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The possibility of using screening testing for antiarrhythmic medication for ventricular premature complexes differential therapy selection in patients without cardiac structural changes

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Abstract

Objective

To determine the differential therapy of ventricular extrasystoles (VEs) in patients without cardiac structural changes by screening testing of antiarrhythmic drugs.

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Materials and Methods

The study included 214 patients without cardiac structural changes aged 19 to 45 years with VE III—V classes, according to B. Rayn classification with subjective sensation of arrhythmia and preserved contractile function of the heart. All patients underwent daily electrocardiography monitoring, followed by the selection of potentially effective antiarrhythmic drugs for VEs elimination using screening testing method. The method considered potentially effective when corrected extrasystole index increased by≥ 2 relative units after the third dose of medication compared with the initial data. The accuracy of the choice (AC) was evaluated according to daily electrocardiography monitoring after a short course of therapy for each tested antiarrhythmic medication for at least 5 days. In case of antiarrhythmic activity of several medications in one patient, a medication with the most pronounced VE number reduction compared with the initial data after a short course of therapy was selected to eliminate ectopic beat. The endpoint of observation was the duration of preserved positive antiarrhythmic effect of the antiarrhythmic medication.

Results

50.47% of patients had positive antiarrhythmic effect of two, 38.32% — of three, and the rest — of four antiarrhythmic medications. AC of potentially effective drugs for eliminating VE in patients without cardiac structural changes was over 90%. In 79.90% of patients, positive antiarrhythmic effect of VE therapy persisted for over 1 year (an average of 3.8±0.08 years). The duration of positive clinical effect for 1 year and higher correlated with the positive results of screening testing of antiarrhythmic drugs (r= 0.94).

Conclusion

All patients without cardiac structural changes with VE had potential positive antiarrhythmic effect for 2 and more drugs. AC of potentially effective drugs for elimination of VE in these patients averaged over 90%.

Key words: *ventricular extrasystole, differential antiarrhythmic therapy selection*

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Introduction

Treatment of ventricular cardiac arrhythmias, including ventricular extrasystoles (VEs), is one of the most difficult issues that may prevent such life-threatening arrhythmias as ventricular tachycardia and ventricular fibrillation [1,2]. Patients with frequent and persistent extrasystoles, should perform differential antiarrhythmic therapy selection**,** which consists of assessment of the frequency and nature of premature complexes before and after the prescription of antiarrhythmic medications, according to the data of daily electrocardiography monitoring, and the effectiveness of each subsequent antiarrhythmic medication determined at least after 5 half-life of the previous one [1]. In general, it takes from 4–5 to 10–12 days to determine the effectiveness of one antiarrhythmic drug [1]. It can be assumed that several antiarrhythmic medications of the same or different classes may be effective in one patient. Recently, method has been proposed for screening testing of antiarrhythmic drugs to determine effective antiarrhythmic therapy in patients with VEs [3]. The method is based on the assessment of the extrasystole index (EI), which was previously used to assess the risk of life-threatening ventricular arrhythmias development. Antiarrhythmic agent was considered effective when this index increased by at least≥2 relative units compared with the initial values after two and / or three doses of the drug [3]. However, differential antiarrhythmic therapy selection for VEs management in patients without cardiac structural changes has not been described in the available literature yet.

Objective of the study was to determine the differential therapy of VEs in patients without cardiac structural changes by screening testing of antiarrhythmic drugs.

Materials and methods

The study included 214 patients aged from 19 to 45 years (33.5±0.95 years). The inclusion criteria were: the absence of cardiac structural changes, sinus rhythm, VEs of IV–V classes according to B. Rayn

classification (1984) [1], subjective arrythmia sensations, left ventricular ejection fraction ⩾ 52 % [4], signed written informed consent to participate in the study. The absence of cardiac structural changes was established after the exclusion of cardiac and extracardiac diseases (chronic rheumatic heart disease, cardiomyopathy, heart defects, mitral valve prolapse, myocarditis, thyrotoxicosis, various clinical forms of coronary artery disease, any form of anemia, chronic lung diseases, nasopharynx, diabetes mellitus, gastrointestinal tract diseases, etc.), electrolyte imbalance, the use of drugs and / or toxic products (primarily diuretics, oral contraceptives, alcohol abuse, etc.), independently or indirectly leading to development of VEs, as well as other criteria, including the use of various stress tests, invasive and non-invasive coronary angiography, contrast magnetic resonance imaging of the heart that have been described previously [5].

All patients, in addition to general clinical examination, underwent 1–3 daily electrocardiography monitoring and echocardiographic examination using the Hitachi EUB-5500 apparatus according to generally accepted methods. The calculation of left ventricular ejection fraction, left ventricular myocardial mass index, etc. were described earlier [5, 6].

After daily electrocardiography monitoring, all patients underwent cardioprotective therapy, including potassium supplements, sedation therapy, polyunsaturated fatty acids, etc. to eliminate VEs [5]. In the absence of an effect, the choice of VEs therapy was based on antiarrhythmic drugs testing: according daily electrocardiography monitoring, the frequency and nature of premature ventricular contractions were assessed before and after average therapeutic dose of antiarrhythmic medication for at least 4–5 days [1, 2]. The criterion for positive effect was the reduction of extrasystoles frequency by over 75 % compared with its initial level, as well as the elimination of paired and group extrasystoles [1, 2]. To identify effective medications, primarily class II antiarrhythmic agents were used, followed by classes I and III. It should be noted that amiodarone was not used in this study, because the main indication for its use in patients without cardiac structural changes is decreased cardiac contractile function [1, 7]. When eliminating VEs in patients without cardiac structural changes, the nature of ectopia, its prognostic assessment, the presence of contraindications, as well as the possible development of adverse effects of antiarrhythmic agents were taken into account [1, 2]. When considering antiarrhythmic therapy, we used 50–100 mg / day of metoprolol, propranolol — 80–160 mg / day, carvedilol — 25–50 mg / day, allapinin — 50–75 mg / day, moricizine — 50–100 mg / day, ethacyzin — 100–150 mg / day, propaphenone — 300–600 mg / day, sotalol — 160–240 mg / day. In all patients, all medications were prescribed twice before reaching the daily dose. Each subsequent drug was tested after at least 5 half-lives of the previous one [1, 2].

The screening testing method to identify effective antiarrhythmic medications for VEs elimination included the following steps. For all patients before and after taking each medication, after a half the period of its half-life, EI was calculated using the following formula: EI= A ÷ B, where EI is the extrasystole index (in units), A is the linear deviation (LD) of the corrected pre-ectopic interval (ms) for at least 20 ventricular extrasystoles, calculated separately for left and right VE, and B — analyzed ventricular extrasystole number (per hour) [3]. Corrected pre-ectopic interval over 20 extrasystoles exclude false positive result in the assessment of this indicator [3,5]. Then the corrected ΔEI (ΔEIcorr.) was calculated according to the formula: ΔEIcorr= [(EIn — EI initial) ÷ EI initial] ÷ √N, where ΔEIcorr.n (in relative units) is the change of EI after each sequential intake of the medication compared with the initial data, EI initial — EI values before using the medication (initial data), EIn — half-life after the first, second, third dose of the medication, N — coefficient corresponding to the amount of dosses, i.e. after first intake of an antiarrhythmic medication this coefficient was «1» (ΔEIcorr.1), after second — «2» (ΔEIcorr.2), after third — 3 (ΔEIcorr.3). The tested medication was considered effective when ΔEIcorr.3 ⩾ 2 relative units [3]. Due to high variability of VEs during the day [1,2], the determination of EI was carried out according to the data of 1–3-day electrocardiography monitoring.

The choice of VE therapy was determined according to daily electrocardiography monitoring compared with potentially effective antiarrhythmic medications based on the VEs changes [3]. In case of antiarrhythmic activity of several medications in one patient, a medication with the most pronounced VE number reduction compared with the initial data after a short course of therapy was selected to eliminate an ectopic beat. To exclude arrhythmogenic effect of antiarrhythmic therapy, all patients, when taking especially class Ic medications, initially and once every 3–4 days for the first 7–14 days underwent daily electrocardiography monitoring [1,2].

The accuracy of choice (AC) of potentially effective medication was determined according to the following formula: AC= (TP+ TN) ÷ (TP+ TN+ FP+ FN), where AC is the accuracy of the choice of a potentially effective antiarrhythmic drug, determined based on the ΔEIcorr.3⩾ 2 relative units (in%), TP — true positive, TN — true negative, FP — false positive, FN — false negative results obtained according to daily electrocardiography monitoring performed before and after a short course of antiarrhythmic therapy.

The endpoint of observation was the duration of preserved positive antiarrhythmic effect of the antiarrhythmic drugs. All studies, including daily electrocardiography monitoring, were carried out at least once in 3–4 months, the examination of patients, ECG registration — once a month. The patients carried out regular arterial pressure and heart rate monitoring independently.

Statistical analysis of obtained results was carried out using Student's t-test, chi-squared test, as well as standard software "Statistica", version 11.0.

Results

The number of VEs per day in included patients ranged from 5570 to 36150 extrasystoles (20850± 1098 extrasystoles on average), left ventricular ejection fraction — from 53 % to 75 % (64.27± 0.79 % on average), which corresponded to the reference values [6]. The percentage of VEs ranged from 6 % to 15 % in 32 (14.95 %) patients of the total ventricular complexes number per day of observation, in the rest — over 15 %. 76 (35.51 %) of patients had episodes of unstable ventricular tachycardia. 106 (49.53 %) of patients had only left ventricular extrasystoles, the rest — right ventricular extrasystoles (p> 0.05), 84 patients (39.25 %) — polymorphic, the rest — monomorphic VEs (p>0.05).

The results of antiarrhythmic drugs testing in included patients are presented in Table 1. As can be seen from the table, the sensitivity, specificity and positive predictive value of ΔEIcorr.3⩾2 relative units when assessing potentially effective medications for VEs were over 86 % on average, and AC — 90 %. When analyzing the changes of ΔEIcorr.1–10, it was revealed that in cases of true positive effect of antiarrhythmic therapy index increased after the first and second administrations of medication mostly due to increased LD of corrected pre-ectopic interval (r=0.87), and after the third and subsequent intakes — due to a decreased number of premature ventricular complexes (r=–0.85). Decreased number of VEs after a short course of antiarrhythmic therapy in patients with true positive and false negative results did not differ significantly and amounted to 76 % — 99 % (88.5±0.8 % on average) and 76 % — 96 % (86.2±1.6 % on average), respectively (p>0.05).

In 108 (50.47 %) patients two antiarrhythmic medications had positive effect, in 82 (38.32 %) — three, in the rest — four antiarrhythmic medications. 24 (11.21 %) patients took metoprolol to eliminate VEs, 22 (10.28 %) — propranolol, 12 (5.61 %) — carvedilol, 26 (12.15 %) — allapinin, 34 (15.89 %) — moricizine, 60 (28.04 %) — ethacyzin, 75 (35.05 %) — propafenone, the rest — sotalol.

Positive clinical effect of class II antiarrhythmic medications highly correlated with LD of corrected pre-ectopic interval⩾11 ms of polymorphic VE (r=0.88), and for classes I and III — with LD of corrected pre-ectopic interval⩽ 10 ms of monomorphic VE (r= 0.84).

43 (20.10 %) patients, had preserved antiarrhythmic effect of VEs therapy for less than 1 year (0.7± 0.04 years on average), the rest — from 1 to 5 years (3.8±0, 08 years on average) (p<0.05). The duration of preserved positive clinical effect of VEs treatment for over 1 year highly correlated with true positive results of screening testing for antiarrhythmic medications (r= 0.94).

Table 1. **Results of testing for antiarrhythmic agents in studied patients***

Medication	Sensitivity, %	Specificity, %	PPV, %	AC, %
Metoprolol, n= 214	90,41 %	94,32 %	89,19 %	92,99 %
Propranolol, n= 212	91,30 %	97,28 %	91,30 %	96,22 %
Carvedilol, n= 214	87,10 %	97,81 %	87,10 %	96,26 %
Allapinin, n= 214	91,67 %	95,45 %	88,79 %	94,39 %
Moricizine, n= 206	90,57 %	97,39 %	92,31 %	95,63 %
Ethacyzin, n= 212	94,92 %	92,71 %	94,12 %	93,93 %
Propafenone, n= 214	93,06 %	94,36 %	89,33 %	93,93 %
Sotalol, n= 204	86,27 %	96,07 %	88,00 %	93,63 %

Comment: * — potential positive effect of tested medication was determined when DEIcorr.3⩾ 2 relative units; PPV — positive predictive value (%), AC – accuracy of choice (%).

Discussion

Nowadays it is known that despite positive prognosis of VEs in patients without cardiac structural changes, according to the classification of B. Bigger (1984), antiarrhythmic therapy of premature ventricular contractions should be prescribed in patients with subjective sensation of arrythmia to prevent the development of arrhythmogenic cardiomyopathy and fatal arrythmias [1, 2, 7].

The study included 214 patients without cardiac structural changes aged from 19 to 45 years with VEs of III—V classes, according to B. Rayn classification [1], subjective sensation of arrhythmia, preserved LVEF (≥52 %). 14.95 % of patients had from 6 % to 15 %, the rest — over 15 % of VEs initially of total number of ventricular complexes per day. Episodes of non-sustained ventricular tachycardia were reported in 35.51 % of patients.

According to the latest guidelines, 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 [2,8]. This statement was the basis for pharmacological antiarrhythmic therapy in included patients.

Nowadays, it is known that VEs can be caused by various cellular mechanisms, including early or delayed after-depolarization, re-entry, and ectopic pacemaker development [1]. For example, progressive hyperpolarization of cardiomyocyte membranes, for example, from –50 to –60 mV, causes local slowdown of excitation with the formation of unidirectional and / or frequency-dependent block of the propagation of excitation with Wenckebach's phenomenon in this area, leading to the development of re-entry [1].

In the current study, in case of ineffectiveness of cardioprotective drugs, the choice of potentially effective medications for the elimination of VEs, screening testing for antiarrhythmic medication was performed based on the changes of EI initially and after their use in medium therapeutic doses [3]. EI was calculated as linear deviation of the corrected corrected pre-ectopic interval (ms) to the analyzed ventricular extrasystole number (per hour) [3]. Due to the wide range in the number of VEs per day of observation and EI values [3], ΔEIcorr.n was determined by comparing the change of EI after each administration of the medication with the initial data related to the number of subsequent doses of the medication [3]. To identify effective medications, primarily class II antiarrhythmic agents were used, followed by classes I and III. Amiodarone was not used in this study, because the main indication for its use in patients without cardiac structural changes is decreased cardiac contractile function [1,7]. In all patients, each medication was used twice before reaching the daily dose. Tested drug was considered effective when after the third dose ΔEIcorr.3≥2 relative units [3].

To exclude false negative and false positive results all tested medications were prescribed as a short course for at least 4–5 days. ΔEIcorr. was calculated after each intake of medication in all patients. 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 and group extrasystoles according to daily electrocardiography monitoring [1,2]. In case of antiarrhythmic activity of several medications in one patient, a medication with the most pronounced VE number reduction compared with the initial data after a short course of therapy was selected to eliminate ectopic beat.

The results of this study showed that in 50.47 % of patients two medications had positive antiarrhythmic effect, in 38.32 % — three, in the rest — four antiarrhythmic medications. The sensitivity, specificity, and positive predictive value of the ΔEIcorr.3≥2 relative units was over 80 % for the detection of potentially effective medications for VEs elimination.

In recent years, the choice of VEs antiarrhythmic therapy is one of the main issues. Summarizing the known data, there are three main ways to choose VEs antiarrhythmic therapy. First, most common but less effective, is the empirical method that is based on physician's personal experience and research data on the effectiveness of medication. The second way is testing of antiarrhythmic medications using medicinal tests, but there is often a discrepancy between test results and long-term therapy effects [1]. The third method is the selection of antiarrhythmic therapy using 1–3 daily electrocardiography monitoring when each subsequent agent is prescribed no earlier than after five half-lives of the previous one in a short course (for 3–5 days) at an average therapeutic dose [1]. However, the last method of selection is very expensive, requires a rather long time of patient observation and / or the patient's admission to the hospital, as well as the performance of multiple 1–3 daily electrocardiography monitoring.

Current study has also shown that in cases of true positive effect of antiarrhythmic therapy index increased after the first and second administrations of

medication mostly due to increased LD of corrected pre-ectopic interval (r=0.87), and after the third and subsequent intakes — due to a decreased number of premature ventricular complexes (r=–0.85). Therefore, using the proposed method, several potentially effective drugs can be identified even before the onset of clinical effect, by the assessment of the reduction of the number of VEs according to the data of daily electrocardiography monitoring after a short course of therapy. This method allows to evaluate the effectiveness of antiarrhythmic drug only after at least the third intake compared with other methods. It should be noted that the true positive test results obtained using this method were confirmed by 24-hour electrocardiography monitoring data with more than 90 % AC.

11.21 % of patients took metoprolol to eliminate VEs, 10.28 % — propranolol, 5.61 % — carvedilol, 12.15 % — allapinin, 15.89 % — moricizine, 28.04 % — ethacyzin, 35.05 % — propafenone, the rest — sotalol.

Previous clinical and experimental studies have shown that the value of LD of the corrected pre-ectopic interval, for example, ⩽10 ms, indirectly confirmed the presence of "re-entry" and / or the development of pathological ectopic focus, and the large variability of this indicator — the presence of trigger mechanisms [6]. Therefore, after several doses of an antiarrhythmic drug in patients with trigger mechanisms, the hyperpolarization of the cardiomyocyte membrane decreases, and, therefore, corrected pre-ectopic interval increases and VEs frequency decreases. After the development of an excitation wavefront, for example, by the "re-entry" mechanism, it is fractionated, divided into smaller waves, each of which becomes independent, that causes different corrected pre-ectopic intervals on the electrocardiogram — early complexes, followed by complete conduction blockage and elimination of ectopic beats [1, 6].

The results obtained earlier are indirectly confirmed by the data obtained in this study: the positive clinical effect of class II drugs highly correlated with the LD of the corrected pre-ectopic interval ⩾ 11 ms (r=0.88), classes I and III drugs — with ⩽10 ms (r= 0.84).

In 20.10 % of patients, the antiarrhythmic effect of VEs therapy persisted for less than 1 year (0.7±0.04 years on average), in the rest — from 1 year to 5 years (3.8±0.08 years on average) ($p<0.05$). The duration of preserved positive clinical effect of VEs treatment for over 1 year highly correlated with the true positive results of antiarrhythmic drugs screening testing (r=0.94). It is also remarkable that, according to daily electrocardiography monitoring data, the reduction of VEs did not differ significantly between groups with preservation of positive effect for less than 12 months and for over 1 year and averaged 87 %. Similar data were obtained earlier [9]. This fact, apparently, should be taken into account when choosing therapy for VEs in patients without cardiac structural changes.

The duration of positive VEs therapy effect in patients without cardiac structural changes for less than 1 year, may be explained by the following factors. First, the damage of ion channels and / or receptors of cardiomyocytes due to "oxidative stress" [10,11]. Second, premature ventricular complexes can indicate the development of myocarditis, cardiomyopathy, arrhythmogenic right ventricular dysplasia, etc., and in patients with these diseases, pharmacotherapy of arrhythmias is ineffective or less effective, or has very short-term positive effect [1,2]. Therefore, in patients without cardiac structural changes with 10 % or more VEs of the total number of ventricular complexes, predictors of the development of arrhythmogenic cardiomyopathy and life-threatening ventricular arrhythmias, as well as the absence or short-term positive effect of antiarrhythmic therapy radiofrequency ablation of the arrhythmogenic focus is recommended [1, 2, 8].

Conclusion

Thus, the proposed screening testing method for the selection of antiarrhythmic medications allows to determine several potentially effective medications to eliminate VEs in one patient in a fairly short period of time (up to 5–7 days). In current study 50.47 % of patients had positive antiarrhythmic effect of two, 38.32 % — of three, and the rest — of four antiarrhythmic medications. AC of potentially effective drugs for eliminating VE in patients without cardiac structural changes was over 90 %. Therefore, in case of decreased antiarrhythmic effect of medication, selected according to the results of screening testing for long-term VEs therapy, as well as in case of the development of complications, the physician has a number of other potentially effective agents to replace selected therapy, and, if necessary, preform another testing in a short period of time.

We can make several conclusions from our study: AC of potentially effective drugs for eliminating VE using method of screening testing in patients without cardiac structural changes was over 90 %, and positive predictive value — over 80 %.

In 79.90 % of patients, positive antiarrhythmic effect of VE therapy persisted for over 1 year (an average of 3.8±0.08 years). The duration of positive clinical effect for 1 year and higher correlated with the positive results of screening testing of antiarrhythmic drugs (r=0.94).

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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. ISBN: 978–0-323–55593-7
2. 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.
3. Olesin A.I., Konstantinova I.V., Litvinenko V.A., Zueva J.S. The method of choosing the effective antiarrhythmic drug for patients with extrasystole. Patent RU № 2707261, publ. 25.11.2019, Bul. № 33. — 33 p. Russian.
4. 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.
5. 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.
6. Olesin A.I., Konovalova O.A., Koziy A.V. et al. Ventricular extrasystolia in patients with non-ST elevation acute coronary syndrome: assessing the risk of life-threatening ventricular arrhythmias (clinico-experimental study). Russian Journal of Cardiology, 2009;1:24–31. Russian.
7. Panizo J.G., Barra S., Mellor G. et al. Premature Ventricular Complex-induced Cardiomyopathy. Arrhythm. Electrophysiol. Rev., 2018; 7(2): 128–134.
8. 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.
9. Olesin A.I, Konstantinova I.V., Zueva Yu.S., Kozyi A.V. Individualization of pharmacological therapy of ventricular extrasystoles by analysis premature ventricular complexes in patient without structural changes of heart. International Journal of Heart and Vascular Diseases. 2020; 8 (25): 38–47. Russian.
10. Wang Y., Eltit J.M., Kaszala K. et al. Cellular mechanism of premature ventricular contraction-induced cardiomyopathy. Heart Rhytm, 2014; 11(11): 2064–2072.
11. Sovari A.A. Cellular and molecular mechanisms of arrhythmia by oxidative stress. Cardiol. Res. Pract., 2016; 2016: 9656078.