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Comparative efficacy of pharmacological and non-pharmacological management of monomorphic right ventricular premature contractions in patients without structural heart disease

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To date, antiarrhythmic medication and radiofrequency ablation (RFA) are the primary methods of right ventricular premature contractions (PVCs) management in patients without structural heart disease (SHD).

Aim of the study. The aim of the study was to evaluate the efficacy of pharmacological and non-pharmacological (RFA) strategies of monomorphic right ventricular PVCs management, depending on the identification of

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arrhythmogenic cardiomyopathy (ACM) predictors in patients without SHD.

Methods. In this study, 452 patients with high frequency of PVCs (mean 23529±561 PVCs per day) and without SHD aged 16-39 were observed. In addition to the basic parameters, such ACM predictors as the QRS complex maximum intrinsicoid deflection index, QRS complex duration, etc. were electrocardiographically assessed. The observation period was 5 years.

Results. In 95.13% of patients the early monotopic right ventricular PVCs without ACM predictors were diagnosed. No cardiovascular diseases developed in these patients, and Class I antiarrhythmic drugs were the most effective at suppressing ventricular ectopy. In this group, 15.71% of the patients declined the long-term antiarrhythmic therapy or RFA. The rest of the group continued pharmacologic therapy. In 95.28% of patients with the early monotopic right ventricular PVC without registered ACM predictors, the duration of antiarrhythmic therapy, according to the "therapeutic sufficiency" principle, was 11.1 ± 0.3 months from the beginning of the period of observation. This duration highly correlated (r = 0.89) with the observation period of patients receiving cardioprotective therapy. In 4.87% of patients with registered right ventricular PVC with ACM predictors, no effect of antiarrhythmic therapy was observed and/or clinically significant heart failure developed. These patients underwent RFA for ventricular ectopy management. In all patients of this subgroup RFA induced remission and in 85.71% of them remained free of PVC recurrence throughout the entire follow-up period.

Conclusion. Patients with the early monotopic right ventricular PVCs, without SHD and any ACM predictors treatment with Class I antiarrhythmics was the most effective, while in patients with monomorphic right ventricular PVCs and ACM predictors, RFA was the effective therapeutic option.

Keywords: Premature ventricular contractions, anti-arrhythmic therapy personalization, pharmacologic treatment, radiofrequency ablation.

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Introduction

In patients without structural heart disease (SHD), in most cases, good prognosis of monomorphic right ventricular premature contractions (PVCs) is observed, except for the development of myocardial contractility depression in high frequency ventricular ectopy [1, 2]. Despite the use of various cardiac mapping methods, which assist with the definition of the source of premature ventricular complexes, they might be ineffective for the verification of PVCs mechanism in patients without SHD. In particular, these methods can not help to differentiate between trigger activity and re-entry mechanism [3, 4].

Prior clinical and experimental studies have shown that in most cases, early monomorphic right ventricular PVCs in patients without SHD and in the absence of electrocardiographic (ECG) predictors of arrhythmogenic cardiomyopathy, such as the duration of the ectopic QRS complex and the sinus rhythm QRS complex, their ratio, the measurement of the maximum intrinsicoid deflection index of the ectopic complex, and the variability of the corrected pre-ectopic interval assessed by its linear deviation (LD), etc., is caused by a mechanism of early afterdepolarization (EAD) and follows a predominantly benign course. Furthermore, prospective follow-up of these patients revealed no subsequent cardiovascular pathology [5].

The available literature lacks data on the comparative efficacy of pharmacological therapy versus non-pharmacological management, specifically radiofrequency catheter ablation (RFA), as well as on the natural history of early monomorphic right ventricular PVCs in patients without SHD. This is specifically for cases predominantly caused by an EAD mechanism, for instance, when antiarrhythmic drug therapy is declined to eliminate the ventricular ectopy.

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Aim of the study

The aim of the study was to evaluate the efficacy of pharmacological and non-pharmacological (RFA) strategies of monomorphic right ventricular PVCs management, depending on the identification of arrhythmogenic cardiomyopathy (ACM) predictors in patients without SHD.

Methods

A total of 452 patients without SHD, aged 16 to 39 years (mean 22.1 ± 0.1 years), with monomorphic right ventricular PVCs of IV-V gradation according to the M. Ryan classification [6], were observed.

The inclusion criteria were: documented sinus rhythm; absence of SHD, confirmed by ruling out cardiac and extracardiac diseases, electrolyte imbalances, use of medications and/or toxic products (primarily diuretics, oral contraceptives, alcohol abuse, etc.) that directly or indirectly lead to the development of ventricular arrhythmias; confirmation of the absence of SHD using various stress tests, invasive and non-invasive coronary angiography, echocardiography, and contrast-enhanced cardiac magnetic resonance imaging; presence of subjective palpitations; left ventricular ejection fraction ⩾ 54%; and provision of informed consent for participation in the study and treatment (as previously described) [5, 7].

All patients underwent general clinical examination, 24-72-hour Holter ECG monitoring, and echocardiography using a Hitachi EUB-5500 device according to standard protocols. The calculation of hemodynamic parameters, determination of the topographic localization of the premature ventricular complexes, comparison of the pre-ectopic interval (PEI) of the PVC to the QT interval of the sinus rhythm (QTsr), determination of the linear deviation (LD) of the corrected PEI (PEIcor), measurement of the QRS duration of the PVC (QRSpvc) and sinus rhythm (QRSsr), their ratio (QRSpvc/QRSsr), and the maximum intrinsicoid deflection time (MIDpvc) of the right ventricular extrasystole were performed as previously described [5, 9].

Pathological values for MIDpvc, QRSpvc duration, and the QRSpvc/QRSsr ratio were defined as ⩾ 0.5 units, ⩾ 150 ms, and ⩾ 1.5 units, respectively [2, 5]. Monotopic premature ventricular complexes were defined by an LD of the corrected PEI (PEIcor LD) of < 10 ms [3].

The selection of antiarrhythmic therapy for ventricular ectopy was based on 24-hour Holter ECG monitoring data. This included the identification of potentially effective Class I-III antiarrhythmic drugs, which were used in medium therapeutic doses [3].

The treatment protocol was initiated with Class II agents. If these were ineffective, Class I or III drugs were used. Amiodarone was employed as a last resort, if necessary. The scope and nature of antiarrhythmic drug therapy, as well as the criteria for treatment efficacy for ventricular ectopy, have been described previously [5, 6].

Pharmacological therapy followed the principle of «therapeutic sufficiency» This meant that antiarrhythmic drugs were withdrawn every 3-6 months. If PVCs recurred, the previous antiarrhythmic pharmacotherapy was reinstated. If no premature ventricular complexes were recorded, the treatment was discontinued [5, 8].

In cases where mono- or combined antiarrhythmic therapy was ineffective, or if depression of myocardial contractility developed leading to a refusal of long-term antiarrhythmic drug use, RFA became the treatment of choice for PVCs in patients without SHD [2, 3, 5].

The duration of patient follow-up after inclusion in the study was 5 years. All assessments, including patient status evaluation and ECG recording, were performed once a month. 24-hour Holter ECG monitoring was conducted no less than once every 3-4 months.

Statistical analysis

For the statistical analysis of the obtained data, the following methods were used: means and standard errors of the mean (M±m), the 95% confidence interval for the means, Student's t-test, and the x^2 test. A p-value of less than 0.05 ($p<0.05$) was considered statistically significant. The normality of distribution for quantitative variables was assessed using the Kolmogorov-Smirnov and Gaussian tests. Linear pairwise correlation (Pearson's r) and rank correlation (Spearman's r) were employed. The association between quantitative and qualitative binary variables was evaluated using logistic regression analysis with the calculation of odds ratios (OR).

Results

Among the patients without SHD included in the study, the number of PVCs over 24 hours ranged from 11,256 to 39,798 (mean 23,529 ± 561 PVCs per day). Furthermore, 384 patients (84.96%) had ventricular ectopy accounting for 15% or more of all ventricular

complexes, and 98 patients (21.68%) had non-sustained ventricular tachycardia.

The most effective drug for suppressing PVCs was etacizin in 356 patients (78.76%), allapinin in 58 (12.83%), propafenone in 23 (5.09%), Class II agents in 9 (2.00%), and sotalol in the remaining 6 patients (1.32%).

Seventy-one patients (15.71%) declined long-term antiarrhythmic drug therapy for various reasons, including the development of headaches, dizziness, diplopia, nausea, constipation or diarrhea, allergic reactions, financial constraints, etc. These patients received cardioprotective therapy, which included cardiometabolic agents such as potassium supplements and polyunsaturated fatty acids. Among them, 4 patients (5.63%) underwent RFA 6-8 months after the start of observation to eliminate ventricular ectopy due to the development of impaired pump function, which manifested as clinically overt heart failure. The remaining 381 patients (84.29%) continued antiarrhythmic medication. Of these, 18 patients (4.72%) underwent RFA 7–14 months (mean 10.8 ± 0.9 months) after initiating therapy due to the ineffectiveness of pharmacological antiarrhythmic treatment, which included the use of Class I-III drugs and their combinations.

All patients were divided into two groups. Group I consisted of 430 patients (95.13%) who used drug therapy to manage PVCs. The remaining patients were included in Group II and underwent RFA to eliminate ventricular ectopy. Group I was further divided into two subgroups. Subgroup Ia included 67 patients (15.58%) who were treated for PVCs with cardiometabolic agents only; this subgroup was used to study the «natural history» of right ventricular ectopy in patients without SHD. Subgroup Ib included 363 patients (84.42%) who received pharmacological antiarrhythmic therapy to eliminate PVCs.

All patients in subgroups Ia and Ib exhibited early monomorphic premature ventricular contractions (PVCs) without pathological values of ACM predictors. No statistically significant difference in the studied parameters was found between these subgroups (Table 1).

In Group II, all parameters reflecting ACM predictors for PVCs were significantly higher compared to subgroups Ia and Ib. No significant changes in the other studied parameters were observed between subgroups Ia and Ib when compared to Group II.

A positive clinical effect was observed in 32 patients (47.76%) of subgroup Ia within 3-9 months (mean 6.2 ± 0.5 months), and in the remaining patients within 10-23 months (mean 16.3 ± 0.8 months). In all patients of this subgroup, the PVC burden decreased by an average of 92% compared to baseline.

In 178 patients (49.04%) of subgroup Ib, the duration of antiarrhythmic therapy, guided by the principle of «therapeutic sufficiency,» ranged from 4 to 10 months (mean 6.7 ± 0.2 months) from the start of observation. For the remaining patients, it ranged from 11 to 21 months (mean 16.7 ± 0.5 months). This duration strongly correlated with the observation period of patients in subgroup Ia (r = 0.89).

In all patients of Group II, the PVCs were eliminated immediately after RFA. A positive effect from RFA was maintained throughout the entire follow-up

Table 1. **Electrocardiographic parameters of PVCs in subgroups Ia, Ib, and group II patients**

Patient groups Parameters	Subgroup Ia n = 67	Subgroup Ib n = 363	Group II n = 22
PEIpvc/QTSR, ratio	1.26±0.01 (1.18-1.36)	1.25±0.01 (1.14-1.36)	1.75±0.12 (1.22±2.32)*
LD of cor. PEI pvc, ms	8.62±0.08 (7.97-9.26)	8.61±0.01 (8.12-9.14)	82.35±10.51 (39-126)*
MIDpvc, ratio (PV ⩾ 0.5)	0.41±0.01 (0.31-0.52)	0.42±0.01 (0.32-0.53)	0.58±0.01 (0.44-0.71)* †
QRS duration of PVC, ms (PV ⩾ 150 ms)	137±1 (125-152)	138±1 (122-154)	179±5 (145-212)* †
QRSpvc/QRSsr, ratio (PV ⩾ 1.5)	1.38±0.01 (1.24-1.53)	1.39±0.01 (1.22-1.56)	1.88±0.07 (1.46-2.23)* †
Number of PVCs per 24 hours	23787±1235 (11657-35875)	23423±531 (14856-31987)	24787±2456 (14678-36784)

Note: * — significant difference compared to subgroup Ia, ♦ — significant difference compared to subgroup Ib, † — significant difference compared to pathological values ($p < 0.05$).

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period in 16 patients (72.73%) of this group. In 6 patients (27.27%), PVCs recurred 2 years after the ablation and were successfully eliminated with a repeat RFA procedure; the morphology of the recurrent premature ventricular complexes was similar to the original. Endomyocardial biopsy was performed in 8 patients (36.36%) of this group, revealing myocardial inflammatory fibrosis (myocarditic cardiosclerosis).

The positive effect of RFA highly correlated with the following ACM predictors: MID of the PVC ⩾ 0.5 units (OR = 15.4), a PVC QRS complex duration ⩾ 150 ms (OR = 12.9), and a ratio of PVC QRS to sinus rhythm QRS duration ⩾ 1.5 units (OR = 9.6).

No cardiovascular diseases were detected in any patient of Group I throughout the entire observation period.

Discussion

It is currently known that frequent monomorphic right ventricular PVCs are detected in 3% to 5% of young patients (typically under 40 years of age) without SHD, and in most cases, are typically benign [2, 3]. In patients without SHD, the indications for antiarrhythmic therapy for monomorphic PVCs are: the presence of subjective symptoms, or the detection of ventricular ectopy accounting for 15% or more of total heartbeats. If patients decline pharmacologic antiarrhythmic therapy or if it proves ineffective, RFA becomes the treatment of choice for eliminating the premature ventricular complexes [1-3].

A total of 452 patients without SHD, aged 16 to 39 years, with frequent monomorphic PVCs (mean 23,529 ± 561 PVCs per 24 hours) were observed. Early monomorphic right ventricular PVCs without predictors of ACM were recorded in 95.13% of them.

Clinical and experimental studies have shown that early monomorphic right ventricular PVCs in patients without SHD and without ACM predictors is most often caused by a mechanism of early afterdepolarization (EAD) [5].

EADs are caused by an increase in the membrane potential of cardiomyocytes to a level between –40 mV and –10 mV. This can result from, for example, inhibition or delayed inactivation of the sodium channel system, leading to the emergence of spontaneous action potentials [10, 11]. This phenomenon can be induced experimentally by various toxic agents, such as aconitine, and in humans, it may result from «oxidative stress» or other local metabolic disturbances affecting cardiomyocyte function [10, 11]. For suppressing ventricular ectopy caused by the EAD mechanism, Class I antiarrhythmic drugs are the most effective [12].

Similar findings were obtained in the present study: etacizin was the most effective drug in 78.76% of patients, allapinin in 12.83%, and propafenone in 5.09%.

For various reasons, 15.71% of patients declined long-term antiarrhythmic pharmacotherapy, while the remaining patients continued treatment with antiarrhythmic drugs.

In patients without SHD presenting with early monomorphic right ventricular PVCs, the rationale for antiarrhythmic therapy extends beyond preventing «arrhythmia-induced cardiomyopathy.» The fact that frequent ventricular ectopy itself may induce disturbances in myocardial metabolism—potentially through increased sympathetic activity, ventricular dyssynchrony, and other factors leading to stabilization of the ectopic focus, also serves as a basis for treatment [13–15].

In patients without SHD receiving cardioprotective therapy, a positive clinical effect was observed after an average of 11.8 ± 0.7 months: the PVC burden decreased by an average of 92% compared to baseline. The duration of pharmacological antiarrhythmic therapy in patients without SHD, guided by the principle of «therapeutic sufficiency,» averaged 11.1 ± 0.3 months from the start of observation. This duration strongly correlated with the observation period of patients receiving cardioprotective therapy (r = 0.89).

In patients without SHD, the occurrence of early monomorphic right ventricular PVCs without ACM predictors, typically caused by trigger mechanisms such as EAD, reflects a reversible dysfunction of cardiomyocytes [1, 5, 6]. This is supported by the results of the present study: no cardiovascular pathology was detected in these patients throughout the entire follow-up period.

In 4.87% of patients without SHD who had monomorphic PVCs with ACM predictors and who declined antiarrhythmic drug therapy, RFA was performed 6-14 months after the start of observation to eliminate ventricular ectopy due to the development of clinical heart failure and/or inefficacy of pharmacological antiarrhythmic therapy.

The immediate success rate of RFA, used, for example, when long-term antiarrhythmic drug therapy is declined or ineffective—is 80–90% [1–3], and according to some data, reaches nearly 100% [14,

15]. Similar results were obtained in the present study.

The development of monomorphic PVCs with ACM predictors in patients without SHD is likely caused by the formation of small focal areas of fibrosis or cardiosclerosis, which are usually not detected by conventional diagnostic methods. These areas may facilitate the generation of premature ventricular complexes, possibly through the induction of an ectopic focus or a re-entry mechanism [10–12]. Furthermore, previous clinical and experimental studies have shown that the identification of ACM predictors in patients without SHD with PVCs indicates an organic cause of the arrhythmia and is a risk factor for the development of cardiovascular pathology [5].

This notion is indirectly confirmed by the results of the present study. A positive effect from RFA was maintained throughout the entire follow-up period in 72.73% of patients; this outcome highly correlated with the presence of ACM predictors. An endomyocardial biopsy was performed in 36.36% of these patients, revealing myocardial fibrosis consistent with myocarditic cardiosclerosis. In 27.27% of patients, PVCs recurred 2 years after the ablation and were successfully eliminated with a repeat RFA procedure; the morphology of the recurrent premature ventricular complexes was similar to the original.

Conclusion

In 94.37% of patients without SHD who declined antiarrhythmic drug therapy for early monomorphic right ventricular PVCs, a positive clinical effect was observed after an average of 11.8 ± 0.7 months of cardioprotective therapy. In these patients, the burden of premature ventricular complexes decreased by an average of 92% compared to baseline.

In 95.28% of patients without SHD, the duration of pharmacological antiarrhythmic therapy for early monomorphic right ventricular PVCs, guided by the principle of «therapeutic sufficiency,» highly correlated with the observation period of patients receiving cardioprotective therapy (r = 0.89).

The presence of monomorphic PVCs with predictors of ACM in patients without SHD is a predictor of ineffective pharmacological antiarrhythmic therapy and/or the development of clinically overt heart failure. For these patients, RFA is the treatment of choice for eliminating ventricular ectopy. Following this procedure, premature ventricular complexes were eliminated and did not recur throughout the entire follow-up period in 72.73% of patients.

Conflict of interests: none declared.

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