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Ventricular extrasystoles in patients without cardiac structural changes: mechanisms of development, arrhythmogenic cardiomyopathy predictors, pharmacological and non-pharmacological treatment strategies

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The review article presents critical analysis of clinical studies over the last years, dedicated to ventricular extrasystoles (VEs) detection in practically health individuals, i. e. patients without cardiac structural changes. The development of frequent premature ventricular contractions can induce left ventricular (LV) dysfunction and lead to the formation of arrhythmogenic cardiomyopathy. Therefore, the objective of this article is to determine, based on the analysis of literature and research data, the main mechanisms of VEs development in patients without cardiac structural changes, predictors of LV dysfunction and arrhythmogenic cardiomyopathy induced by premature

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ventricular complexes, and to evaluate the effectiveness of pharmacological and interventional antiarrhythmic therapy. The analysis will show the direction of future clinical studies to improve VEs treatment in patients without cardiac structural changes.

Key words: *ventricular extrasystoles in patients without cardiac structural changes, arrhythmogenic cardiomyopathy prevention principles.*

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Introduction

Ventricular premature contractions or ventricular extrasystoles (VEs) are the most common ventricular arrythmias [1]. Its prognosis depends on the presence of cardiac or extracardiac organic disease, and it is usually considered benign in patients without cardiac structural changes, according to the classification of B. Bigger (1984) [1].

In the 1970s and 1980s, frequent VEs were considered triggers for the development of ventricular tachycardia, ventricular fibrillation, and sudden cardiac death in patients after myocardial infarction (MI) [1]. Therefore, the suppression of VEs was considered essential in these patients. The CAST study showed that antiarrhythmic VEs treatment, especially using class I agents, increased mortality in patients after MI, due to its arrhythmogenic effect, despite effective suppression of premature ventricular complexes [1].

More recent studies have shown that, despite the benign prognosis of VEs in patients without cardiac structural changes, frequent premature ventricular contractions contribute to the development of LV dysfunction and heart failure, and its suppression improves cardiac function [1–3]. On the other hand, VEs in patients without cardiac structural changes can indicate the so-called "arrhythmic" form of arterial hypertension, coronary artery disease, myocarditis, cardiomyopathies, stroke and other cerebrovascular pathology onset, as well as be an independent life-threatening ventricular arrhythmias, atrial fibrillation, and sudden cardiac death predictor [4–10].

Thus, mechanisms of premature ventricular contractions development in patients without cardiac structural changes, risk factors of arrhythmogenic cardiomyopathy development, as well as the effectiveness of VEs pharmacological and interventional treatment are one of the main issues in modern cardiology.

The prevalence of premature ventricular complexes in patients without cardiac structural changes

In early 60s with the introduction of Holter monitor or daily electrocardiogram (ECG) into clinical practice, from 1 to 5 VEs / hour were revealed in 75% of healthy individuals without cardiac structural changes, and over 60 / hour — in 4% during 48-hour ECG monitoring [11–14]. The frequency of VEs detection increased with age, with the presence of any extracardiac pathology and with ECG monitoring duration, and reached about 80% [14]. Similar premature ventricular complexes frequency in patients without cardiac structural changes was found in later studies, the frequency did not differ significantly between men and women [15–19].

Mechanisms of premature ventricular complexes development in patients without cardiac structural changes

Nowadays, it is known that VEs can be caused by various mechanisms, including early or delayed after-depolarization, re-entry, and ectopic pacemaker development [20]. The studies of these mechanisms are mainly based on experimental models and its extrapolation in the development of premature ventricular complexes in patients without cardiac structural changes is limited [21]. The development of delayed after-depolarization is based on Ca++ ions overload in cardiomyocytes [20]. Delayed after-depolarizations are generated by a "transient inward currents" (iti), carried by Na+ and partially K+ ions, controlled by the intracellular concentration of Ca++ ions that are also affected by the entry of Ca++ ions into the cell [20]. Triggered activity induced by delayed after-depolarization is stimulated by heart rate increase, catecholamines, "oxidative stress" in cardiomyocytes, various substances or drugs toxic effects that inhibit intracellular Na-K pumps, for example, digoxin, ß1-adrenoreceptor agonists, etc. [20,22].

Early after-depolarization of cardiomyocytes occur during repolarization or before its completion and cause the development of VEs at the low level of membrane potential — 30 mV. In case such after-depolarization is sufficient, it leads to the appearance of low amplitude action potential. Normally, total ionic current during repolarization is directed outward the cell. When inhibiting the outward and / or increasing background inward current, total current becomes inward that leads to the beginning of membrane depolarization [20,22]. Depolarization can cause cardiomyocyte re-excitation [20,22]. Outward (repolarizing) current decrease can occur in case of decreased membrane permeability to potassium during pronounced extracellular potassium concentration decrease due to hypoxia, heart rate reduction, for example, due to increased vagal tone or action of some toxic substances [20]. VEs caused by early and delayed after-depolarizations are associated with lower cell membranes hyperpolarization compared with arrhythmias caused by re-entry mechanism, thus, cardiomyocyte dysfunctions are potentially reversible: in over 90 % cases, VEs, caused by trigger mechanisms were eliminated after lifestyle modifications (elimination of acute or chronic stress, excessive vagal effects, electrolyte imbalance, autonomic, dysmetabolic disorders, hypoxia, alcohol abuse, coffee, energy drinks, etc.) or after cardioprotective therapy (antihypoxants, antioxidants, potassium preparations, etc.), as well as after classes II or IV antiarrhythmic agents treatment [20–22]. Further membrane hyperpolarization, caused by deeper metabolic disturbances, increases action potential duration and decreases outward and inward currents, for example, the lesion of calcium channels in L-type cardiomyocytes increases repolarization heterogeneity that is usually seen in VEs caused by re-entry mechanism [20–23]. The formation of this mechanism is associated with increased risk of sudden cardiac death due to malignant ventricular arrhythmias development [21,24]. To eliminate premature ventricular contractions, caused by the re-entry mechanism, mainly I and / or III classes of antiarrhythmic agents are used, while II (IV) classes of antiarrhythmic agents have no positive effect [20,21,23,24]. In the absence of positive antiarrhythmic pharmacotherapy effect, the development of VEs in patients without cardiac structural changes is usually caused by ectopic pacemaker development, that is mainly eliminated by radiofrequency ablation [1,21,24].

Clinical evaluation of premature ventricular complexes in patients without cardiac structural changes

VEs in patients without cardiac structural changes are considered "idiopathic" after eliminating potential causes of this arrhythmia and may manifest as heart rate interruptions, subjective sensation of " a beat followed by heart sinking", inspiratory dyspnea during physical activity, lightheadedness, chest pain behind the sternum or in the left side of the chest [1.16.17.21]. Some of these patients have asymptomatic premature ventricular contractions that are usually diagnosed during regular examination [1.17.21]. The absence of clinical symptoms in patients without cardiac structural changes and with VEs may be one of the risk factors for LV dysfunction development that leads to the formation of arrhythmogenic cardiomyopathy. It is also remarkable that many patients without cardiac structural changes with asymptomatic VEs have normal LV function. Time before accidental detection of VEs in these patients and the development of LV dysfunction can be quite long. Some patients have asymptomatic VEs for years or decades before the development of heart dysfunction [1.17.21].

Clinical examination of patients without cardiac structural changes and without clinical manifestations of heart failure often does not reveal any abnormalities, except for irregular heartbeat caused by premature contractions. Standard ECG and 1–3 day 12-lead ECG monitoring can identify VEs and assess its morphology and localization in such patients [1,21]. It should be noted that patients without cardiac structural changes often have variability of VEs during the day, thus, it is better to assess the number of premature ventricular complexes by continuous 48–72-hour ECG monitoring. It is also essential to determine whether LV dysfunction developed before VEs or was caused by premature complexes.

The initial absence of cardiac structural changes is established by transthoracic echocardiography [25] and exclusion of cardiac and extracardiac diseases (rheumatic heart disease, cardiomyopathies, heart defects, mitral valve prolapse, myocarditis, thyrotoxicosis, postmyocarditis cardiosclerosis, obesity, hyperlipidemia, arterial hypertension, various clinical forms of coronary artery disease, short and long QT syndromes, early repolarization, complete blockade of the bundle of His, anemia, chronic lung diseases, nasopharynx, diabetes mellitus, diseases of the gastrointestinal tract, etc.), electrolyte disorders, the use of drugs and / or toxic substances abuse (primarily diuretics, oral contracep-

tives, inhaled beta-adrenoreceptor agonists, alcohol, coffee, energy drinks, etc.) that directly or indirectly cause VEs [1,16,17,21]. When heart dysfunction is detected, it is necessary to assess if it preceded VEs development or was its result [1,17,21]. In case patient's echocardiographic examination does not reveal any structural and functions cardiac impairments [1,25] in patients without any cardiac and extracardiac pathologies, it is necessary to perform stress echocardiography [1,21]. Patients with positive or doubtful results of the stress test, as well as with one large or two small criteria for right ventricular (RV) arrhythmogenic dysplasia, ventricular late potentials, unstable ventricular tachycardia, or who's profession is associated with other people's live risks (pilots, public transport drivers, etc.), underwent invasive and / or non-invasive coronagraph, contrast magnetic resonance heart imaging or stress myocardial scintigraphy with technetium 99 or thallium-201 to determine latent myocarditis, cardiomyopathy or latent myocardial ischemia. [1,21]. If ventricular late potentials are detected in patients with negative results of stress echocardiography, as well as in the case of VEs frequency increase, the development of unstable ventricular tachycardia after the stress test, it is necessary to conduct non-invasive coronary angiography and contrast magnetic resonance imaging, since the results of these research methods identify potential candidates for the surgical removal of premature ventricular contractions in patients without cardiac structural changes [1,21].

Predictors of left ventricular dysfunction development in patients with premature ventricular contractions without cardiac structural changes

LV dysfunction and arrhythmogenic cardiomyopathy do not develop in all patients without cardiac structural changes with premature ventricular contractions [1,21,34]. Asymptomatic VEs may be seen before the development of heart failure [1,17,21]. Predictors of LV dysfunction in patients without cardiac structural changes include the nature of the ventricular contraction (duration of the QRS complex, adhesion intervals), its localization, frequency per hour and / or amount per day of observation, and variability during the day.

The duration of QRS complex of premature ventricular contraction, adhesion intervals, the presence of interpolated VEs

The duration of QRS complex≥ 140 m/s and interpolated VEs are independent predictors of LV systolic and, less often, diastolic dysfunction [26–30]. The causes of QRS complex expansion haven't been well understood yet, however, according to some authors, they may include with cardiac impulse slowdown from the cardiomyocyte to ventricular myocardiocyte during premature contraction [31]. The adhesion interval≤ 600 m / s with low variability (less than 60 m/s) is associated with LV ejection fraction decrease, possibly due to incomplete LV filling and stroke volume decrease [32,33]. However, larger studies are needed to identify the causes of QRS complex changes [1,21].

Ventricular extrasystoles frequency

Previously, the detection of≥ 24 % VEs of all ventricular complexes was considered as independent predictor of arrhythmogenic cardiomyopathy development [18]. However, recent studies have shown that the detection of≥ 10–15 % of premature ventricular complexes of all ventricular contractions can already induce the development of LV dysfunction [21,34]. It is also remarkable that the amount of VEs is a modifiable risk factor for LV dysfunction: pharmacological therapy and / or surgeries reduce total number of premature ventricular complexes, as well as the risk for arrhythmogenic cardiomyopathy [1,17,21].

Premature ventricular contractions localization

About 70–75 % of VEs originate from the right ventricular outflow tract, and the rest — from interventricular septum, papillary muscles, left ventricle free wall or His bundle [1,17,21]. Arrhythmias originating from the right ventricular outflow tract have typical 12-lead ECG pattern — positive QRS complexes in II, III and aVF leads. This VEs morphology is similar to blockade of the left leg of the bundle of His and often indicates origin from the right ventricular outflow tract, although arrhythmias from the aortic valve can also have similar pattern, but with earlier QRS transition [26]. On the other hand, premature ventricular complex morphology, similar to blockade of the right leg of the bundle of His, usually indicates origin from the LV [1,16,17,21]. Nowadays, we can determine the origin of VEs by its various morphologies on ECG: if the QRS complex transition zone (when the R wave of the ventricular extrasystole is approximately equal to the S wave) is seen in the chest leads later than in sinus rhythm, this indicates right ventricular outflow tract origin, and early transition zone in the chest leads — LV origin [35,36]. If the QRS complex transition zone in sinus rhythm and in VEs is detected in

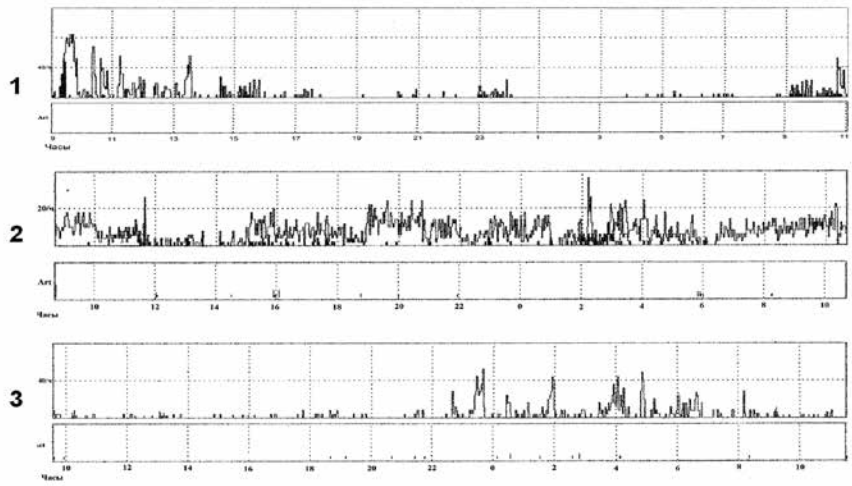

Figure 1. Distribution of VEs during the day: 1 — sympathetic type — extrasystoles are mainly detected in the daytime; 2 — permanent or mixed — extrasystoles are detected continuously throughout 24-hours; 3 — vagal or night type — extrasystoles are detected mainly in the evening and in the nighttime, its frequency decreases after waking up.

lead V3, when the amplitude of the R wave of premature ventricular contraction compared with the amplitude of the R wave of the QRS complex of the sinus rhythm in V2 lead is≥0.6, premature ventricular depolarization from the left ventricle is determined with 95 % sensitivity of and 100 % specificity [37]. In addition, it was proposed to calculate premature ventricular contraction maximum deflection index — the ratio of time from the beginning to the maximum of R or S wave to the duration of QRS complex of premature ventricular contraction. When premature ventricular contraction maximum deflection index≥ 0.55, epicardial origin of VE can be determined [38].

Discussed above ECG features are essential in the initial assessment of VEs in patients without cardiac structural changes to determine treatment strategies to eliminate premature ventricular contractions. Ventricular dyssynchrony can contribute to the development of LV dysfunction, and the right ventricular and epicardial origins of VEs are associated with the highest risk of LV dysfunction and arrhythmogenic cardiomyopathy [39,40].

Variability of premature ventricular contractions during the day

Frequent VEs during the day (Fig. 1, type 2) is an independent predictor of arrhythmogenic cardiomyopathy development [1,21,26].

Gender effect on arrhythmogenic cardiomyopathy development in patients with VEs

Women are more sensitive, therefore, VEs in women are diagnosed earlier than in men. For this reason, women are less likely to develop arrhythmogenic cardiomyopathy, since VEs treatment is usually started earlier. Therefore, male gender is an independent risk factor for the development of arrhythmogenic cardiomyopathy in patients without cardiac structural changes and VEs [1,21,39,40].

Treatment strategies in patients with premature ventricular contractions without cardiac structural changes

VEs treatment in patients without cardiac structural changes with subjective arrhythmia feelings include lifestyle modification, antiarrhythmic pharmacotherapy and radiofrequency ablation to reduce or completely eliminate premature ventricular complexes [1,21,41,42]. Therapy effectiveness was evaluated using 1–3 daily Holter ECG monitoring: before and after pharmacotherapy (for 5–7 days) or catheter ablation, the criterion for positive effect is the reduction of extrasystoles frequency by over 75 % compared with its initial level, as well as the elimination of paired, group extrasystoles and unstable ventricular tachycardia [1,16,17,21]. Lifestyle modification, including reduced caffeine / alcohol consumption, psycho-emotional state monitoring, etc. has low effectiveness in VEs frequency reduction in patients without cardiac structural changes [1,21,39–41]. On the other hand, interventional treatment is generally not considered in patients without subjective arrythmia feeling with frequent premature ventricular complexes and preserved heart function [1,21,41,42]. Most patients without cardiac structural changes with frequent but asymptomatic VEs have normal LV ejection fraction and usually do not develop arrhythmogenic cardio-

myopathy [1,21,40,41,42]. Beta-blockers or calcium channel blockers can be used to reduce VEs frequency. All patients using these antiarrhythmic agents should be informed to contact physician on any heart failure symptoms and conduct ECG at least once every 3–6 months to assess LV ejection fraction [1,21].

Pharmacological treatment

According to the latest guidelines [1,21], radiofrequency ablation of the arrhythmogenic focus is recommended in patients without cardiac structural changes who have over 10–15 % VEs of the total ventricular complexes, as well as in patients who refuse to take antiarrhythmic pharmacotherapy or in case of its ineffectiveness [1,21,34]. This recommendation is the basis of initial antiarrhythmic pharmacotherapy of VEs in this category of patients.

Beta-blockers or calcium antagonists are usually first-line pharmacological treatment for patients without cardiac structural changes with subjective arrhythmia feeling. [1,21]. Numerous randomized studies have shown metoprolol, propranolol, carvedilol and atenolol positive effect on VEs frequency in this category of patients. It is also remarkable that these drugs were most effective in sympathetic or daytime distribution of VEs (Fig. 1, type 1) [1,21,24, 34,40]. It should be noted that anticholinergics, beta-blockers with intrinsic sympathomimetic activity or non-dihydropyridine calcium channel blocker are more effective in patients with vagal or nighttime type of VEs distribution (Figure 1, type 3) [1,21,24,34,40]. The effectiveness of beta-blockers or calcium channel blockers ranges from 15 to 20 %, and its positive clinical effect is observed for 1–2 or, rarely, 3 years [1,21,24,34,40]. Meanwhile, beta-blockers and calcium channel blockers are first-line treatment due to its relative safety and the minimal amount of side effects [1,21].

Classes I and / or III antiarrhythmic agents, such as flecainide, propafenone, mexiletine, ethacyzin, moricizine, allapinin, and sotalol, are referred to second line treatment of VEs in patients without cardiac structural changes [1,16,17,21]. It is known that class I antiarrhythmic agents are contraindicated in patients with LV dysfunction and cardiac structural changes [1,16,17,21]. Therefore, amiodarone is recommended in patients with LV dysfunction, predominantly systolic, without cardiac structural changes to reduce VEs frequency [1,21,24,40,41]. However, its long-term use in patients without cardiac structural changes, especially of a young age, is undesirable due to numerous side effects [1,16,17,21]. Many studies have shown that the efficacy of classes I and III antiarrhythmic agents reaches about 90 %, and positive antiarrhythmic effect, in most cases, does not exceed 4–5 years [1,16,17,21,24,40,41]. A few studies showed that class I antiarrhythmic agents can be effective after at least one unsuccessful radiofrequency ablation [40,41,42]. Now it is known that combinations of antiarrhythmic agents (class II with class I or class III with I) can be effective in VEs frequency reduction in patients without cardiac structural changes, however, unfortunately, there are no large-scale clinical studies on effectiveness and safety of these treatment strategies.

Catheter ablation

Catheter ablation is recommended in patients without cardiac structural changes with frequent monomorphic VEs, only in case of ineffective antiarrhythmic pharmacotherapy or in patients refusing to take antiarrhythmic agents [21,34]. Potential benefits of radiofrequency ablation need to be weighed against the risks of serious complications, that occur in 3 % of patients on average [43–45]. Vascular complications include: ileal artery false aneurism, arteriovenous fistula or inguinal hematoma, cardiac perforation with tamponade, intraprocedural stroke, or sudden death [45,46,47]. In addition, efficacy and risks of complications of catheter ablation depend on VEs anatomical location, and surgeon experience [45,46,47]. These factors are most important when choosing radiofrequency ablation center [45,46,47]. Nevertheless, continuous improvements in ablation technology, energy sources, and advanced software for three-dimensional mapping have allowed radiofrequency ablation to become relatively safe and effective method to reduce frequency or completely eliminate VEs in patients without cardiac structural changes [43,45]. Nowadays, successful ablation can be performed in patients without cardiac structural changes with almost all known localizations of VEs [43,45]. The key to successful interventional elimination of VEs is fluoroscopy control, as well as cardiostimulation, electroanatomical intracardiac mapping and intracardiac echocardiography [43,45]. Cryoablation can be a promising alternative to radiofrequency ablation in cases of complex localization of VEs, for example, left aortic root, the orifice of the left main coronary artery or papillary muscles due to catheter stabilization difficulties and high mobility of the papillary muscles [43,45]. According to many authors, ra-

diofrequency ablation of VEs, originating from right ventricular outflow tract, in patients without cardiac structural changes is superior to drug therapy [43–45.48]. Some researchers showed that the duration of ablation positive effect was longer compared with antiarrhythmic pharmacotherapy [43,44], others — that it was approximately the same [44, 45, 48].

Conclusion

VEs are often observed in patients without cardiac structural changes and can cause LV dysfunction and arrhythmogenic cardiomyopathy. Radiofrequency ablation is recommended in patients with ineffective antiarrhythmic pharmacotherapy, subjective arrythmia feelings as well as with 10–15% monomorphic VEs from of total ventricular complexes. Interventional treatment methods are becoming first-line treatment in patients without cardiac structural changes with monomorphic VEs, especially originating from right ventricular outflow tract. Currently, there is no sufficient evidence to recommend radiofrequency ablation in patients with asymptomatic VEs without cardiac structural changes and preserved LV function. Catheter ablation in these patients, guided only by the frequency and / or amount of VEs, can be a potentially dangerous method with unpredictable result. Further studies are needed to discover molecular, cellular and hemodynamic mechanisms of VEs development in patients without cardiac structural changes as well as LV dysfunction predictors.

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References

1. Braunwald's Heart Disease. A textbook of cardiovascular medicine. 11th ed. Zipes D.P., Libby P., Bonow R.O. et al., Elsevier Science. 2018. 5174 p.
2. Kanei Y., Friedman M., Ogawa N. et al. Frequent premature ventricular complexes originating from the right ventricular outflow tract are associated with left ventricular dysfunction. Ann Noninvasive Electrocardiol. 2008;13 (1): 81–85.
3. Duffee D.F., Shen W.K., Smith H.C. Suppression of frequent premature ventricular contractions and improvement of left ventricular function in patients with presumed idiopathic dilated cardiomyopathy. Mayo Clin Proc. 1998;73:430–433.
4. Gaita F., Giustetto C., Di Donna P. et al. Long-term follow-up of right ventricular monomorphic extrasystoles. J Am Coll Cardiol. 2001;38 (2): 364–370.
5. Agarwal S.K., Heiss G., Rautaharju P.M. et al. Premature ventricular complexes and the risk of incident stroke: the Atherosclerosis Risk In Communities (ARIC) Study. Stroke. 2010;41 (4): 588–593.
6. Prystowsky E.N., Padanilam B.J., Joshi S., Fogel R.I. Ventricular arrhythmias in the absence of structural heart disease. Am Coll Cardiol., 2012;59 (20): 1733–1744.
7. Massing M.W., Simpson R.J.Jr., Rautaharju P.M. et al. Usefulness of ventricular premature complexes to predict coronary heart disease events and mortality (from the Atherosclerosis Risk in Communities Cohort). Am J Cardiol. 2006;98 (12): 1609–1612.
8. Cheriyath P., He F., Peters I. et al. Relation of atrial and/or ventricular premature complexes on a two minute rhythm strip to the risk of sudden cardiac death (the Atherosclerosis Risk in Communities [ARIC] study). Am J Cardiol. 2011;107 (2): 151–155.
9. Olesin A.I., Koziy A.V., Semenova E.V. et al. Clinical assessment of life-threatening ventricular arrhythmia predictor in patients with ventricular exstrasystolia and no morphological heart pathology (a prospective study). Russian Journal of Cardiology. 2010;(1): 5–12. Russian.
10. Koziy A.V., Olesin A.I., Litvinenko V.A., Konstantinova I.V. Clinical evaluation of the detection of ventricular extrasystole in patients without structural changes in the heart: a prospective study. Pediatr, 2017; 8 (4): 64–72. Russian.
11. Hiss R.G., Lamb L.E. Electrocardiographic findings in 122043 individuals. Circulation. 1962;25:947–961.
12. Kostis J.B., McCrone K., Moreyra A.E., et al. Premature ventricular complexes in the absent of identifiable heart disease. Circulation. 1981;63:1351–1356.
13. Clarke J.M., Hamer J., Shelton J.R., et al. The rhythm of the normal human heart. Lancet. 1976;1:508–512. DOI:10.1016/s0140–6736 (76) 90801–1
14. Kennedy H.L., Whitlock J.A., Sprague M.K. et al. Long-term follow up of asymptomatic healthy subjects with frequent and complex ventricular ectopy. N Engl J Med. 1985;312:193–197.
15. Lee A.K., Devel M.W. Premature ventricular contraction-induced cardiomyopathy. Curr.Opion. Cardiol., 2016; 31 (1): 1–10.
16. Kushakovsky M.S., Grishkin Yu.N. Cardiac arrhythmias. St. Petersburg: Foliant, 2017. 720 p. Russian.
17. Cardiology: national guideline / ed. by E.V. Shlyaxto. 2 ed. Upd. and rev. M: GEOTAR-Media, 2015. 800 p. Russian.
18. Priori S.G., Blomström-Lundqvist C., Mazzanti A. et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). *European Heart Journal, 2015;*36 (41): 2793–2967.
19. Van Huls van Taxis C.F., Piers S.R., de Riva S.M. Fatigue as presenting symptom and a high burden of premature ventricu-

lar contractions are independently associated with increased ventricular wall stress in patients with normal left ventricular function. Circ Arrhythm Electrophysiol. 2015;8 (6): 1452–1459.
20. Antzelevitch C., Burashnikov A. Overview of Basic Mechanisms of Cardiac Arrhythmia. Card. Electrophysiol. Clin. 2011;3 (1): 23–45.
21. Cronin E.M., Bogun F.M., Maury P. et.al. 2019 HRS/EHRA/APHRS/LAHRS expert consensus statement on catheter ablation of ventricular arrhythmias. J. Arrhythm., 2019; 35 (3): 323–484.
22. Sovari A.A. Cellular and molecular mechanisms of arrhythmia by oxidative stress. Cardiol. Res. Pract., 2016; 2016: 9656078.
23. Wang Y., Eltit J.M., Kaszala K. et al. Cellular mechanism of premature ventricular contraction-induced cardiomyopathy. Heart Rhytm, 2014; 11 (11): 2064–2072.
24. Panizo J.G., Barra S., Mellor G. et al. Premature Ventricular Complex-induced Cardiomyopathy. Arrhythm. Electrophysiol. Rev., 2018; 7 (2): 128–134.
25. Lang R.M., Badano L.P., Mor-Avi V. et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015; 28 (1): P.1–39.
26. Del Carpio Munoz F., Syed F.F., Noheria A. et al. Characteristics of premature ventricular complexes as correlates of reduced left ventricular systolic function: study of the burden, duration, couplinginterval, morphology and site of origin of RVCs. J Cardiovasc Electrophysiol. 2011;22:791–8.
27. Yokokawa M., Kim H.M., Good E. et al. Impact of QRS duration of frequent premature ventricular complexes on the development of cardiomyopathy. Heart Rhythm. 2012;9:1460–4.
28. Huizar J.F., Kaszala K., Rotfay J. et al. Left ventricular systolic dysfunction induced by ventricular ectopy: a novel model for premature ventricular contraction-induced cardiomyopathy. Circ Arrhythm Electrophysiol. 2011;4:543–9.
29. Carballeira P.L., Deyell M.W., Frankel D.S. et al. Ventricular premature depolarization QRS duration as a new marker of risk for the development of ventricular premature depolarization-induced cargiomyopathy. Heart Rhytm 2014; 11 (2): 299–306.
30. Yamada S., Chung F.P., Lin Y.J. et al. Electrocardiographic characteristics for predicting idiopathic right ventricular outflow tract premature ventricular complex-induced cardiomyopathy. J interv Card Electrophysiol., 2018: 53 (2): 175–185.
31. Sheikin F., Ross R., Chen J. Cell-cell connection to cardiac disease. Trengs Cardiovasc. Med., 2009;19 (6): 182–190.
32. Bradfield J.S., Homsi M., Shivkumar K., Miller J.M. Coupling interval variability differentiates ventricular ectopic complexes arising in the aortic sinus of valsalva and great cardiac vein from other sources: mechanistic and arrhythmic risk implications. J Am Coil Cardiol. 2014;63:2151–8.
33. Dukes J.W., Dewland T.A., Vittinghoff E. et al. Ventricular ectopy as a predictor of heart failure and death. J Am Coll Cardiol. 2015;66:101.
34. Al-Khatib S.M., Stevenson W.G., Ackerman M.J. et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol., 2018; 72 (14): 1677–1749.
35. Scanavacca M., Lara S., Hardy C., Risani C.F. How to identify & treat epicardial origin of outflow tract tachycardias. JAtr Fibrillation. 2015;7:1195.
36. Hutchinson M.D., Garcia F.C. An organized approach to the localization, mapping, and ablation of outflow tract ventricular arrhythmias. J Cardiovasc Electrophysiol. 2013;24:1189–97.
37. Betensky B.R., Rark R.E., Marchlinski F.E. et al. The V (2) transition ratio: a new electrocardiographic criterion for distinguishing left from right ventricular outflow tract tachycardia origin. J Am Coil Cardiol. 2011;57:2255–62.
38. Daniels D.V., Lu Y.Y., Morton J.B. et al. Idiopathic epicardial left ventricular tachycardia originating remote from the sinus of Valsalva: electrophysiological characteristics, catheter ablation, and identification from the 12-lead electrocardiogram. Circulation. 2006;113:1659–66.
39. Latchamsetty R., Bogun F. Premature ventricular complex-induced cardiomyopathy. RevEsp Cardiol (Engl Ed) 2016;69:365–9.
40. Latchamsetty R., Bogun F. Premature ventricular complex-induced cardiomyopathy. JACC Clin Electrophysiol. 2019;5 (5): 537–550.
41. Callans D.J. Premature ventricular contraction-induced cardiomyopathy. Arrhyth Electrophysiol Rev. 2017;6:153–155.
42. Hyman M.C., Mustin D., Supple G. et al. Class IC antiarrhythmic drugs for suspected premature ventricular contraction-induced cardiomyopathy. Heart Rhythm. 2018;15:159–63.
43. Sharma E., Arunachalam K., Di M. et al. PVCs, PVC –Induced Cardiomyopathy, and the Role of Catheter Ablation. Crit Pathw Cardiol., 2017; 16 (2): 76–80.
44. Ling Z., Liu Z., Su L. et al. Radiofrequency ablation versus antiarrhythmic medication for treatment of ventricular premature beats from the right ventricular outflow tract: Rrospective randomized study. Circ Arrhythm Electrophysiol. 2014;7:237–243.
45. Oomen A.W.G., Dekker L.R.C., Meijer A. Catheter ablation of symptomatic idiopathic ventricular arrhythmias. A five-year single-centre experience. Neth Yeart J., 2018; 26 (4): 210–216.
46. Lamba J.L., Redfearn D.P., Michael K.A. et al. Radiofrequency catheter ablation for the treatment of idiopathic premature ventricular contractions originating from the right ventricular outflow tract: a systematic review and meta-analysis. Pacing Clin Electrophysiol. 2014;37:73–78.

47. Penela D., Van Huls Van Taxis C., Aguinaga L. et al. Neurohormonal, structural, and functional recovery pattern after premature ventricular complex ablation is independent of structural heart disease status in patients with depressed left ventricular ejection fraction: a prospective multicenter study. J Am Coll Cardiol. 2013;62:1195–1202.

48. El Kadri M., Yokokawa M., Labounty T. et al. Effect of ablation of frequent premature ventricular complexes on left ventricular function in patients with nonischemic cardiomyopathy. Heart Rhythm. 2015;12:706–713.