

Clinical evaluation to identify the predictors of arrhythmogenic cardiomyopathy in patients with ventricular extrasystoles without structural heart changes.

Clinical and experimental study

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The aim of the study was to evaluate the complex determination of predictors of “arrhythmogenic cardiomyopathy” in patients with ventricular extrasystoles (VE) without structural heart changes to predict the development of cardiovascular diseases in a prospective study.

Methods. Experimental study. Rats were used to model VE by the mechanism of early postdepolarization (aconitine arrhythmia), rabbits — for delayed postdepolarization (barium chloride-induced arrhythmia), and dogs — for re-entry peroxide arrhythmia. In the electrocardiogram (ECG), in addition to the conventional parameters, the pre-excitation interval, its variability and the index of intrinsic deviation of VE (IDVEi) were analyzed.

Clinical study. We observed 412 patients without structural changes of the heart aged from 16 to 43 years (mean 28.4 ± 0.8 years), and the number of VEs per day of observation ranged from 6157 to 37254 (mean 19706 ± 656 VEs). The same parameters were determined by the ECG as in experimental arrhythmias: they were calculated separately for mono- and polymorphic left- and right ventricular extrasystoles (LVE and RVE). The duration of patient follow-up was up to 10 years.

Results. In the modeling of ventricular arrhythmias by the mechanism of delayed postdepolarization, polymorphic VE, early postdepolarization — early monomorphic VE, re-entry — early and late monomorphic VE were registered. In the animals with the modeling of arrhythmia by the mechanism of re-entry IDVEi was significantly higher in comparison with VE caused by the mechanisms of early and delayed postdepolarization. The main predictors of “arrhythmogenic cardiomyopathy” in patients without structural changes of the heart with VE, which determine the development of organic heart pathology, such as coronary heart disease (CHD) and mitral valve prolapse (MVP), are IDVEi and QRS_{VE} complex duration. Increased values of these parameters (>0.42 units and

148 m/s, respectively), characterize the risk group of cardiovascular pathology formation.

The development of CHD in patients without structural heart changes with VE highly correlated with IDVEi ≥ 0.56 units, duration of QRS_{VE} complex ≥ 157 m/s in monomorphic LVE, use of class III drugs. The development of MVP in these patients highly correlated with duration of QRS_{VE} complex ≥ 159 m/s in polymorphic VE, efficacy of class I drugs and to a lesser extent of the class III drugs.

Conclusion. In patients without structural heart changes with VE, the increase in IDVEi values and QRSVE complex duration >0.48 units and 149 m/s, respectively, determine the risk group of cardiovascular pathology formation. In patients without structural heart changes with VE, the development of CHD highly correlated with IDVEi ≥ 0.56 units, QRSVE complex duration ≥ 157 m/s in monomorphic LVE, and MVP — with QRSVE complex duration ≥ 159 m/s in polymorphic VE.

Keywords: ventricular extrasystoles, predictors of the development of organic heart pathology in patients without structural heart changes.

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Introduction

It is now known that despite the benign course of ventricular extrasystoles (VE) in patients without structural heart disease, frequent ventricular ectopy may contribute to the development of left ventricular dysfunction manifested by clinical symptoms of heart failure, and suppression of premature ventricular complexes usually leads to improvement in cardiac function [1, 2]. In most cases, it is relatively harmless, but VE may be one and only manifestation of the onset of various diseases, particularly of the cardiovascular system, such as coronary heart disease (CHD), mitral valve prolapse (MVP), etc. [1, 2]. In these patients, various predictors are used to assess the risk

of “arrhythmogenic cardiomyopathy”. Most often, the number of premature ventricular contractions per day of observation is determined (for example, more than 15% of premature ventricular ectopias from all cardiac contractions, including the number of paired, grouped VEs and/or ventricular complexes that constitute unstable ventricular tachycardia [2, 3]). Also, the duration of the QRS complex in VE and sinus rhythm (QRS_{VE} and QRS_{Sr}), the index of internal deviation of VEs (IDVEi) are sometimes taken into account. The duration of the corrected premature ventricular ectopic interval (PEIVEc), its variability, e.g. by determining the linear deviation (LD) of PEIVEc have also been used in clinical practice [1, 3]. Hypothetically, it

is possible to assume that in experimental modeling of VE it is possible to estimate the frequency of detection and significance of predictors of the occurrence of “arrhythmogenic cardiomyopathy” depending on the mechanism of development of induced ventricular arrhythmia. In the available literature no information was found on the possibility of using the predictors of “arrhythmogenic cardiomyopathy” in patients with VE without structural heart changes (including those depending on the mechanism of its development) to predict the development of cardiovascular diseases.

The aim of the study was to evaluate the complex determination of predictors of “arrhythmogenic cardiomyopathy” in patients with ventricular extrasystoles (VE) without structural heart changes to predict the development of cardiovascular diseases in a prospective study.

Methods

Experimental study

Experiments were performed on 11 Wistar rats (male and female, body weight 180-240 g), 12 rabbits and 14 mongrel dogs weighing 1.2–2.4 kg (average — 1.7 ± 1.4 kg) and 5.5–12.3 kg (average — 9.2 ± 1.3 kg). The choice of experimental arrhythmias was made taking into account the electrophysiological mechanisms involved in their formation. Arrhythmias with the mechanism of early postdepolarization were modeled with aconitine, delayed postdepolarization — with barium chloride, re-entry — with hydrogen peroxide [4].

In rats, the early postdepolarization mechanism was modeled by intravenous injection of aconitine hydrobromide at a dose of 10.0 µg/kg, and in rabbits, the delayed postdepolarization mechanism was modeled by intravenous injection of barium chloride at a dose of 5 mg/kg [4]. In dogs, after removal of the pericardium under hexenal anesthesia, ventricular arrhythmias were modeled in the open heart by injection of arrhythmogen (0.3% hydrogen peroxide) into the ventricular myocardium [4]. After hydrogen peroxide injection, vascular damage is first observed with the subsequent development of “oxidative stress” of cardiomyocytes [4–6] and the occurrence first of VE due to the mechanism of early postdepolarization [7] and then, with further membrane hyperpolarization and prolongation of action potential duration — to re-entry [4, 8]. In all dogs, the mechanism of arrhythmia development was assessed by excitation conduction

mapping [8]. Electrograms and electrocardiograms (ECG) in standard and augmented leads were recorded on a digital electrocardiograph “Poly-Spectrum” (Neurosoft, Ivanovo). On ECG, after modeling of each ventricular arrhythmia, we calculated PEIVEc and its LD separately for left and right ventricular extrasystoles (LVE and RVE). We also calculated the ratio of PEIVE to QT of sinus rhythm (QTsr.), IDVEi, defined as the ratio of the time from the onset of the premature ventricular contraction to the apex of the maximum R or S wave of the premature ventricular complex to the duration of QRS_{VE} [4, 9, 10].

Clinical study

412 patients aged 16 to 43 years (mean — 28.4 ± 0.8 years) were observed. Inclusion criteria: absence of structural cardiac changes, presence of sinus rhythm, detection of class IV–V VE according to Rayn M. (1985) classification [1], subjective sensation of arrhythmia, LVEF $\geq 54\%$, chronic heart failure class I–II according to NYHA [1, 9], informed patient consent for research and treatment. The study was approved by the local ethics committee.

The absence of structural cardiac changes was confirmed after exclusion of cardiac and extracardiac diseases, electrolyte disorders, use of medications and/or toxic products (mainly diuretics, oral contraceptives, alcohol abuse, etc.) that independently or indirectly led to the development of VE, as well as other exclusion criteria. Those included the use of various stress tests, invasive and noninvasive coronary angiography, and contrast-enhanced magnetic resonance imaging, which were described earlier [1, 9].

In addition to a general clinical examination, all patients underwent ECG monitoring (1–3 days) and echocardiographic examination with the Hitachi EUB-5500 according to generally accepted methods. Calculation of hemodynamic parameters such as LVEF, etc. and determination of the localization of premature ventricular complexes have been described previously [8–10]. In addition, PEIVEc and its LD separately for LVE and RVE, the ratio of PEIVE to QTsr, IDVEi, QRS_{VE} complex duration were calculated as in the experimental study.

In the first stage, all patients were treated primarily with cardioprotective therapy, including potassium supplements, sedatives, polyunsaturated fatty acids, etc., to eliminate VE. [1, 9], and if there was no effect, the choice of differentiated antiarrhythmic therapy

Table 1

ECG parameters of VEs induced in the experiment ($M \pm m$, 95% confidence interval of mean values in parentheses)

Parameters	Early postdepolarization (aconitine arrhythmia), n = 11	Delayed postdepolarization (barium chloride-induced arrhythmia), n = 12	Early postdepolarization (peroxide arrhythmia), n = 14	Re-entry (peroxide arrhythmia) n = 14
PEIVE/QTsr, units	1.11±0.02 (1.03–1.18)	1.83±0.16* (1.36–2.28)	1.12±0.02 (1.04–1.21)	1.78±0.17* (1.14–2.28)
LDcPEVEi, ms	1.71±0.03 (1.64–1.83)	42.12±3.69* (25.05–58.14)	1.73±0.06 (1.55–1.92)	39.33±3.17* (24.82–54.93)
IDVEi, units	0.29±0.02 (0.25–0.34)	0.31±0.02 (0.22–0.38)	0.32±0.03 (0.24–0.42)	0.66±0.02* (0.58–0.72)
QRSVE/QRSsr	1.36±0.03 (1.25–1.44)	1.37±0.03 (1.27–1.48)	1.31±0.03 (1.21–1.43)	1.91±0.09* (1.56–2.23)

Note. * — reliable difference of parameters in comparison with VE caused by the mechanism of early postrepolarization (at $p < 0.05$).

for VE was based on screening tests with antiarrhythmic drugs of classes I–III used in average therapeutic doses [9]. Class II drugs were used first, and if they were ineffective, class I or III drugs were used, with amiodarone used last if necessary. The antiarrhythmic drugs of choice were metoprolol at 50–100 mg/day, propranolol at 80–160 mg/day, carvedilol at 25–50 mg/day, and lappaconitine hydrobromide (Allapinin) at 50–75 mg/day, diethylaminopropionylethoxycarbonylaminophenothiazine (etacizine) — 100–150 mg/day, sotalol — 160–240 mg/day, propafenone (propanorm) — 300–600 mg/day, amiodarone — 600–800 mg/day. In the absence of effect of monotherapy, the combined therapy was used instead. Daily ECG monitoring was performed before and after antiarrhythmic therapy, and the criterion of positive effect was reduction of the number of extrasystoles by 75% or more in comparison with their initial number, as well as elimination of paired and group extrasystoles [1, 2].

For statistical processing of the obtained data we used mean values and error of mean values ($M \pm m$), standard deviation (σ), 95% CI of mean values, Student's t-test, χ^2 criteria, ($p < 0.05$ values were considered as statistically significant). The normality of the distribution of the studied quantitative parameters was checked using the Kolmogorov-Smirnov test and $\pm 3\sigma$ rule (Gaussian distribution), Pearson's and Spearman's linear pairwise and rank correlations (r) (for nonparametric parameters) were used, respectively. The comparison of two binary variables was assessed using the logistic regression method with determination of the odds ratio (OR) using the computer program "Statistica", version 11.0.

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

Results

Experimental study

Polymorphic LVE or RVE were registered in modeling of barium chloride-induced arrhythmia, in aconitine arrhythmia — early monomorphic LVE or RVE, in re-entry peroxide arrhythmia — first early, then early and late monomorphic LVE. Development of unstable VT was observed in all animals with aconitine arrhythmia modeling, in 6 (42.86%) of 14 dogs with re-entry peroxide arrhythmia. In animals with barium chloride-induced arrhythmia modeling, PEIVE/QTsr and LDPEIVEc values were significantly greater compared to aconitine arrhythmia, whereas all indices studied were significantly greater when VE was induced by the re-entry mechanism compared with ventricular ectopy induced by the early postdepolarization mechanism caused by aconitine and hydrogen peroxide administration. There were no significant changes in the other parameters studied (Table 1).

Clinical study

In 412 patients without structural heart changes, the number of premature ventricular contractions per day of observation ranged from 6157 to 37254 (mean — 19706 ± 656 VEs). In 166 patients (40.29%) the development of cardiovascular or gastrointestinal diseases was observed during 1–10 years after the first examination (main group), and in the rest of the patients during this period of observation there were no structural changes of the heart at the first and subsequent examinations, as well as cardiovascular system diseases and pathology of other organs and systems (comparison group). Various clinical forms of CHD were detected in 41 (24.70%) patients of the main group, 11 (26.83%) of them had myocardial infarction, and in 22 (73.33%) of 30 patients the diagno-

Table 2

Characteristics of ventricular extrasystole and efficacy of antiarrhythmic therapy in patients without structural heart changes

Parameters	Patients group	Comparison group, n = 246	Main group, n = 166		
			CHD, n = 41	MVP, n = 15	GI diseases, n = 110
Number of VEs from 6,000 to 15,000/day		115(46.75 %)	27(65.85 %)	8(53.33 %)	56(50.91 %)
Number of VEs more than 15000/day		131(53.25 %)	14(34.15 %)	7(46.67 %)	54(49.09 %)
Monomorphic LVE		5(2.03 %)	38(92.68 %)*	—	---
Polymorphic LVE		10(4.07 %)	—	9(60 %)*	34(30.91 %)*
Monomorphic RVE		215(87.40 %)	3(7.32 %)*	---	---
Polymorphic RVE		16(6.50 %)	---	6(40 %)*	76(69.09 %)*
Class II drugs		24(9.76 %)	4(9.76 %)	—	14(12.73 %)
Ethacizin		176(71.54 %)	—	—	—
Propafenone		42(17.07 %)	—	10(66.67 %)*	—
Allapinin		4(1.63 %)	—	—	85(77.27%)*
Sotalol		—	32(78.05 %)	5(33.33%)	11(10 %)
Amiodarone		—	5(12.19 %)	—	—

Note. * — reliable difference of parameters with the comparison group (at $p < 0.05$), dash — parameters were not registered.

sis was confirmed by coronary angiography (clinically significant stenosis of coronary arteries was detected), 15 (9.04%) had MVP, 16 (9.64%) had peptic ulcer disease, 58 (34.94%) had gastroesophageal reflux disease, 22 (13.25%) had hyperacid gastritis type "B", and the rest had hiatal hernia.

In the control group, monomorphic RVE was more common (87.40%), and class I drugs were most effective in treating ventricular ectopy. In patients with the development of CHD, monomorphic LVE and, less frequently, monomorphic RVE were significantly more common than in the comparison group, and class III drugs were most effective for the treatment of premature ventricular complexes. In patients with MVP, polymorphic LVE and RVE were significantly more frequent compared with the control group, with a positive clinical effect of VE treatment with class I drugs. In patients with formation of gastrointestinal tract pathology, polymorphic LVE and RVE were significantly more frequently registered in comparison with the control group with the highest efficacy of ventricular ectopia elimination by class I drugs with vagolytic activity. There was no significant difference in other studied parameters of the main group in comparison with the control group (Table 2).

In the comparison group, the ratio of PEIVE of monomorphic VE to QTsr were ≤ 1.35 units, LDcPEVEi — ≤ 10 m/s, the values of IDVEi and duration of QRS_{VE} complex did not exceed 0.42 units and 148 m/s, respectively, while polymorphic ventricular ectopy in these patients was characterized by significantly higher variability of PEIVEc, and other ECG

parameters were not significantly different in comparison with monomorphic extraordinary ventricular complexes. In case of CHD, all ECG parameters of monomorphic VE, including IDVEi, QRS_{VE} complex duration, were significantly greater compared with similar ectopy in the control group. In patients with MVP, the duration of QRS_{VE} complex of polymorphic VE was significantly longer compared with similar premature ventricular depolarization in the control group, while no significant difference was found in other studied parameters. In patients with gastrointestinal pathology, ECG signs of polymorphic VE were not significantly different from similar ectopy in the control group (Table 3).

In the comparison group, ECG signs of monomorphic LVE and RVE highly correlated with similar parameters characteristic of modeling ventricular ectopy by the mechanism of early postdepolarization ($r = 0.92$), and polymorphic — with delayed postdepolarization ($r = 0.94$). In patients without structural heart changes with subsequent CHD formation, ECG parameters of monomorphic LVE corresponded to experimental arrhythmias induced by the re-entry mechanism ($r = 0.96$), and in the cases of MVP and gastrointestinal pathology, ECG parameters of polymorphic LVE and RVE highly correlated with experimental arrhythmias induced by the delayed postdepolarization mechanism ($r = 0.92$ and $r = 0.96$, respectively).

In patients without cardiac and extracardiac pathology, control of VE, mainly due to the mechanism of early repolarization, highly correlated with the

Table 3

ECG parameters of VE in patients without structural heart changes
($M \pm m$, 95% confidence interval of mean values in parentheses)

Parameters	Patients groups	Comparison group, n = 246	Main group, n = 166		
			CHD, n = 41	MVP, n = 15	GI diseases, n = 110
PEIVE/QTsr, units		1.27 ± 0.01 (1.18-1.35) $1.74 \pm 0.11 \dagger$ (1.23-2.19)	$1.79 \pm 0.07^*$ (1.34-2.24) —	— 1.66 ± 0.11 (1.22-2.04)	— 1.68 ± 0.05 (1.18-2.15)
LDPEIVEc, ms		9.21 ± 0.08 (8.11-10.02) $82.53 \pm 2.31 \dagger$ (50.81-115.67)	$85.37 \pm 6.58^*$ (44.12-121.36) —	— 72.54 ± 9.18 (37.11-105.14)	— 83.45 ± 4.28 (42.16-123.57)
IDVEi, units		0.35 ± 0.01 (0.24-0.42) 0.36 ± 0.02 (0.27-0.46)	$0.67 \pm 0.02^*$ (0.56-0.78) —	— 0.34 ± 0.02 (0.28-0.42)	— 0.37 ± 0.01 (0.26-0.48)
QRSVE complex duration, ms		134 ± 1 (125-148) 138 ± 1 (133-146)	$185 \pm 4^*$ (157-210) —	— $189 \pm 8^*$ (159-226)	— 137 ± 1 (129-144)

Note. * — reliable difference of parameters with the comparison group, † — with monomorphic VE (at $p < 0.05$); above the isoline are the parameters characterizing monomorphic VE, below — polymorphic VE, dash — parameters were not registered.

use of class I drugs, represented mainly by etacizine (OR = 11.7). Development of CHD was highly correlated with IDVEi ≥ 0.56 units (OR = 12.9), QRS_{VE} complex duration ≥ 157 m/s (OR = 9.8), monomorphic VE due to re-entry mechanism, using class III drugs (OR = 8.1). The development of MVP highly correlated with the duration of the QRS_{VE} complex ≥ 159 m/s (OR = 10.7) in polymorphic VE due to the mechanism of delayed postdepolarization, the efficacy of class I drugs represented by propafenone (OR = 6.2) and, to a lesser extent, class III drugs (OR = 1.6). The formation of GI pathology highly correlated with polymorphic VE caused by the mechanism of delayed postdepolarization (OR = 4.1) and the use of class I drugs, represented mainly by allapinin (OR = 10.2).

Discussion

Currently, classical genetics has shown that the heritability of various cardiovascular diseases, such as CHD and other pathologies, is approximately 40% [1]. The presence of various risk factors or their association in apparently healthy patients leads to a local disturbance of cardiomyocyte metabolism and may cause the development of VE. In the absence of structural heart disease, cardiac or extracardiac pathology, the course of VE is usually considered benign according to the classification of Bigger B. (1984) [1]. These patients are likely to develop “arrhythmogenic cardiomyopathy”, and in addition to estimating the number

of premature ventricular complexes, the presence of such predictors as increased duration of the QRS_{VE} complex, PEIVEc and its variability, IDVEi, etc. are determined [1, 3]. On the other hand, in patients without structural heart disease with VE, the presence of predictors inducing the development of “arrhythmogenic cardiomyopathy” may become the first symptoms of “arrhythmic form” of the beginning of the formation of various clinical forms of CHD, myocarditis, cardiomyopathy, MVP or other pathology [1].

In experimental modeling of VE, the informative value of predictors of arrhythmogenic cardiomyopathy depends on the mechanism of development of induced ventricular ectopy. VE with the mechanism of early postdepolarization was modeled with aconitine, delayed postdepolarization — with barium chloride, early postdepolarization and re-entry — with hydrogen peroxide [4, 8]. In modeling of barium chloride-induced arrhythmia, polymorphic VE was recorded, in aconitine arrhythmia — early monomorphic VE, in re-entry peroxide arrhythmia — first early, then early and late monomorphic LVE. In animals with arrhythmia modeled by re-entry mechanism, IDVEi was significantly greater compared to VE caused by early and late postdepolarization mechanisms, as well as PEIVE/QTcr ratio and LDcPEVEi values were greater compared to ventricular ectopy caused by early postdepolarization mechanism.

Aconitine depresses or delays the inactivation of the sodium channel system, artificially increasing the membrane potential to a level between -40 mV and -10 mV, which leads to the emergence of spontaneous action potentials by the mechanism of early postdepolarization [1, 11]. The same phenomenon can occur in human myocardium: under the influence of aconitine or "oxidative stress" it depolarizes and spontaneously activates [1, 7, 11]. The appearance of delayed postdepolarizations is preceded by hyperpolarization of the cell membrane in the range of -60 – -70 mV with the subsequent appearance of a premature action potential when the threshold of sub-threshold excitation is reached [11]. In addition, their development requires an increase in the concentration of calcium ions in cardiomyocytes. VEs caused by early and delayed postdepolarization are associated with less hyperpolarization of cell membranes compared to arrhythmias caused by the re-entry mechanism, reflecting the potentially reversible nature of cardiomyocyte dysfunction [11]. Further increase of membrane hyperpolarization due to deeper metabolic disturbances leading to prolongation of action potential duration, as well as decrease of outward and inward currents, (especially when L-type cardiomyocyte calcium channels are damaged) may provoke an increase of heterogeneity of repolarization. Such areas usually show unidirectional and/or frequency-dependent conduction block and Wenckebach phenomenon, which is characteristic of VE caused by the re-entry mechanism [1, 11].

166 (40,29 %) out of 412 patients without structural changes of the heart had cardiovascular or GI diseases in the first ten years after the first examination, and the rest had no structural changes of the heart at the first and subsequent examinations, as well as cardiovascular diseases and pathology of other organs and systems. In 41 (24,70 %) out of 166 patients of the main group various clinical forms of CHD, in 15 (9,04 %) — MVP, and in the rest — GI diseases represented by peptic ulcer, gastroesophageal reflux disease, hyperacid gastritis type "B", hiatal hernia were found.

In patients without detected cardiac and extracardiac pathology during the whole period of observation, the ECG-signs of monomorphic LVE and RVE highly correlated with similar indices characteristic for modeling of experimental ventricular ectopy by the mechanism of early postdepolarization ($r = 0.92$),

and polymorphic — by the delayed postdepolarization ($r = 0.94$). In them, the PEIVE ratios of monomorphic VE to QTsr were ≤ 1.35 units, LDcPEVEi — ≤ 10 m/s, values of IDVEi and duration of QRS_{VE} complex did not exceed 0.48 units and 149 m/s, respectively, while polymorphic ventricular ectopy in these patients was characterized by a significantly higher variability of PEIVEc. Other ECG parameters were not significantly different in comparison with monomorphic premature ventricular complexes. In these patients, the positive effect of VE elimination highly correlated with the use of class I drugs, mainly represented by etacizine (OR = 11.7).

Apparently, in patients without cardiovascular and extracardiac pathology, the occurrence of VE due to the mechanisms of early and delayed postdepolarization is associated with less hyperpolarization of cell membranes compared to re-entry, which probably reflects the reversible nature of cardiomyocyte dysfunction caused by local metabolic changes [1, 11]. In these patients, ventricular arrhythmias usually resolve as cardiomyocyte function normalizes [1, 9, 11].

In patients without structural heart changes with subsequent CHD formation, ECG parameters of monomorphic VE corresponded to experimental arrhythmias induced by re-entry mechanism ($r = 0.96$), and in patients with MVP and GI pathology, ECG parameters of polymorphic LVE and RVE highly correlated with experimental arrhythmias induced by delayed postdepolarization mechanism ($r = 0.92$ and $r = 0.96$, respectively).

CHD development highly correlated with IDVEi ≥ 0.56 units (OR = 12.9), QRS_{VE} complex duration ≥ 157 m/s (OR = 9.8), monomorphic VE with class III drugs (OR = 8.1).

Increased values of IDVEi and QRS_{VE} complex duration in monomorphic VE probably determine its epicardial or intramural localization, in which slow depolarization from the epicardium to the endocardium is observed [10]. The occurrence of epicardial or intramural VE is associated with occlusion of small branches of epicardial arteries with the formation of small foci of fibrosis or "mute" myocardial ischemia, which are not verified by conventional methods of investigation [1], but represent an organic anatomical substrate of re-entry loop formation [11]. It should be noted that the efficacy of class III antiarrhythmic drugs indirectly confirms the presence of ventricular arrhythmias caused by the re-entry mechanism [1, 8,

11]. On the other hand, in patients with acute CHD, a high risk of fatal arrhythmias in the first 72 hours (up to 80%) from the onset of the disease was found for LDPEIc <10 m/s not only for monomorphic, but also polymorphic LVE and RVE. This is probably due to the mosaic nature of myocardial damage with the appearance of zones of ischemia, damage and necrosis with the occurrence of ventricular arrhythmias with different mechanisms of their development and unpredictable course [8].

The development of MVP highly correlated with the duration of QRS_{VE} complex ≥ 159 m/s of polymorphic VE (OR = 10.7), and the efficacy of class I drugs represented by propafenone (OR = 6.2) and to a lesser extent — class III (OR = 1.6).

VE in patients without structural changes of the heart with localization in the papillary muscles of the mitral valve, less often in the tricuspid valve or in the mitral annulus, LV outflow tract, may induce the development of non-myxomatous MVP due to superficial fibrosis of the mitral valve leaflets, thinning and/or chordal elongation [1, 2, 10]. These patients may have LVE and/or RVE with QRS_{VE} complex duration >150 m/s, and radiofrequency ablation is indicated when class I drugs are ineffective [1, 2].

The development of GI pathology highly correlated with polymorphic VE (OR = 4.1) and with the use of class I drugs for the treatment of VE, represented mainly by allapinin (OR = 10.2).

The occurrence of VE in patients without structural heart changes and subsequent development of GI pa-

thology is associated with excessive vagal influence on the heart as a result of functional dyspepsia [1, 9]. This is indirectly confirmed by the results of the present study: in these patients, the positive clinical effect of therapy was achieved mainly by the use of class I drugs with vagolytic effect.

Conclusion

When modeling ventricular arrhythmias by the mechanism of delayed postdepolarization, polymorphic VE were registered; in early postdepolarization — early monomorphic VE; in re-entry — early and late monomorphic LVE. In animals with modeling of arrhythmia by the mechanism of re-entry, there is significantly higher IDVEi in comparison with VE caused by the mechanisms of early and delayed postdepolarization. In patients with VE without structural changes of the heart the increase of IDVEi values and QRS_{VE} complex duration ≥ 0.48 units and ≥ 149 m/s, respectively, in addition to estimation of the number of ventricular ectopias per day of observation, determine the risk group of cardiovascular system pathology. The development of CHD in patients without structural heart changes with VE highly correlated with IDVEi ≥ 0.56 units, QRS_{VE} complex duration ≥ 157 m/s monomorphic LVE, and the use of class III drugs. The development of MVP correlated with QRS_{VE} complex duration ≥ 159 m/s of polymorphic VE, the effectiveness of class I drugs, and to a lesser extent with class III drugs.

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