BP, 6-minute walk test distance, and $R_{CHARGE-AF}$ and a significant increase in PACs and end-diastolic volume of the left atrium (EDVLA) index were found.

In group I, only a significant decrease in mean BP and $R_{CHARGE-AF}$ was found, whereas other indicators in these groups did not change significantly when compared with initial data (Table 2). In group II, AF development was noted despite a significant decrease in $R_{CHARGE-AF}$, mean BP, EDVLA index, and PAC and a significant increase in LVEF, E/A, and 6-minute walk test distance when compared with baseline data (Table 2). In all patients, the decrease in PI during follow-up was mainly due to a decrease in the variability of the PAC coupling interval (OR = 5.2), an increase in Pd (OR = 4.9) and, to a lesser extent, as a result of a change in the number of supraventricular extrasystoles (OR = 0.91).

Table 1. Clinical and instrumental indicators and PTRAF in groups I and II upon inclusion in the study[1]

Indicators	Control group *n* = 206	Group I *n* = 557	Group II *n* = 93
Age, years	66.9 ± 0.63 (58.4–74.7)	65.9 ± 0.36 (61.8–73.9)	65.9 ± 0.8 (57.7–69.8)
BMI, kg/m^2	36.4 ± 0.48 (30.3–41.4)	36.1 ± 0.32 (30.1–42.1)	35.8 ± 0.42 (31.5–39.4)
WC, cm	129.2 ± 1.5 (108–147)	131.4 ± 1.1 (110–152)	130.2 ± 1.9 (105–148)
BG, mmol/L	9.4 ± 0.4 (6.4–14.7)	9.1 ± 0.25 (6.3–13.9)	8.8 ± 0.8 (6.8–14.9)
TC, mmol/L	7.9 ± 0.1 (6.2–9.6)	8.1 ± 0.1 (6.5–10.7)	8.2 ± 0.2 (6.4–9.9)
LDLC, mmol/L	4.6 ± 0.2 (3.6–5.8)	4.8 ± 0.1 (3.8–6.2)	4.1 ± 0.2*♦ (3.2–5.6)
HDLC, mmol/L	1.0 ± 0.1 (0.7–1.4)	0.9 ± 0.1 (0.7–1.5)	1.1 ± 0.5 (0.8–1.4)
TG, mmol/L	2.5 ± 0.1 (1.5–3.4)	2.4 ± 0.1 (1.4–3.5)	2.6 ± 0.2 (1.7–4.4)
Duration of MS registration before correction, years	39.3 ± 0.8 (29–52)	38.7 ± 0.8 (27–54)	14.1 ± 1.1*♦ (8–20)
Potential period of time for the onset of primary AF, months	34.6 ± 2.1 (4–59)	35.2 ± 1.3 (6–58)	36.9 ± 3.2 (5–60)

Note: [1], above *M* ± *m*; below, 95% confidence interval of mean values; * significant difference in indicators when compared with the control group, ♦ group II compared with group I ($p < 0.05$). MS, metabolic syndrome; AF, atrial fibrillation; PTRAF, potentially predictive time range for AF development; BMI, body mass index; WC, waist circumference; BG, blood glucose; TC, total cholesterol; LDLC and HDLC, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol, respectively; TG, triglycerides.

Table 2. Clinical and instrumental indicators and $R_{CHARGE-AF}$ in groups I and II upon inclusion in the study (A) and by the end of the predicted period of AF development or when it occurs (B)[1]

Patient groups	Control group *n* = 206		Group I *n* = 557		Group II *n* = 93	
Indicators	A	B	A	B	A	B
LVEF, %	61.84 ± 0.67 (54–69)	54.01 ± 0.68† (46–62)	61.54 ± 0.32 (55–68)	60.38 ± 0.35 (52–70)	61.47 ± 0.89 (54–68)	68.35 ± 0.91† (59–77)
E/A, units	0.95 ± 0.02 (0.71–1.23)	0.78 ± 0.01† (0.61–0.95)	0.94 ± 0.01 (0.75–1.15)	0.96 ± 0.01 (0.84–1.08)	0.94 ± 0.01 (0.74–1.15)	1.07 ± 0.01† (0.92–1.21)
EDVLA index, ml/m^2	36.78 ± 0.25 (34–39)	41.93 ± 0.57† (35–46)	37.54 ± 0.24 (33–41)	37.53 ± 0.23 (34–41)	36.54 ± 0.24 (32–42)	31.53 ± 0.43† (27–38)
Number of PAC per hour	372 ± 6 (303–441)	598 ± 22† (326–887)	382 ± 3 (309–456)	371 ± 8 (189–564)	389 ± 11 (298–463)	342 ± 16† (259–418)
Average BP, mm Hg	117.1 ± 1.2 (103–131)	108.7 ± 0.9† (97–121)	118.1 ± 0.7 (102–132)	107.8 ± 0.5† (96–119)	118.9 ± 1.4 (104–131)	105.2 ± 1.3† (95–116)
6–minute walk test, meters	436.5 ± 6.7 (365–510)	375.7 ± 5.1† (315–436)	447.9 ± 6.3 (372–516)	442.7 ± 6.7 (368–518)	422.9 ± 7.3 (358–489)	546.5 ± 9.8† (445–648)
$R_{CHARGE-AF}$, units	0.82 ± 0.02 (0.73–0.91)	0.86 ± 0.01† (0.76–0.94)	0.81 ± 0.01 (0.74–0.92)	0.69 ± 0.01† (0.62–0.78)	0.83 ± 0.01 (0.79–0.92)	0.48 ± 0.01† (0.43–0.56)

Note: [1], above *M* ± *m*; below, 95% confidence interval of mean values, * significant differences in indicators when compared with the control group at $p < 0.05$, † initial data ($p < 0.05$). AF, atrial fibrillation; LVEF, left ventricular ejection fraction; E/A, ratio of the maximum blood flow rates through the mitral valve during left ventricular diastole (E) and atrial systole (A); EDVLA, end–diastolic volume of the left atrium; PAC, premature atrial complexes; BP, blood pressure; $R_{CHARGE-AF}$, prognostic index for AF development according to CHARGE–AF risk stratification.

Table 3. Efficiency of the correction of potentially modifiable components and predictors of AF development in groups I and II (points)[1]

Indicators	Control group *n* = 206	Group I *n* = 557	Group II *n* = 93
BMI	0.23 ± 0.21 (0–3)	22.15 ± 0.52* (12–34)	38.84 ± 3.02*♦ (12–70)
WC	0.21 ± 0.19 (0–3)	16.4 ± 0.21* (12–25)	39.2 ± 3.04*♦ (112–70)
BG	0.12 ± 0.17 (0–2)	37.24 ± 1.38* (12–72)	35.32 ± 3.67* (12–68)
TC	0.11 ± 0.14 (0–2)	29.43 ± 1.46* (12–52)	32.48 ± 3.37* (12–56)
Smoking cessation	0.21 ± 0.16 (0–3)	25.16 ± 0.96* (12–46)	26.84 ± 1.87* (12–45)
Arterial pressure	0.22 ± 0.19 (0–3)	36.45 ± 1.35* (12–69)	37.32 ± 3.74* (10–67)
Aerobic exercise	0.12 ± 0.12 (0–2)	25.27 ± 0.42* (11–43)	41.17 ± 3.34*♦ (11–70)
LDLC	0.12 ± 0.11 (0–2)	31.67 ± 1.24* (10–54)	33.87 ± 3.46* (12–58)
HDLC	0.22 ± 0.16 (0–3)	23.76 ± 0.75* (12–39)	24.96 ± 1.65* (12–38)
TG	0.19 ± 0.15 (0–3)	35.28 ± 1.38* (12–68)	36.73 ± 3.34* (12–66)

Note: The designations are the same as in Table 1.

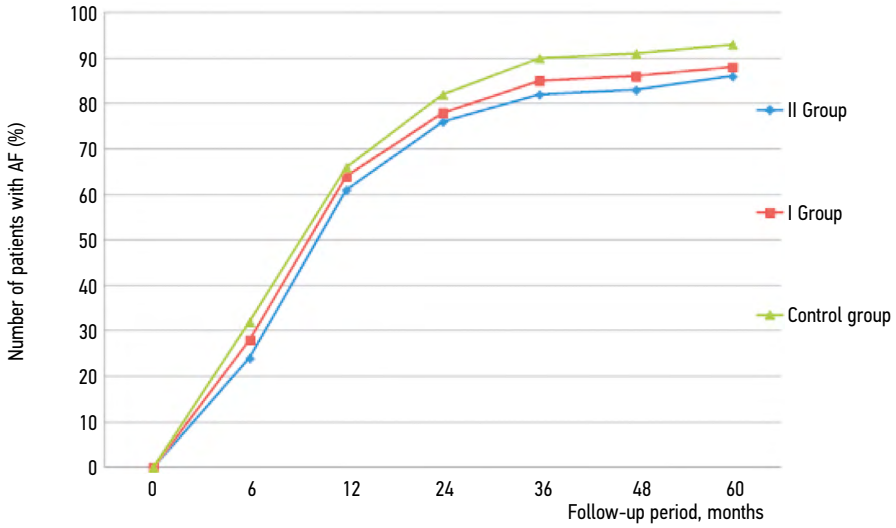

Fig. 1. Cumulative proportion of patients with AF (%) in groups I and II. * — significant difference in indicators when compared with the control group ($p < 0.05$). AF, atrial fibrillation.

DISCUSSION

For the early diagnosis of AF in all patients with MS, especially in the older age group with risk factors for AF development including those at risk of thromboembolic complications, particularly according to the CHA_2DS_2-VASc scale, a daily assessment of pulse regularity according to the "pulse screening test" principle, determined by both palpation and use of household blood pressure monitors, followed, if necessary, by ECG registration on a smartphone or when visiting a medical institution, is recommended [1, 6, 7, 15–17].

To assess the risk of the first episodes of AF, including in patients with MS, along with the Framingham scales (1994–2019), at least 21 risk stratifications were proposed [18]. A meta-analysis of risk stratifications showed that the CHARGE-AF system was found to be the most informative 5-year model for predicting AF development [19], including indicators such as age, anthropometric parameters, ethnicity, BP level, etc. [13, 19]. According to a retrospective analysis of more than 110,000 patients aged > 40 years, the accuracy of the primary prediction of AF using the CHARGE-AF model in detecting the $R_{CHARGE-AF}$ values in the range of 0.70–0.72 units

averaged about 50%, and with values of this indicator of about 0.80 units, the prognostic significance increased to 70% [13, 19]. In the majority of patients with MS in the older age group, the probability of AF was high when CHARGE-AF risk stratification was used [13, 19]. In patients with MS, there is an obesity paradox or metabolic paradox, in which patients who are obese have a minimal probability of lethal outcomes from various cardiovascular diseases and their complications [2–7].

Similar data were obtained in the present study.

The study of the mechanisms of AF development in patients with MS remains one of the urgent problems of arrhythmology and is the subject of ongoing study based, in most cases, on experimental data [2, 6, 7, 20]. Currently, in these patients, the theory of AF induction resulting from Ca^{++} ion overload in atrial cardiomyocytes during diastole due to oxidative stress is widespread, including inflammation of the epicardial adipose tissue [20]. These events result in atrial ectopia caused by the activation of trigger mechanisms and/or re-entry, specifically in the posteroinferior wall of the left atrium, leading initially to the formation of a "rotor" in this zone. Consequently, AF developed with its subsequent recurrence and/or preservation as a permanent type [6, 7, 20]. In patients with MS and AF, ectopic foci in the pulmonary veins and/or atria are rarely detected, and their detection is usually accidental [2, 5–8].

In the present study, in patients with MS, PI was determined based on the assessment of the R-R sinus rhythm-corrected coupling interval of PAC, their number, FiP-P, and Pd [10, 11]. Based on the analysis of PI during follow-up, PTRAF (months) was determined, presented as the original equation

$$PTRAF = [PI_1 - 0.01] \div [PI_1 - (PI_2, PI_3, \text{etc.})] \times I,$$

where PI_1 is the value after study 1; PI_2, PI_3, etc., are PI values at studies 2–3 and subsequent studies, respectively; 0.01 is the PI value at which spontaneous AF attacks occur [11]; and I is the interval (months) between study 1 and subsequent (2–3, etc.) studies [12].

After inclusion in the study, PTRAF ranged from 6 to 12 months in 33.18% of patients with MS, from 1 to 3 years in 29.79% of patients, and from 4 to 5 years in the remaining patients.

Currently, the primary prevention for cardiovascular diseases is determined by four main health factors, namely, normal BP values (BP ⩽ 129/84 mm Hg), BMI (19–25 kg/m^2), lipids, and blood glucose, and three behavioral factors, namely, cessation of bad habits (smoking, drinking alcohol, etc.), regular aerobic exercises, and adherence to a diet, mainly Mediterranean diet [6–8, 14]. It can hypothetically be assumed that the achievement of the target values of MS components related to health factors may be the basis for the primary prevention of AF in these patients. With the use of modern drug therapy in the vast majority of patients with MS, generally, the target values of BP, cholesterol, and blood glucose levels are achieved, whereas the normalization of BMI and/or waist circumference requires targeted induction or ingenuous sincere desire of the patient, for example, by self-monitoring with weekly recording of these parameters and their registration in case diary [3–8, 14]. Even if the ideal body weight is achieved, it does not necessarily mean that it will be maintained for an indefinitely long time [3, 4, 14].

Therefore, in this study, the efficiency of the correction of potentially modifiable MS components and predictors of AF development were determined (in points) taking into account cases of absent correction (0) or incomplete correction (1), achievement of target values of potentially modifiable AF predictors (2), and duration of the maintenance of the modifiable factors achieved (months). The main components of MS, used as a basis in the analysis of the correction efficiency, were BMI and waist circumference [3, 4, 6–8, 24]. In this study, 65.07% of the patients had incomplete correction of BMI and waist circumference, and 10.86% of the patients achieved the target values of all MS components and risk factors for AF. In 24.07% of the patients, despite the recommendations for the implementation of a healthy lifestyle, almost no correction of all predictors of AF was registered. In patients with incomplete reversal of BMI and/or waist circumference to the target values, other risk factors for AF development (levels of BP, lipids, and blood glucose, smoking cessation, etc.) approached the values corresponding to apparently healthy individuals, maintained as usual for at least 6 months. The achievement of the target values of the main components of MS, including BMI and/or waist circumference, correlated with the performance of regular aerobic exercises (OR = 10.9), adherence to a diet (OR = 8.5), duration of MS registration < 20 years before the start of correction (OR = 12.8), and intake of a glucagon-like peptide-1 receptor agonist (Liraglutide) (OR = 5.4).

In the overwhelming majority of cases, the effect of the correction of potentially modifiable MS components and predictors of AF is assessed retrospectively to determine a change in the risk (%) of AF development. In the REGARDS study, the significance of correction of each MS component and behavioral factors that reached the target values in relation to reducing the AF risk, depending on the degree of correction of potentially modifiable factors, was 5%–10% [24], whereas in the ARIC study, it was 12%–17% [8], and the normalization of BP and body weight play the leading role in reducing the risk of AF [8, 24, 25, 26]. The heterogeneity in the significance of the correction of each AF predictor was attributed to the use of different assessment methods. In another review that focused on primary AF prevention through the correction of potentially modifiable factors, the reduction in AF risk was approximately 18% with the normalization of BP and BMI, up to 10% with regular aerobic exercises, up to 10% with smoking cessation, and 2.5% and 5% with the normalization of lipid and blood glucose levels, respectively [25]. In summary, it can be assumed that the total correction of all MS components and behavioral factors, except for BMI and/or waist circumference, can hypothetically reduce the risk

of AF by approximately 40% and by 60% when the latter two parameters are included. Based on the proposed reduction in the risk of primary AF due to the correction of potentially modifiable predictors of its development, it can be hypothetically assumed that in the prospective monitoring of patients with a high cardiometabolic risk, at least a twofold decrease in the occurrence of AF can be expected, compared with patients with abdominal obesity and other components of MS.

The study results showed that in patients, upon reaching the target values, without correction and with incomplete correction of all MS components and risk factors for AF development, the incidence of primary AF attacks did not differ significantly, as it was recorded in 84.95%, 93.20%, and 88.15% of the cases, respectively.

In most cases, PAC in patients with MS is regarded as supraventricular ectopia with a favorable prognosis, usually not requiring antiarrhythmic drugs, except for the presence of a subjective sensation of extrasystole [1–3]. On the contrary, in these patients, sustained and/or recurrent supraventricular ectopia with a coupling interval, for example, of ⩽600 ms with low variability (< 60 ms) may, alone or indirectly, along with an increase in calcium current to atrial myocardiocytes, be activated simultaneously, rectifying input potassium flows, thereby initially inducing myocardial regions with heterogeneous refractoriness, followed by electrical and structural remodeling of the left heart, causing particularly atrial arrhythmogenic cardiomyopathy and subsequently AF [2, 5–7, 20–22]. This fact is indirectly confirmed by the results of our study, that is, a decrease in PI values due to a reduction in the variability of the PAC coupling interval, an increase in Pd, and, to a lesser extent, a change in the number of extrasystoles, which, apparently, reflects the process of formation of the substrates for AF development [21, 23].

Thus, the complex correction of potentially modifiable predictors of AF development, reaching target values, as primary prevention of AF in MS patients with PAC, when a high risk of its development is detected, is ineffective. One of the reasons for the lack of influence of the modification of MS components, including reaching the target values, on the course of PAC and primary AF development, is the registration of atrial ectopia indefinitely before study inclusion, inducing the occurrence of atrial myocardial zones with the dispersion of conduction and refractoriness and/or the formation of multiple ectopic foci [5–7], and the rather slow regression of the excess volume of epicardial adipose tissue in patients with MS [1–4]. Therefore, frequent and persistent atrial premature beats in comorbid patients with abdominal obesity, apparently, is one of the independent predictors of AF development, determining independently or indirectly the high risk of its development [7, 8, 10, 23]. Thus, in MS patients with PAC, the use of antiarrhythmic therapy or other treatment methods is indicated as primary prevention of AF in high-risk cases [5–10].

CONCLUSIONS

1. Despite the recommendations for lifestyle modification, only 10.86% of patients achieved the target values of potentially modifiable MS components and other risk factors for AF.

2. The achievement of the target values of the main components of MS, including BMI and/or waist circumference, correlated with the performance of regular aerobic exercises (OR = 8.9), adherence to a diet (OR = 7.5), duration of registration of MS of < 20 years before the start of correction (OR = 12.8), and intake of a glucagon-like peptide-1 receptor agonist (Liraglutide) (OR = 5.4).

3. When a high 5-year risk of primary AF was detected in MS patients with PAC without correction, with incomplete correction, and with the achievement of the target values of potentially modifiable predictors of AF development, the incidence of AF did not differ significantly, which amounted to 93.20%, 88.15%, and 84.95% of the patients, respectively.

4. A decrease in the $R_{CHARGE-AF}$ index in MS patients with PAC during follow-up determines the efficiency of correction of potentially modifiable predictors of AF development, but its changes do not reflect the degree of risk of AF development.

ADDITIONAL INFORMATION

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

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Research article

A Case of Mitral Annular Disjunction Combined with Ventricular Arrhythmias

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The article presents a clinical case of a combination of mitral valve prolapse (MVP), mitral annular disjunction (MAD), and ventricular arrhythmia. The presence of MAD worsens the prognosis in MVP and predisposes to life-threatening ventricular arrhythmias. In a 42-year-old patient, MAD was detected during echocardiography to determine the indications for surgical correction of mitral insufficiency in MVP. Severe myxomatous degeneration of the mitral valve leaflets, polysegmental prolapse, and typical auscultatory pattern (systolic click followed by systolic murmur in the second half of systole) were the indications for the targeted search for MAD. Multi-day (ECG) monitoring recorded nonsustained ventricular tachycardias and premature ventricular complexes (PVCs). Cardiac magnetic resonance imaging was performed for confirmation the diagnosis and searched for left ventricular myocardial fibrosis accompanying MAD. Finally, MAD was confirmed, but myocardial fibrotic changes were not detected. Owing to the absence of myocardial fibrosis, the patient was treated conservatively with a beta-adrenoblocker (25 mg/day slow-release metoprolol succinate) in combination with 25 mg/day allaforte. Repeated 24-h ECG monitoring did not detect ventricular tachycardias and nonsustained registered a significant decrease of number of PVCs. The patient is followed up prospectively due to high risk factors for fibrosis and worsening prognosis, which may require surgical correction of the existing disturbances and/or implantation of a cardioverter-defibrillator.

Keywords: mitral annular disjunction; mitral valve prolapse; nonsustained entricular tachycardia.

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Научная статья

Случай митральной аннулярной дизъюнкции в сочетании с желудочковыми нарушениями ритма

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В статье представлен клинический случай сочетания пролапса митрального клапана (ПМК), митральной аннулярной дизъюнкции (МАД) и желудочковых нарушений ритма. Наличие МАД ухудшает прогноз при ПМК и предрасполагает к жизнеугрожающим желудочковым аритмиям. У пациентки 42 лет МАД выявлена при эхокардиографическом обследовании, которое она проходила для определения показаний к хирургической коррекции митральной недостаточности на фоне ПМК. Выраженная миксоматозная дегенерация створок митрального клапана, полисегментарный пролапс, классическая аускультативная картина (систолический клик, следующий за ним систолический шум во второй половине систолы) стали основанием для прицельного поиска МАД. При многосуточном мониторировании электрокардиографических данных зарегистрированы неустойчивые желудочковые тахикардии, частая желудочковая экстрасистолия. Для подтверждения диагноза и поиска фиброза миокарда левого желудочка, аккомпанирующего МАД, выполнена магниторезонансная томография сердца. Наличие МАД подтверждено, фиброзные изменения миокарда не выявлены. В связи с отсутствием фиброза миокарда принято решение о консервативном лечении бета-адреноблокатором (метопролола сукцинат замедленного высвобождения в дозе 25 мг в сутки) в сочетании с аллафорте 25 мг в сутки. На фоне терапии при повторном суточном мониторировании ЭКГ не зарегистрированы неустойчивые желудочковые тахикардии, уменьшилось количество желудочковых экстрасистол. За пациенткой осуществляется проспективное наблюдение в связи с наличием факторов высокого риска появления фиброза и ухудшения прогноза, которые в свою очередь могут потребовать хирургической коррекции имеющейся патологии и/или имплантации кардиовертера-дефибриллятора.

Ключевые слова: митральная аннулярная дизъюнкция; пролапс митрального клапана; неустойчивая желудочковая тахикардия.

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ЭКО•ВЕКТОР

BACKGROUND

Mitral valve prolapse (MVP) is a common pathology in the clinical practice of a cardiologist and therapist. In the adult population, the prevalence of MVP reaches 2%–3% [1, 2], with favorable prognosis in most cases [3–6]. According to Nishimura et al., the 8-year survival rate of patients with MVP is 88% and is not significant different compared with the main parameters of the control group [3]. However, the disease course may be complicated by malignant ventricular arrhythmias and sudden death in some young and middle-aged patients [7–9]. The risk stratification criteria for adverse ventricular arrhythmias in MVP are under development. The prolapse of both mitral valve leaflets, its degree of severity, papillary muscles fibrosis, and mitral annular disjunction (MAD) are associated with the risk of ventricular arrhythmias [8–12].

MAD is a structural abnormality defined as separation (disconnection) or absence of the direct transition of the left atrial (LA) myocardium into the left ventricular (LV) myocardium in the area of the mitral valve annulus and partial replacement of the LV myocardium under the mitral valve annulus with fibrous tissue [2]. MAD is a common finding in patients with MVP [2]. Its detection varies from 42% to 98% and correlates with the degree of prolapse severity [2, 13]. MAD was first described in combination with MVP in the 1980s [14]. The clinical significance of this structural abnormality remained unclear, and the problem was not studied until 2005. Eriksson et al. observed MAD with transesophageal echocardiography (EchoCG) and described direct surgical cardiac examination in this patients during surgery for severe mitral insufficiency resulting from myxomatous degeneration of the mitral valve leaflets in 2005 [13]. They demonstrated a direct correlation between the severity of MAD, number of altered leaflet segments, and severity of MVP. Moreover, MAD plays an important role in arrhythmogenesis [2, 15]. The physician's task is to promptly recognize this abnormality, establish its correlation with arrhythmias, prescribe antiarrhythmic therapy, and dynamically monitor the patient to determine indications for cardioverter-defibrillator implantation and surgical correction of the existing disturbances.

CLINICAL CASE

Patient I., 42 years old, came to our clinic to decide on indications for surgical treatment of mitral insufficiency. On admission, complaints included frequent heart palpitations for 6 months. The patient was treated in the outpatient clinic at the place of residence. The examination revealed MVP with moderate-to-severe mitral regurgitation. Low-dose therapy with beta-adrenoblockers (2.5 mg/day bisoprolol) was ineffective. When trying to increase the drug dose, the patient became hypotensive, and the resting heart rate decreased to 45 bpm during the daytime.

Family history is not burdened. The patient gave birth to three healthy children.

On physical examination, the condition was assessed as satisfactory. The color of the skin and visible mucous membranes were normal. No peripheral edemas were observed. The patient had a normal build. The body mass index was 21.30 kg/m^2. Arterial pressure was 115/70 mm Hg. The resting heart rate and pulse were 65 bpm. Percussion revealed a slight left shift of the left heart border. On auscultation, the sonority of the first and second sounds was unchanged, and no additional sounds were detected. A systolic click was heard in the middle systole, followed by a systolic murmur at Botkin-Erb's point with irradiation toward the aorta and apex. There were pulmonary sound on percussion and vesicular breathing on auscultation. On palpation, the abdomen was soft and painless, and the liver was not enlarged. The six-minute walk test was 560 m.

EchoCG was performed using modern technologies of three-dimensional image reconstruction and Mitral Valve Quantification model on Vivid-9 ultrasound device. The results showed that mitral regurgitation was mild [16]. The effective regurgitation orifice area was 0.18 cm^2, and the regurgitation volume was 20 mL. Both mitral valve leaflets were myxomatous, thickened, and prolapsed up to 8 mm into the LA cavity (Fig. 1–3). The prolapse was

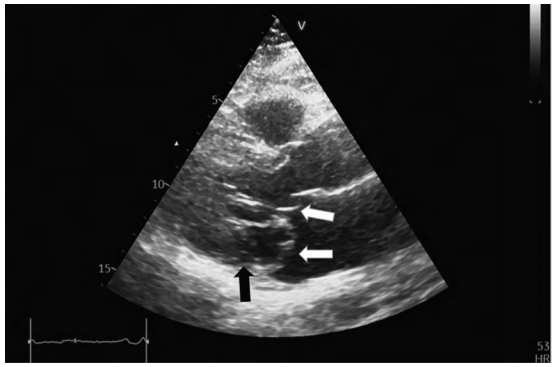

Fig. 1. Parasternal long-axis view–of the left ventricle. Systole. White arrows indicate elongated and thickened mitral valve leaflets prolapsing into the left atrial cavity. The black arrow indicates the disjunction area

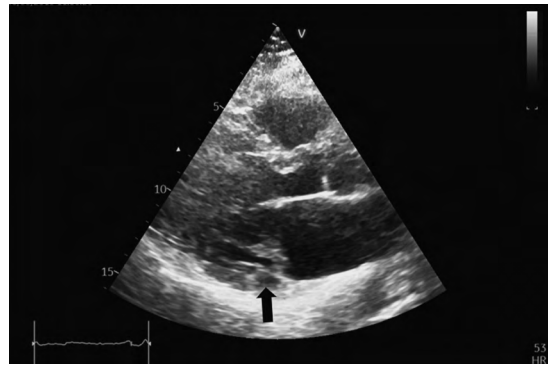

Fig. 2. Parasternal long-axis view–of the left ventricle. Diastole. The elongated and thickened mitral valve leaflets (predominantly posterior) are visible. The black arrow indicates the disjunction area below the posterior mitral valve leaflet.

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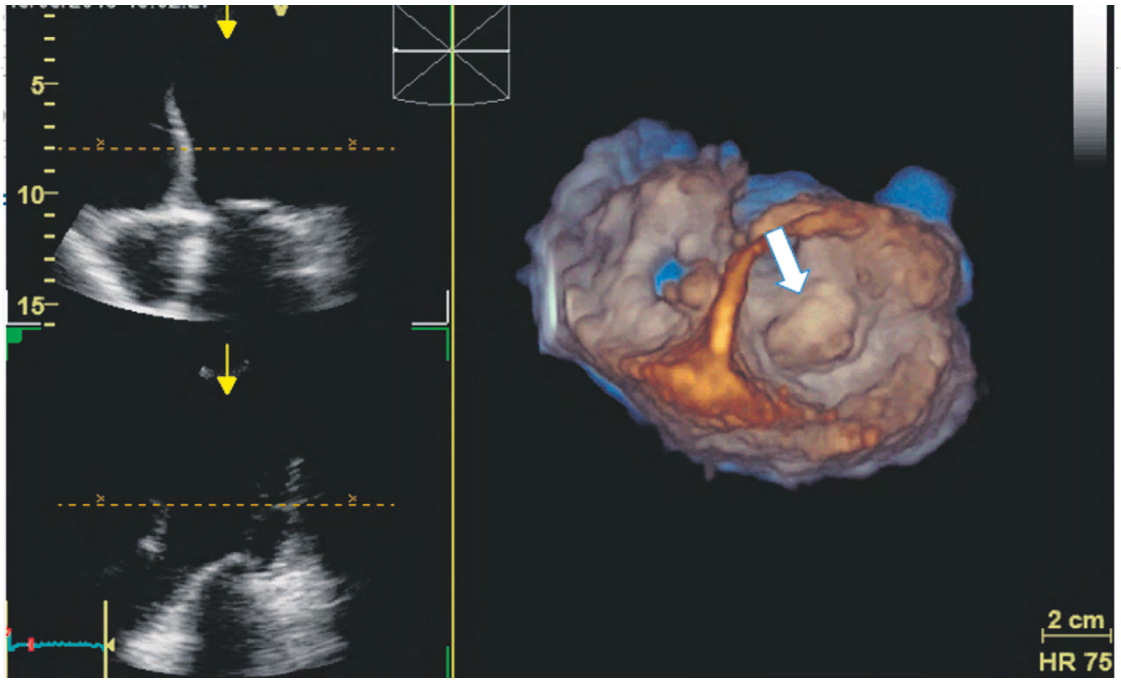

Fig. 3. Three-dimensional reconstruction of the mitral valve. The white arrow indicates the elongated and prolapsed mitral valve leaflets

polysegmental (Fig. 4). Signs of MAD (absence of myocardial tissue up to 9 mm under the posterior mitral valve leaflet) were revealed (Fig. 1, 2).

LV was slightly dilated, and the end-diastolic volume (EDV) index was 68 mL/m^2. LV myocardial hypertrophy was revealed, and the myocardial mass index was 98/m^2. Systolic function was preserved, and ejection fraction (EF) was 68%. The calculated pulmonary artery pressure was not elevated.

Cardiac magnetic resonance imaging (CMR) was performed on a Signa Pioneer 3.0 T scanner (General Electric Healthcare, Chicago, IL, USA) using 16-channel and 32-channel body coils to verify the diagnosis. Scans were performed according to a standard protocol with late contrast enhancement 8–15 min after injection of gadolinium-based contrast agent at a dose of 0.02 mmol/kg (0.5 mmol/L gadodiamide). The following pulse sequences were used: Fiesta Cine (dynamic cine imaging), T1 double-inversion recovery (DIR), T2 DIR fat saturation, and delayed myocardial enhancement (MDE) performed with breath-holding in standard cardiac projections. Postprocessing image analysis was performed using the CardiacVX software package (General Electric Healthcare). The following parameters were assessed: EF of 47% (normal range, 58%–76%), stroke volume of 84 (normal range, 59–115) mL, EDV of 180 (normal range, 90–171) mL, end-systolic volume (ESV) of 96 (normal range, 25–62) mL, EDV index of 105 (normal range, 59–93) mL/m^2, ESV index of 56 (normal range, 16–34) mL/m^2, myocardial mass of 160 (normal range, 71–143) g, and LA bi-plane volume of 112 (normal range, 47–131) mL.

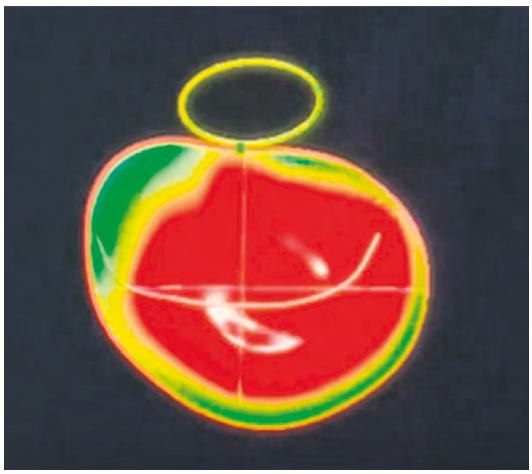

Fig. 4. Three-dimensional model of the mitral valve. Mapping in red shows the prolapse of all segments of both leaflets at end-systole

Despite the good comparability of EchoCG and CMR data in assessing EF and LV volumes, many studies have demonstrated the differences between these methods. The range of over- and underestimation of contractile function in CMR may reach 20% according to the Bland–Altman plots [17]. In addition, differences in EchoCG and CMR results are due to different counting techniques. Standardly, automatic or semiautomatic counting based on short axis LV images is used for CMR. In addition, measurement errors obtained with CMR may be due to insufficient spatial resolution and the effect of volume averaging associated with nonoptimal slice thickness, which is not always technically to be corrected. Moreover, arrhythmias contribute to inaccuracies in obtaining LV volumes and, accordingly, to errors in EF calculation. Based

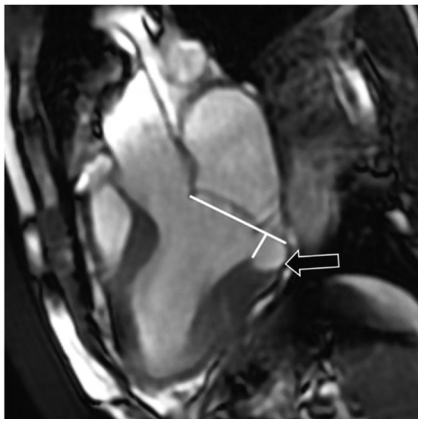

Fig. 5. Left ventricular three-chamber axis, cine end-systolic image. Measurement of the mitral annular disjunction distance for the posterior mitral valve leaflet. Mitral annular disjunction is indicated by an arrow

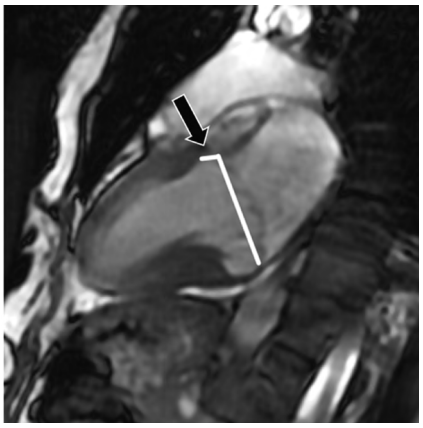

Fig. 6. Left ventricular long axis (two chamber view), cine end-systolic image. Measurement of the mitral annular disjunction distance for the anterior mitral valve leaflet. Mitral annular disjunction is indicated by an arrow

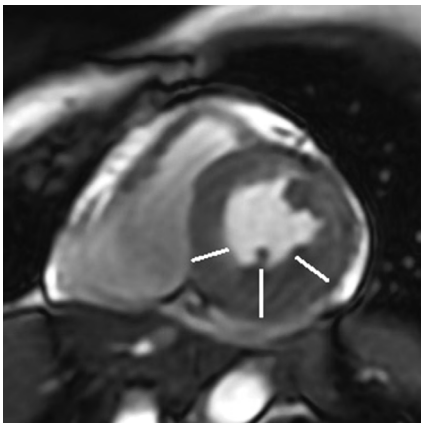

Fig. 7. Dynamic cine imaging along the short axis of the left ventricle. End-systolic frame shows thickening of basal myocardial segments

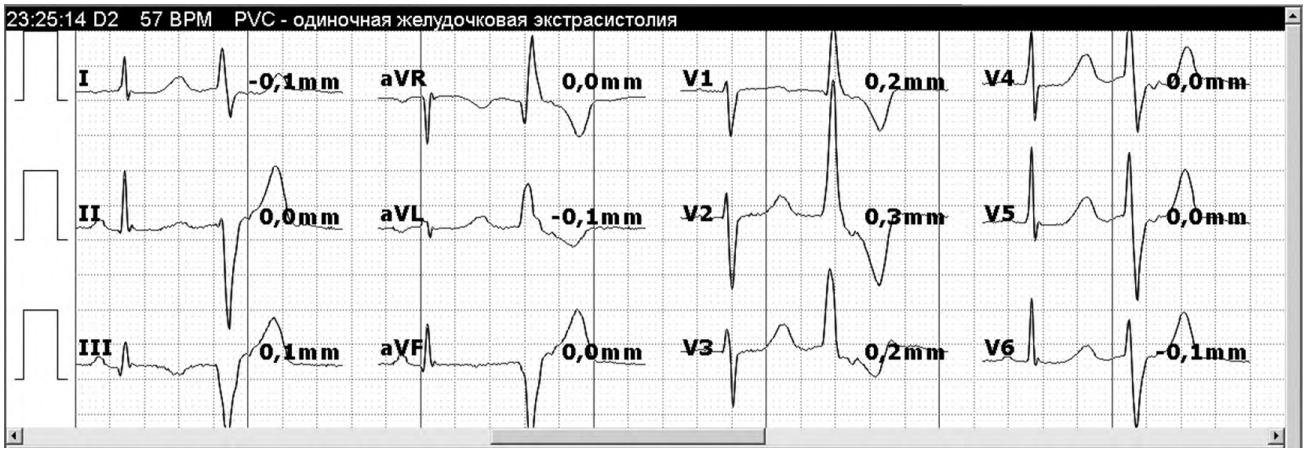

Fig. 8. Resting 12-lead electrocardiogram

on the difference in EF values (EchoCG showed normal EF values, whereas CMR showed decreased EF), the decision was to dynamically monitor the patient's clinical condition, cardiac chamber size, and EF.

The distance from the base of the mitral valve fibrous annulus to the upper contour of the LV myocardium was measured on end-systolic cine images. The MAD extent at the level of the posterior and anterior mitral valve leaflets was measured along the three-chamber and long LV axis, respectively. The MAD extent was 11 mm and 5 mm unde the posterior and anterior leaflets, respectively (Fig. 5, 6).

Additionally, a descending systolic motion of the posterior part of the mitral valve annulus with hyperkinetic contraction of the adjacent basal myocardium was observed (systolic curling). Myocardial thickening of the posterior wall and adjacent segments of the interventricular septum and lateral wall were assessed on short axis and three-chamber-axis LV images. The end-systolic myocardial thickness of basal inferior septal and inferolateral segments was 13 mm and that of the inferior basal segment was 15 mm (Fig. 7).

No reliable areas of late gadolinium enhancement (LGE) in the myocardium, corresponding to fibrous changes, were found. The patient was recommended for follow-up and dynamic CMR monitoring to exclude fibrotic structural changes in the long term and assess the risk of adverse ventricular arrhythmias.

Resting 12-lead ECG showed sinus rhythm, early repolarization syndrome, and single premature ventricular complexes (PVCs) (Fig. 8).

Multi-day ECG monitoring (154 h) was performed. single monomorphic premature ventricular complexes (PVCs) (54,529 [8.5%]) and paired (1,078 [2.1%]) and runs of monomorphic nonsustained ventricular tachycardia of 3–7 complexes (46 episodes in 154 h) were detected (Fig. 9).

Thus, the diagnosis of MVP and MAD was confirmed by instrumental methods of examination. No indications for surgical intervention were revealed at this stage. Ventricular arrhythmias requiring medical correction were registered. At the previous treatment stage, beta-blocker monotherapy (2.5 mg/day bisoprolol) was ineffective. Therefore, combined

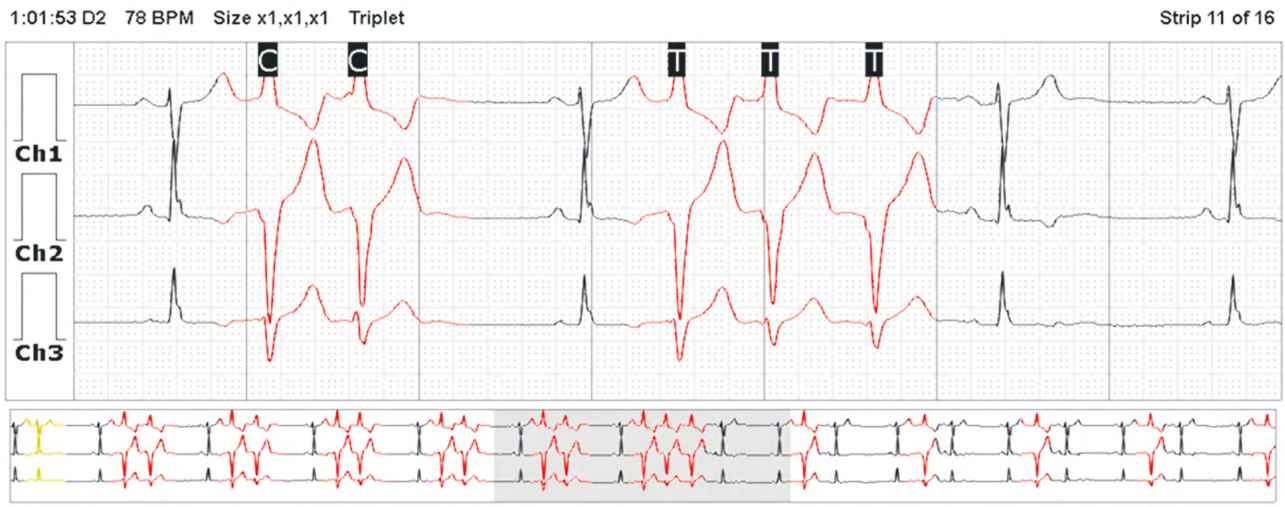

Fig. 9. Fragment of multi-day electrocardiographic monitoring

antiarrhythmic therapy was decided. Slow-release metoprolol succinate was recommended at a starting dose of 25 mg once daily in the morning, followed by dose titration, if necessary, in combination with 25 mg allaforte in the evening. During therapy, repeated 24-h ECG monitoring revealed no runs of nonsustained ventricular tachycardia and registered a significant decrease of number of PVCs from 8,520 in 24 h to 5,000 in 24 h. The patient is still being followed up.

DISCUSSION

Given the correlation of MAD with the severity of MVP and mitral insufficiency and the association with life-threatening ventricular arrhythmias, prompt diagnosis of this pathological condition and dynamic monitoring of patients is extremely important.

Chakrabarti et al. presented a generalized scheme of examination of patients with MVP [18]. The first steps are detailed history taking, including family history of fatal ventricular arrhythmias and sudden death, physical examination with assessment of systolic click and severity of systolic murmur, and resting ECG and EchoCG with targeted MAD searches. EchoCG is the most significant and accessible method for diagnosing changes in valvular apparatus and LV contractile function. However, it has several limitations, i.e., the need for a good acoustic window, limited possibilities for assessing the myocardial structure, and operator dependence. In patients with a high risk of poor prognosis (arrhythmias, MAD on EchoCG findings, and family history of sudden death), CMR is recommended to clarify the presence of MAD and its severity and assess fibrotic changes in the LV myocardium and papillary muscles as additional risk factors. The longitudinal distance of disjunction may vary from 1 to 15 mm around the mitral valve annulus in the same patient, and its severity is most frequently associated with the severity of mitral valve changes [19]. In addition, disjunction may occur in patients without MVP. Marra et al. revealed that abnormal morphology and pathology of mechanical movement of the mitral valve and annulus in MVP may lead to fibrous changes of the LV walls detected by contrast-enhanced CMR [9]. CMR allows accurate assessment of the motion of the mitral annulus, djacent myocardium and inferior or anterior systolic curling at the level of the posterior leaflet. An systolic curling defined by the authors as exceeding the median value of 3.5 mm is associated with a higher frequency and greater volume of areas LGE (fibrosis). Furthermore, a linear correlation was found between the disjunction extent and the severity of systolic motion [9]. Intramural areas of LGE in the inferior basal regions of the LV wall were observed in 72% of patients with MAD and systolic curling. A positive linear correlation between MAD length and degree of fibrosis was detected. Marra et al. reported that the median long axis MAD extent in patients with MVP was 4.8 mm with myocardial fibrosis and 1.8 mm without fibrosis [9]. CMR allows the detection of both local fibrosis and diffuse (interstitial) myocardial fibrosis. Currently, only a few studies have focused on the assessment of diffuse fibrosis in patients with MVP. In 2021, a retrospective description of the results of CMR in 30 patients with MVP combined with MAD was published; the comparison group included patients with mitral regurgitation without MAD and those with normal CMR characteristics [20]. Areas of LGE corresponding to fibrosis were observed in 47% of the patients with MVP-MAD and were absent in all control groups. By using T1 mapping after contrast agent injection, the extracellular volume (ECV) was calculated, which reflected the size of the extracellular space in the myocardium. Increase of EVC may indicate diffuse myocardial fibrosis. In the study, the ECV was higher in MVP-MAD, even in the absence of delayed accumulation of contrast. Remarkably, ECV values were increased in all basal segments of the myocardium, demonstrating fibrous remodeling not limited to the inferior and inferolateral segments in the area of prolapsing leaflet attachment.

Compared with LGE, the ECV of LV basal segments had a stronger association with MAD severity and a similar association with the frequency of sudden cardiac death. The MAD length also correlated with ECV, but not with the extent of LGE. Complex ventricular arrhythmias PVCs and nonsustained ventricular tachycardias) were observed in 87% of patients with MVP-MAD. In these patients, ECV exceeded the threshold level, whereas only 53% had areas of LGE.

The presence and severity of systolic curling and mitral valve changes (prolapse and regurgitation) are associated with basal segment hypertrophy in patients with MVP [9]. Basal hypertrophy may have local or concentric distribution. More frequently, the phenomenon of "ballerina's foot" is observed, i.e., hypertrophy of the basal segments with systolic bulging of the LV anterior wall [9]. Probably, local hypertrophy contributes to arrhythmogenesis in MVP-MAD.

In patients with clinical signs of arrhythmia, 24-h ECG monitoring is indicated. In addition, electrophysiological examination may be performed in patients with a high clinical risk and history of ventricular arrhythmias in the presence of structural changes on CMR. However, CMR and electrophysiological examination are not recommended for all patients. In our case, CMR was indicated to verify the diagnosis of MAD and confirm or exclude fibrotic changes in the myocardium to stratify the risk of fatal ventricular arrhythmias due to nonsustained ventricular tachycardias recorded during ECG monitoring. Since CMR revealed no fibrotic changes in the patient and due to the absence of family history of sudden death, electrophysiological examination was not performed.

The majority of authors agree that the combination of MVP, MAD (irrespective of its extent), and myocardial fibrosis of the LV free wall is a "fatal triad," which determines the high frequency of ventricular arrhythmias and is accompanied by a high risk of sudden cardiac death [9, 21–23].

In 2020, Han et al. presented the results of a histological analysis of myocardial fibrotic changes in patients with sudden cardiac death and MVP other cardiac causes of death were excluded in comparison with the group of noncardiac deaths [24]. In sudden cardiac deaths combined with MVP, fibrous changes in the LV wall were significantly more frequently observed in the lateral and posterior walls than in the anterior wall and interventricular septum. The authors separately noted a predominantly endocardial–epicardial gradient of increasing fibrotic changes [24].

Currently, our patient has two components of the "fatal triad" (MVP and MAD), and no myocardial fibrotic changes were found in the CMR. Therefore, a decision was made to treat the patient conservatively. However, considering the severity of MAD and structural changes of the mitral valve leaflets and systolic curling of the basal parts of the LV myocardium in the area of MAD, the case belongs to the high risk category of fibrosis development in the future. Therefore, the patient needs follow-up, regular EchoCG monitoring at least once a year, and multi-day ECG monitoring at least once every 6 months. The decision to repeat the CMR is dependent on the results of the monitoring. If the disease progresses, mitral valve surgery and/or implantation of a cardioverter-defibrillator may be required.

CONCLUSIONS

MVP combined with MAD and myocardial fibrosis is a pathological condition predisposing to life-threatening ventricular arrhythmias and sudden death. Given the high frequency of MAD in patients with MVP, a targeted search for disjunction should be performed during EchoCG. If detected, the patient should be referred for CMR to confirm the diagnosis and diagnostically search for fibrosis, which is an additional marker of poor prognosis.

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.

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

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Research article

Preoperative Prediction of Optimal Method and Site of Left Ventricular Electrode Implantation

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We present a clinical case of cardiac resynchronization device implantation in a patient with a zone of late left ventricular activation in the area of the anterior coronary sinus vein, which, however, was unsuitable for endovascular implantation and stable electrode placement in it. This anatomical feature was diagnosed at the outpatient stage using a noninvasive mapping technique. Using this approach, we were able to understand that an epicardial electrode implantation, instead of traditional endovascular implantation of the left ventricular electrode through the coronary sinus vein, is indicated for the patient. Targeted implantation of an epicardial electrode in the area of interest on the epicardial surface of the left ventricle in the basal part of the anterolateral wall allowed achieving a complete clinical response to resynchronization therapy.

Keywords: Left ventricular lead implantation; noninvasive mapping; cardiac resynchronization therapy; case report.

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Научная статья

Предоперационное прогнозирование оптимального способа и места имплантации левожелудочкового электрода

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Приведен клинический случай имплантации сердечного ресинхронизирующего устройства пациенту с зоной поздней активации левого желудочка в области передней вены коронарного синуса, которая при этом была непригодна для эндоваскулярной имплантации и устойчивого нахождения в ней электрода. Эта анатомическая особенность была диагностирована на догоспитальном этапе с помощью методики неинвазивного картирования. Данный подход позволил понять, что пациенту показана имплантация эпикардиального электрода вместо традиционной трансвенозной имплантации левожелудочкового электрода через вену коронарного синуса. Проведенная целевая имплантация эпикардиального электрода в зону интереса на эпикардиальной поверхности левого желудочка в базальном отделе передне-боковой стенки позволила добиться полного клинического ответа на ресинхронизирующую терапию.

Ключевые слова: имплантация левожелудочкового электрода; неинвазивное картирование; сердечная ресинхронизирующая терапия; клинический случай.

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ЭКО•ВЕКТОР

BACKGROUND

Cardiac resynchronization therapy (CRT) has been proven to be a method for treating patients with chronic heart failure (CHF) and complete left bundle branch block (CLBBB) in addition to optimal drug therapy [1]. Classically, the coronary sinus (CS) has branches, namely, the posterior interventricular vein (or middle cardiac vein) and the posterior vein [3] (or posterolateral vein [2]). Also, there may be one or several lateral veins. The great cardiac vein is a continuation of the CS at the level of the anterior part of the mitral valve. It bypasses the aortic root and is called the anterior vein (anterior interventricular vein) as soon as it passes to the anterior surface where it passes in the anterior interventricular sulcus. The anterolateral vein usually ends in the anterior vein at the level of the left ventricle (LV) basal segments [2]. In some sources, the great cardiac vein and the anterior vein throughout are called the great cardiac vein [3]. Endovascular implantation of left ventricular lead is considered classical; it is inserted into one of the CS veins, preferably into the lateral, posterior, or anterolateral vein [3]. This choice of a vein for implantation is based on the fact that, as a rule, the late activation zone in CLBBB is located in the basal region on the border of the LV lateral and posterior walls.

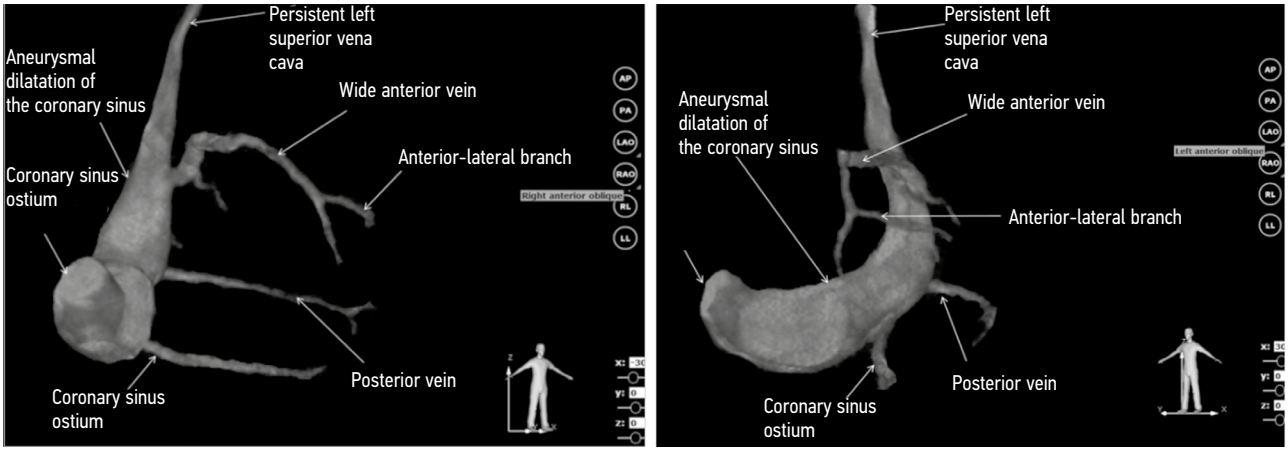
Modern medicine tends to develop personalized approaches for treatment. One of these is the use of the noninvasive mapping system Amycard developed originally in Russia. The previous work revealed that the system can be used to detect a late activation zone, which, as it turned out, can have a diverse location in the LV [4]. In addition, this system enables us to compare the noninvasive activation map and the CS anatomy during the preoperative diagnostics on the same three-dimensional model [5].

The clinical case presented demonstrates the feasibility of using noninvasive mapping for the correct choice of the method and place of implantation of the left ventricular lead in CRT.

CASE REPORT

A 70-yr-old man complained of dyspnea when minimal physical exertion, and swelling of the lower legs. The 6-min walk distance was 100 m. Dyspnea appeared after a recurrent myocardial infarction. The past medical history showed that the patient had arterial hypertension for more than 15 yr; the target level of arterial pressure was achieved during therapy. Previously, he had a myocardial infarction of the LV lower wall (2015) and myocardial infarction with damage to the LV anterior septal region (2018). The risk factors for cardiovascular diseases include smoking, dyslipidemia, and type 2 diabetes mellitus. It is known that after heart attacks, stenting of the anterior interventricular artery, circumflex artery, and right coronary artery was performed using drug-eluting stents with the effect of complete revascularization. The patient was given therapy that included 100 mg/day of metoprolol, 10 mg/day of enalapril, 75 mg/day of clopidogrel, 1.000 mg/day of metformin, 10 mg/day of torasemide, and 50 mg/day of spironolactone. The ejection fraction (EF) of the LV remained within 26%-29%, despite the drug therapy at the specified volume and optimal revascularization. Subsequently, the drug therapy was corrected, and sacubitril/valsartan was prescribed instead of enalapril. The dose was titrated to the maximum possible, considering hypotension associated with CHF, namely, 51.4 mg of valsartan and 48.6 mg of sacubitril twice a day. Dapagliflozin was also prescribed at a dose of 10 mg/day. During the corrective therapy for 3 months, the patient noted an improvement in the form of a decrease in dyspnea with minimal physical exertion; however, the distance of a 6-min walk was 160 m, and the patient corresponded to the III functional class of CHF. According to echocardiography, the LV EF was 32%, and the end systolic volume (ESV) was 178 ml. Considering the intraventricular conduction disorders in the patient in the form of CLBBB with a QRS complex duration of 160 ms, as well as clinically pronounced CHF with LV EF less than 35% during optimal drug therapy, indications for implantation of a resynchronizing device were determined.

Within the preparation for surgery, noninvasive mapping was performed, which was multichannel (up to 240 unipolar leads) electrocardiography using the Amycard 01C EP LAB noninvasive mapping complex (EP Solutions SA, Switzerland) along with multislice computed tomography (MSCT) of the chest and heart in the device Somatom Definition 64 (Siemens, Germany) with intravenous contrast (Ultravist 370, 100 ml) [6]. The multichannel ECG and MSCT data obtained were imported into the Amycard 01C EP LAB software to construct a three-dimensional model of the heart ventricles and to conduct a detailed reconstruction of the CS and its branches, as well as compile an isopotential map of the ventricles based on the reconstructed unipolar endograms and compare the isopotential map with the anatomical model. The study revealed that the CS trunk was aneurysmically dilated up to 26 mm due to the confluence of the persistent left superior vena cava into it. Other branches of the CS were also visualized, namely, a large posterior interventricular vein, posterior vein with an ostial angle of 90°, wide anterior vein, and anterior-lateral branch distal to the anterior vein (Fig. 1). The zone of the latest activation of the intact myocardium was visualized in the basal part of the LV anterior-lateral wall. It was noteworthy that in the projection of this zone, there was no target vein suitable for standard endovascular implantation, since the anterior vein was too wide, and the anterolateral tributary branched off from the anterior vein only in the middle segments, while the late zone was located basally (Fig. 2). As a result, preoperative diagnostics enabled to schedule immediately to the patient the epicardial lead implantation to the basal segments of the LV anterior-lateral wall. It should also be noted that the absence of an ischemic scar in the target zone of late activation of the intact



RAO 30° LAO 30°

Fig. 1. Three-dimensional anatomical model of the coronary sinus with branches, obtained after processing in the Amycard system

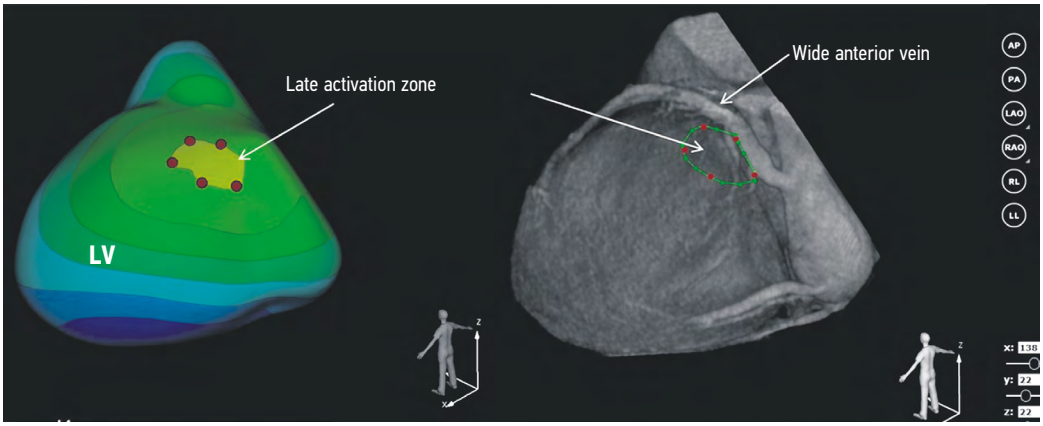


Fig. 2. Noninvasive mapping of the left ventricle. An isopotential map of the left ventricle is presented on the left. The late zone is indicated with red markers. Interpolation of the late zone on a three-dimensional anatomical model with coronary sinus veins are presented on the right. LV, left ventricle

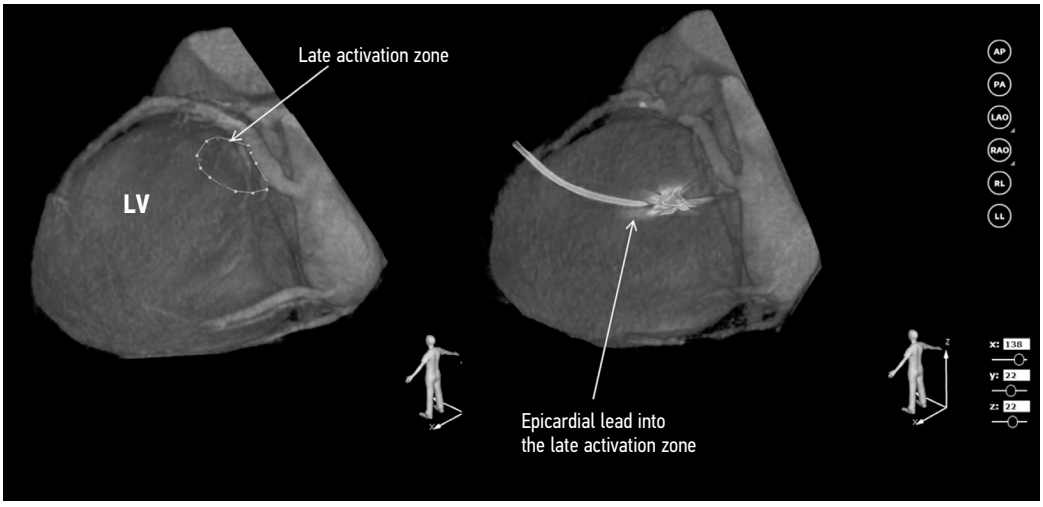


Fig. 3. Left ventricular lead was implanted epicardially in the region of the initial late activation zone of the intact myocardium. LV, left ventricle

myocardium was confirmed by the results of earlier magnetic resonance imaging.

During the surgery, the right atrial and right ventricular leads were first implanted with transvenous access, then the epicardial unipolar lead was implanted through the left lateral mini-thoracoscopic approach into the basal segment of the LV anterior-lateral wall in the late activation zone (Fig. 3). The leads were connected to the device Syncra CRT-P (Medtronic, USA). When programming the device, it was revealed that the QRS complex shortest duration is

determined in the p-controlled biventricular pacing mode with an interventricular delay of 0 ms. The atrioventricular delay after intrinsic P wave was 100 ms, and the atrioventricular delay after a paced atrial event was 140 ms.

The patient noted clinical improvement in the form of a decrease in dyspnea when walking along the corridor in the early postoperative period. The duration of the QRS complex decreased from 160 to 110 ms. After 12 months of follow-up, the patient's response to CRT was confirmed. The distance of the 6-min walk test was 400 m, which corresponds to the functional class II of CHF (the class decreased from III to II). The echocardiography results showed that LV EF was 45% (increase by 13% from the baseline), and ESV was 145 ml (decrease by 19% from the baseline). Consequently, both clinical and echocardiographic responses to CRT were registered.

DISCUSSION

The standard approach to implanting an LV lead is positioning it in the posterior or posterolateral, lateral, or anterolateral veins, as far as possible in the basal regions. The posterior interventricular and anterior veins are not recommended as veins for implantation of the LV lead [3]. According to a previous study using the described noninvasive mapping technique in CRT candidates, the late zone on the LV epicardial surface had a heterogeneous location. Most often, it was determined between the inferolateral and anterolateral LV basal segments [4]. At the same time, in 23% of cases, the zone was determined in the anterolateral basal segment, as in our patient. This work suggests that a personalized approach to determining the zone of late activation of the intact myocardium and subsequent implantation of the lead in this area is more reasonable than empirical surgery.

However, in the present clinical case, the anterolateral and anterior veins could not be used for endovascular implantation in the required LV segment due to their anatomical characteristics. Thus, the anterolateral vein in this patient was visualized in the mid-apical sections of the LV wall of the same name, and the late posture was located basally. Additionally, the anterior vein was too wide and not suitable for the stable presence of the left ventricular lead in it. In this regard, the planning of epicardial implantation immediately enabled to avoid a repeated surgery, unreasonable expenditure of a CS contrast kit, a delivery system for the LV lead, and the endocardial LV lead itself.

CONCLUSION

The noninvasive mapping technique enables us to identify a patient at the outpatient stage, in whom, targeted implantation of the LV lead cannot be performed using the traditional transvenous method due to the anatomical characteristics of the CS, and to schedule immediately alternative implantation methods in this case. By using this clinical case as an example, we strived to demonstrate that an attempt of standard LV lead implantation would have been unsuccessful without a preoperative study in the scope of noninvasive mapping, including CT angiography of the CS and determination of the late zone in the LV.

ADDITIONAL INFORMATION

Patient consent. The patient voluntarily signed an informed consent to publish personal medical information in anonymized form in the journal Cardiac Arrhythmias.

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

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

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