International Heart and Vascular Disease Journal • Volume 9, № 30, June 2021

Journal of the Cardioprogress Foundation

Pharmacologic management of premature ventricular contractions in the absence of structural heart disease: estimation of positive effect duration

Olesin A.I.[1], Konstantinova I.V.[1], Zueva Yu.S.[2], Koziy A.V.[3]

[1] Department of Internal Medicine, North-Western State Medical University named after I.I. Mechnikov, St. Petersburg, Russia.

[2] St. Elizabeth's City Hospital, St. Petersburg, Russia.

[3] Military Hospital № 442, St. Petersburg, Russia.

Authors

Alexander I. Olesin*, M.D, PhD, professor, Department of Internal Medicine, North-Western State Medical University named after I.I. Mechnikov, St. Petersburg, Russia.

Irina V. Konstantinova, M.D, PhD, Department of Internal Medicine, North-Western State Medical University named after I.I. Mechnikov, St. Petersburg, Russia.

Yulia S. Zueva, M.D, Department of Cardiology, St. Elizabeth City Hospital, St. Petersburg, Russia

Anastasia V. Koziy, M.D, PhD, Military Hospital № 442, St. Petersburg, Russia.

Abstract

The objective *of this study was to evaluate the positive effect duration of pharmacologic management of premature ventricular contractions (PVC) according to ventricular ectopy analysis in the absence of structural heart disease.*

Materials and methods. *The current study included 214 patients aged 19–45 years without structural heart disease and with class IV–V PVC (Rayn B. classification (1984)). After 24-hour Holter monitoring, potentially effective antiarrhythmic agents for terminating PVC were selected. Antiarrhythmic drugs were taken for 5–7 days and a decrease in the number of extrasystoles by 75 % or more compared with baseline as well as the elimination of paired, group extrasystoles signified a positive effect. The extrasystole index (IE) and the corrected extrasystole index (IEcorr.) were calculated for all the patients before and after each administration of the drug, respectively. The follow-up duration ranged from 1 to 5 years. The endpoint was the duration of positive antiarrhythmic effect of the drugs used.*

* Corresponding author. Tel. +7-921-329-52-92.E-mail: olesin58@mail.ru

Results. *In 20.10 % of patients the positive antiarrhythmic effect persisted for 0.7±0.04 years, in 80.90 % — for 3.8± 0.08 years. In patients, in whom the positive effect lasted for up to 1 year, metoprolol, propranolol, sotalol were used more frequently, while class I drugs were not used at all. In patients without structural heart disease, the sensitivity, specificity, and positive prognostic value for antiarrhythmic therapy effects persistence for at least 1 year were 97, 03 %, 87.50 % and 96.08 %, respectively for a linear regression slope of ≥ 12 units/IEcorr.*

Conclusion. *In patients without structural heart disease with a linear regression slope of ≥ 12 units/IEcorr.*$_{1-10}$ *the positive effect of antiarrhythmic therapy persists for 1 year or more.*

Keywords. *PVC, duration of the positive effect of therapy.*

Conflict of interest: none declared.

Received: 23.12.2020 **Accepted:** 25.03.2021

Introduction

Today, to choose the most effective treatment for frequent and stable premature ventricular contractions (PVC) various antiarrhythmics are tested. A patient receives therapeutic dosages of antiarrhythmic agent for 4–5 days and then the number and characteristics of premature complexes are assesses using the 24-hour Holter monitoring [1, 2]. The duration of positive effect is usually estimated using repeated 24–72 hours ECG monitoring once in 2–3 months. Lately, it was suggested to use the extrasystole index (EI) to assess the risk of life-threatening ventricular arrythmias (the risk is inversely proportional to the index) [3]. However, the use of this index for the estimation of positive effect in the absence of structural heart disease has not been described.

The objective of this study was to evaluate the positive effect duration of pharmacologic management of premature ventricular contractions (PVC) according to ventricular ectopy analysis in the absence of structural heart disease.

Materials and methods

The current study included 214 patients aged 19–45 years (mean age 33.5±0.95 years). Inclusion criteria were absence of structural heart disease, sinus rhythm, class IV–V PVC (Rayn B. classification (1984)) [1], complains of disrupted regular heart rhythm such as skipped beats or missed beats, congestive heart failure (CHF) NYHA I–II, informed consent for examination and treatment. Absence of structural heart disease was established after cardiac and extracardiac conditions, electrolyte imbalance, use of medications and/or toxic products (diuretics, oral contraceptive pills, alcohol abuse, etc.) that may have led to PVC were excluded. Other exclusion criteria were use of various stress-tests, invasive and non-invasive angiography, contrast-enhanced MRI [1].

All patients underwent 24–72-hour Holter ECG monitoring and echocardiographic examination using the Hitachi EUB-5500 machine. Left ventricular ejection fraction, the left atrial end-diastolic volume index (LAEDVI), left ventricular mass index (LVMI), the ratio of peak velocity blood flow from left ventricular relaxation in early diastole (the E wave) to peak velocity flow in late diastole caused by atrial contraction (the A wave) calculations were described earlier [4, 5].

After 24-hour Holter monitoring all patients were administered cardioprotective therapy that included potassium, sedation, polyunsaturated fatty acids, etc. [4]. If the positive effects were not observed potentially effective pharmacologic antiarrhythmic agents for terminating PVC were selected. When choosing medications, the characteristics of PVC, prognosis, the presence of contraindications and possible adverse effects were taken into consideration [1, 2]. Class II antiarrhythmics were used first, and if they weren't effective — the patient was switched to class I or III; amiodarone was the last choice. We used metoprolol 50–100 mg/day, propranolol 80–160 mg/day, carvedilol 25–50 mg/day, alapinin 50–75 mg/day, moricizine 50–100 mg/day, etacizine 100–150 mg/day, sotalol 160–240 mg/day, propafenone 300–600 mg/day, amiodarone 600–800 mg/day. If the monotherapy didn't work, we used the combinations of these agents. Antiarrhythmic drugs were taken for 4–5 days (8–10 days for amiodarone). Any next agent was started at least 5 half-life periods after the previous one [1, 2]. Before and after the use of antiarrhythmic agents we performed 24-hour ECG monitoring and a decrease in the number of extrasystoles by 75 % or more compared with baseline as well as the elimination of paired, group extrasystoles signified a positive effect [1, 2]. To reduce the risk of ar-

rythmogenic affect of the medications we performed 24-hour ECG monitoring at least once in 3–4 days for 7–14 days, especially in patients taking class Ic antiarrhythmics [1, 2].

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:

$$EI = A \div B,$$

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, 4]. Then the corrected ΔEI (ΔEIcorr.) was calculated according to the formula:

$$\Delta EIcorr = [(EIn - EI\ initial) \div EI\ initial] \div \sqrt{N},$$

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). [3]. If amiodarone was chosen this coefficient corresponded to the days of imodarone use [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 endpoint was the duration of positive antiarrhythmic effect of the drugs used. All examinations including 24-hour electrocardiography monitoring were performed at least once in 3–4 months, physical examination, and ECG — once per month. Regular control of blood pressure and heart rate were performed by patients at home.

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

All patients were divided into two groups depending on the length of positive effects. In 43 (20.10 %) of patients the positive antiarrhythmic effect persisted for 1 year (mean 0.7± 0.04 years) (I group), in 80.90 % — for 1 year and more (mean 3.8± 0.08 years) (II group) ($p<0.05$). This division can be explained by the fact that in the absence of structural heart disease recovery of contractile force after the effective therapy is determined usually lasts for 1 year [1, 2, 6]. We haven't identified any statistically significant differences in sex, age, hemodynamics, body mass index, amount of ventricular extrasystoles in 24 hours between the two groups (Table 1). In 5 (20.83 %) and 22 (22.45 %) patients in groups I and II we identified 6–15 % PVCs in 24 hours of monitoring ($p>0.05$), in other patients — more than 15 %. In 6 (25.00 %) and 29 (29.59 %) patients in groups I and II we identified episodes of unstable ventricular tachycardia ($p>0.05$). In 11 (45.83 %) and 51 (52.04 %) patients in groups I and II we identified left ventricular premature beats, and in the other patients — right ventricular premature contractions ($p>0.05$), in 2(8.33 %) and 48 (48.98 %) — polymorphic, others — monomorphic PVCs ($p<0.05$).

Table 1. **Hemodynamic and clinical values in patients from groups I and II at baseline (M±m, 95 % confidence interval)**

Values \ Groups	Group I n= 24	Group II n= 98
Age, years	30.1±1.3 (22–43)	28.9±1.1 (20–41)
Body mass index, kg/m^2	22.3±0.4 (20–24)	21.9±0.1 (19–25)
LVEF, %	53.86±1.18 (46–59)	54.12±0.78 (45–61)
E/A, units	1.19±0.01 (1.12–1.15)	1.21±0.01 (1.17–1.24)
LAEDVI, ml/m^2	24.56±0.72 (17–31)	23.24±0.64 (18–29)
LVMMI, g/m^2	86.7±1.6 (74–99)	85.3±1.7 (72–101)
PVCs in 24 hours	18900±2450 (5870–30730)	19890±1970 (5980–32900)

Note. E/A — the ratio of peak velocity blood flow from left ventricular relaxation in early diastole (the E wave) to peak velocity flow in late diastole caused by atrial contraction (the A wave); LVEF — left ventricular ejection fraction; LAEDVI — left atrial end-diastolic volume index; LVMMI — left ventricular muscle mass index; PVCs — premature ventricular complexes.

Characteristics of antiarrhythmic therapy in patients from groups I and II are presented in Table 2. According to Table 2, patients in the II group used metoprolol, propranolol and carvedilol less often compared with patients from group I.

Table 2. **Antiarrhythmic therapy in group I and II patients**

Medications	Groups of patients, n= 214	
	Group I (n= 43)	Group II (n= 171)
Metoprolol	12(27,91 %)	9(5,26 %)*
Propranolol	11(25,58 %)	8(4,67 %)*
Carvedilol	12(27,91 %)	11(6,43 %)*
Alapinin	-	19(11,11 %)
Etacizine	-	35(20,47 %)
Moricizine	-	20(11,70 %)
Propafenone	-	48(28,07 %)
Sotalol	6(13,95 %)	16(9,36 %)
Amiodarone	2(4,65 %)	5(2,92 %)

Note. * — statistical significance in $p< 0,05$

Changes in ΔEIcorr.$_{1-10}$ in patients form groups I and II are presented in Figure 1. According to Figure 1, patients in the II group had higher values of ΔEIcorr.$_{1-10}$ starting from the second use of antiarrhythmic agent. We identified that the rise of ΔEIcorr.$_{1-10}$ in patients from the II group after the first and second use of medications was due to increase in linear deviation (LD) of the corrected pre-ectopic interval (r=0.86) t, and after the third and following doses — due to the reduction in the number of premature contractions (r=–0.84). In patients in the groups, I and II ΔEIcorr. linear regression slope was 0.03–0.13 units/ΔEIcorr.$_{1-10}$ (mean 0.08±0.01 units/ΔEIcorr.$_{1-10}$) and 0.12–0.92 units/ΔEIcorr.$_{1-10}$ (mean 0.52±0.03 units/ΔEIcorr.$_{1-10}$) ($p<0.05$). In patients without structural heart disease, the sensitivity, specificity, and positive prognostic value for antiarrhythmic therapy effects persistence for at least 1 year were 97.03%, 87.50% and 96.08%, respectively for a linear regression slope of≥12 units/IEcorr. In patients from groups I and II the reduction of the number of PVCs compared with baseline was from 76% to 92% (mean 85±2%) and from 77% to 96% (mean 86± 1%) ($p>0.05$).

In patients from the I and II groups LVEF increased from 53.86±1.18% to 55.12±1.09% ($p>0.05$) and from 54.12±0.78% to 65.56±1.07% ($p<0.05$) respectively after one year of treatment.

Positive clinical effect from using class II antiarrhythmics in patients from the I and II groups highly correlated with linear deviation of the corrected pre-ectopic interval of PVC≥11 m/s with polymorphic PVC (r=0.88); the use of class I and III agents and the combination of class II and I agents — ≤10 m/s (r=0.84).

Discussion

Treatment of ventricular arrythmias including PVC is one of the most complicated problems as it is often associated with preventing such life-threatening conditions as ventricular tachycardia and ventricular fibrillation [1, 2, 4, 5, 6]. Despite positive prognosis of patients with PVC in the absence of structural disease, according to the B.Bigger (1984) [1] classification antiarrhythmic therapy should be started in all patients who complain on feeling arrhythmic and have worsening quality of life as well as to prevent arrythmogenic cardiomyopathy and fatal arrythmias [1, 2, 6].

One study included 214 patients aged 20–43 years (mean age 31.6±0.9 years). Inclusion criteria were absence of structural heart disease, sinus rhythm, class IV–V PVC (Rayn B. classification (1984)) [1], complains of disrupted regular heart rhythm such as skipped beats or missed beats, congestive heart failure (CHF) NYHA I–II, informed consent for examination and treatment [1]. Absence of structural heart disease was established after cardiac and extracardiac conditions, electrolyte imbalance, use of medications and/or toxic products (diuretics, oral contraceptive pills, alcohol abuse, etc.) that may have led to PVC were excluded.

13% of included patients had 6–15% and the rest had more than 15% of PVCs of the total number of ventricular complexes per day. In 28.69% episodes of unstable ventricular tachycardia were registered.

Catheter ablation of the arrythmogenic area is currently the first line therapy in patients with 15% and more PVCs, in patients in whom pharmacologic therapy is ineffective or in case of any contraindica-

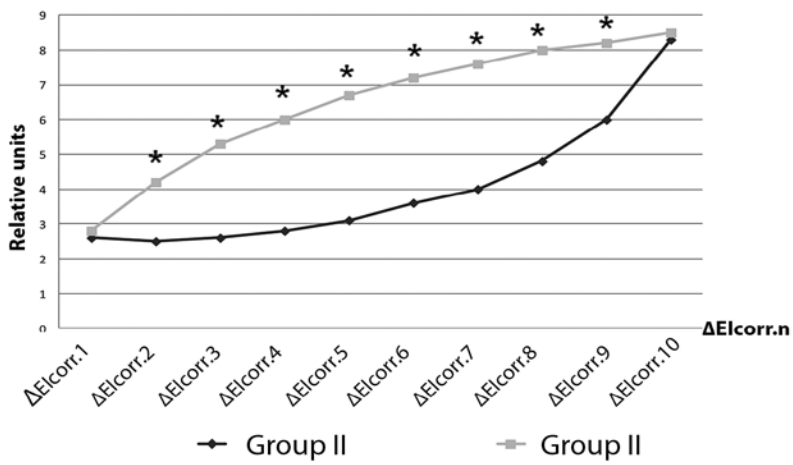

Fig. 1. ΔEIcorr. changes (means) in group I and II patients.
Note. ΔEIcorr.n (in relative units) is the change of EI after each sequential intake of the medication compared with the initial data, N — coefficient corresponding to the amount of dosses, i.e. after first intake of an antiarrhythmic medication this coefficient was "1" (ΔEIcorr.1), after second — "2" (ΔEIcorr.2), after third — 3 (ΔEIcorr.3); * — $p< 0.05$.

tions to antiarrhythmic medications [1, 2]. We based our approach to PVC therapy on this statement.

In the current study testing of antiarrhythmic therapy was performed in all patients included [1]. Class II antiarrhythmics were used first, and if they weren't effective — the patient was switched to class I or III; amiodarone was the last choice. Before and after the use of antiarrhythmic agents we performed 24-hour ECG monitoring and a decrease in the number of extrasystoles by 75 % or more compared with baseline as well as the elimination of paired, group extrasystoles signified a positive effect [1,Relative units2]. Antiarrhythmic drugs were taken for 4–5 days (8–10 days for amiodarone). The follow-up duration ranged from 1 to 5 years. The endpoint was the duration of positive antiarrhythmic effect of the drugs used.

In 20.10 % of patients the positive antiarrhythmic effect persisted for 0.7±0.04 years, in 80.90 % — for 3.8± 0.08 years. In patients, in whom the positive effect lasted for up to 1 year, metoprolol, propranolol, sotalol were used more frequently, while class I drugs were not used at all.

Previous studies have shown that in patients with the absence of structural heart disease in whom positive effects of antiarrhythmic therapy lasted for one year or more the amount of ventricular premature beats didn't differ significantly and made up 86 % of all ventricular complexes [7]. After the most effective agent was chosen the improvement of contractile function of left ventricle lasted for 1 year and more [1, 2, 4, 5, 6].

The results of the current study were similar to the data described before.

For all patients before and after taking each medication EI was calculated as the ratio of linear deviation of the corrected pre-ectopic interval to the ventricular extrasystole number per hour [3, 4].

It was suggested to use the extrasystole index to assess the risk of life-threatening ventricular arrythmias (the risk is inversely proportional to the index) [4, 5]. The number of ventricular premature beats and EI were highly variable and, therefore, we calculated ΔEIcorr as the change of EI after each sequential intake of the medication compared with the initial data. the sensitivity, Specificity, and positive prognostic value for antiarrhythmic therapy effects persistence for at least 1 year were 97, 03 %, 87.50 % and 96.08 %, respectively for a linear regression slope of⩾12 units/ IEcorr.

Previous clinical studies have shown that linear deviation of the corrected pre-ectopic interval⩽10 m/s confirms the "re-entry" mechanism and/or the formation of the pathological ectopic area, and the high variability of this index — the presence of triggers [5]. Thus, after several doses of an antiarrhythmic agent in the presence of triggers, the membrane becomes less hyperpolarized that results in the rise of the corrected pre-ectopic interval and the reduction of the number of PVCs. After the depolarization, for example due to the re-entry mechanism, the fractioning of the depolarization wave occurs, then the wave splits into daughter wavelets and each of them becomes independent. This causes various corrected pre-ectopic intervals to appear of ECG. Eventually, instead of an one-way block the full blocking develops and the ectopic beats become more frequent [1, 2].

The results of our study confirm the previous data: In the presence of positive effects of antiarrhythmic agents the rise of ΔEIcorr. after the first and second use of medications was due to increase in linear deviation (LD) of the corrected pre-ectopic interval (r=0.86) and after the third and following doses — due to the reduction in the number of premature contractions (r=–0.84). Positive clinical effect from using class II antiarrhythmics in patients from the I and II groups highly correlated with linear deviation of the corrected pre-ectopic interval of PVC⩾11 m/s with polymorphic PVC (r=0.88); the use of class I and III agents and the combination of class II and I agents — ⩽10 m/s (r=0.84). This should be taken into consideration when choosing an antiarrhythmic agent for patients with PVC.

The persistence of the positive effect of antiarrhythmic therapy for less than a year is probably due to, first, trigger mechanisms transformation (early or late postdepolarization), for instance, to re-entry and backwards [1]. Secondly, apparently, due to reduced sensitivity to of the myocardium to antiarrhythmic agents, primarily beta-blockers, that develops because of the oxidative stress [8, 9]. Thirdly, apparently, latent myocarditis, cardiomyopathy, right ventricular arrhythmogenic dysplasia and other conditions can manifest with PVCs. In this case medications can be less effective [1, 2]. Therefore, catheter ablation is the first line treatment in these patients, especially in those with 15 % and more PVCs [1, 2, 10].

Conclusion

In patients without structural heart disease IE and ΔEIcorr. should be calculated before and after each administration of the drug when choosing the best agent. In these patients positive prognostic value for

antiarrhythmic therapy effects persistence for at least 1 year was 96.08 % for a linear regression slope of ≥ 12 units/IEcorr. One-time calculation of IE and ΔEIcorr. doesn't estimate the persistence of a positive effect of antiarrhythmic therapy. In the absence of structural heart disease the reduction of the number of PVCs doesn't determine the persistence of a positive effect of antiarrhythmic therapy.

Conflict of interest: none declared.

References

1. Braunwald's Heart Disease. A textbook of cardiovascular medicine. 11th ed. Zipes D.P., Libby P., Bonow R.O. et al., Phyladelfhia, W.B. Saunders Company. 2018. 2040 p.
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. Latchamsetty R., Bogun F. Premature ventricular complex-induced cardiomyopathy. JACC Clin Electrophysiol. 2019;5(5): 537–550.
5. 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.
6. Panizo J.G., Barra S., Mellor G. et al. Premature Ventricular Complex-induced Cardiomyopathy. Arrhythm. Electrophysiol. Rev., 2018; 7(2): 128–134.
7. 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
8. Wang Y., Eltit J.M., Kaszala K. et al. Cellular mechanism of premature ventricular contraction-induced cardiomyopathy. Heart Rhytm, 2014; 11(11): 2064–2072.
9. Sovari A.A. Cellular and molecular mechanisms of arrhythmia by oxidative stress. Cardiol. Res. Pract., 2016; 2016: 9656078.
10. 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.