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Prediction of antiarrhythmic therapy effectiveness in children

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Aim. To optimize treatment tactics in children with arrhythmias based on the evaluation and prediction of the therapy efficacy.

Material and methods. Prospective cohort study was performed from 2007 to 2017. A total of 100 patients aged 0 to 7 years with different types of significant arrhythmias received prophylactic antiarrhythmic therapy. Data of medical history, 12-lead electrocardiography (ECG), Holter ECG monitoring, and echocardiography were studied. To verify electrophysiological variant of tachycardia, some patients underwent transesophageal electrophysiologic study.

Results. The study showed that antiarrhythmic drug therapy was most efficacious in patients till one year old without signs of arrhythmogenic cardiomyopathy (ACM). Older age of children, the presence of pronounced ACM manifestations are factors that increase the risk of ineffective AAT. Based on the data obtained, a multifactor model was developed to predict the effectiveness of prolonged antiarrhythmic therapy.

Conclusion. The study showed that age and intracardiac hemodynamic status affected the efficacy of antiarrhythmic therapy. Proposed model allowed to avoid unnecessary prolonged pharmacological load and to timely administer other methods of treatment in case when ineffective result of the antiarrhythmic therapy was predicted.

Key words: children, arrhythmia, arrhythmogenic cardiomyopathy, prediction model, prolonged antiarrhythmic therapy.

Conflicts of Interest: nothing to declare.

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Pediatric arrhythmology remains one of the most controversial areas in pediatric cardiology. An open question there, first of all, regards patients of the first years of life. Preventive antiarrhythmic therapy is used mainly in early childhood, firstly, due to the high chance of spontaneous resolution of tachycardia and, secondly, because of higher indications for radiofrequency ablation (RFA) in this age group. It should be remembered that antiarrhythmic therapy is not a definitive method in tachyarrhythmia treatment in children, but only helps them "outgrow" arrhythmia. So, the aim of this is to control the rhythm up to 1-1,5 years, when in most children there is a spontaneous remission of tachycardia due to completing of heart development. After the first year of life, the probability of spontaneous tachycardia resolution is significantly reduced [1]. Data on drug resistance, deaths, and life-threatening events resulting from the use of antiarrhythmic therapy (AAT) in children make us cautious about its widespread application in pediatric practice [2-4]. Considering that AAT is currently the main antiarrhythmic strategy in early childhood, it is necessary to optimize treatment tactics based on evaluating the effectiveness of drugs and determining the resistance predictors [5-7].

Material and methods

The prospective cohort study was performed between 2007 and 2017 at the Cardiology Research Institute of Tomsk. A prolonged AAT was received by 100 patients aged 0 to 7 years (2,33 years) (IQR: 0,33-5,0) with different variants of idiopathic clinically significant arrhythmias. Table 1 presents the age groups of children and types of arrhythmias.

There were following inclusion criteria: no congenital heart disease and channelopathies; no acute infectious diseases and exacerbation of chronic ones; no myocarditis signs by laboratory analysis. Indications for AAT use were: sustained paroxysmal supraventricular tachycardia (SVT) and ventricular tachycardia (VT); continuously recurring chronic SVT and VT, including in combination with supraventricular extrasystole (SVES) and ventricular extrasystole (VES), comprising 20% of the diurnal heart rate (HR) value; arrhythmogenic cardiomyopathy (ACM); heart failure signs [8-10].

The study protocol included medical history, electrocardiography (ECG), Holter monitoring (HM), echocardiography (echo). To verify the electrophysiological mechanism of tachycardia in some patients, a transesophageal electrophysiological study was performed.

When performing echo, in addition to standard measurements of intracardiac hemodynamic parameters, the deviation of the atrial volumes and left ventricle end-diastolic volume (LV EDV) from the individually predicted anthropometric standards, expressed as a percentage, was evaluated. This is necessary due to age and anthropometric heterogeneity of patients, as well as for the follow-up echo for assessment of heart changes with age. These parameters were determined automatically, according to the study protocol.

For prolonged therapy, antiarrhythmic agents of IC, II, III, and IV classes was used [11], as well as digoxin. According to recommendations of EHRA and AEPC-Arrhythmia Working Group, these agents are used both for narrow and wide QRS tachycardia, as well as for supraventricular and ventricular arrhythmias in children. Doses were consistent with the recommendations of the EHRA and AEPC-Arrhythmia Working Group [12]. However, despite the wide range of antiarrhythmic agents and their combinations, there are currently no clear recommendations for their use and criteria for the AAT effectiveness in children [13].

We propose the following gradation of the AAT effectiveness in children.

1. Effective therapy:

1.1. Elimination of paroxysmal tachycardia.

1.2. Sinus rhythm restoration in persistent and continuously recurring tachycardia.

1.3. Control of diurnal HR values in persistent and continuously recurring tachycardia until sinus rhythm restoration.

1.4. Ectopic activity decrease in premature heart beat (isolated and grouped extrasystoles, as well as

Table 1

Patient's age groups and types of arrhythmia

Age (Mo; IQR; range) (years)	2,33 (0,33-5,0); 0-7
Age up to 1 year	41/100
Age 1-3 years	23/100
Age 3-7 years	36/100
Wolf-Parkinson-White Syndrome	41/100
Ectopic atrial tachycardia	40/100
Ventricular tachycardia	18/100
AV-nodal reentrant tachycardia	1/100

Note: ectopic atrial tachycardia, including in combination with supraventricular premature beats at least 20%. Ventricular tachycardia, including in combination with ventricular ectopic beats at least 20%.

Table 2

The effectiveness and duration of prolonged AAT

Agent	n	Duration of administration, months, Me (IQR)	Effective, n (%)	Ineffective, n (%)	Partially effective, n (%)
Monotherapy					
Propaphenone	37	1,00 (0,33-5,00)	5 (13,5%)	25 (67,6%)	7 (18,9%)
Propranolol	25	1,00 (0,33-3,00)	2 (8%)	17 (68%)	6 (24%)
Amiodarone	69	4,00 (1,00-6,00)	15 (21,7%)	41 (59,4%)	13 (18,8%)
Sotalol	4	0,42 (0,33-3,25)	-	2 (50%)	2 (50%)
Verapamil	5	0,33 (0,25-1,00)	1 (20%)	4 (80%)	-
Digoxin	14	0,33 (0,33-1,00)		11 (78,6%)	3 (21,4%)
Combination therapy					
Amiodarone+propranolol	7	6,00 (1,83-9,00)	2 (28,6%)	-	5 (71,4%)
Sotalol+propafenone	2	1,17 (0,33-2,00)	-	1 (50%)	1 (50%)
Amiodarone+Digoxin	4	1,00 (0,75-6,50)	1 (25%)	3 (75%)	-
Digoxin+propranolol	1	2,00	-	-	1 (100%)
Digoxin+sotalol	1	2,00	-	-	1 (100%)
Digoxin+propafenone	1	1,00	-	1	-

Table 3

Comparative analysis of patients with effective, ineffective and partially effective therapy by age and baseline echocardiography parameters

Parameter		Effective AAT (1) (n=26)	Ineffective AAT (2) (n=62)	Partially effective AAT (3) (n=12)	Intergroup p	Pair P		
						P 1-2	P 1-3	P 2-3
Mean age, years	Me	0,3	3,0	2,3	<0,001	<0,001	0,001	0,628
	IQR	0,1 -1,0	0,9 — 5,5	0,9 — 4,4				
LA volume,%	Me	90,0	125,0	85,9	0,002	0,003	0,730	0,014
	IQR	76,4-116,0	103,7-161,5	79,1 — 86,5				
RA volume,%	Me	91,9	124,0	105,0	0,001	<0,001	0,283	0,186
	IQR	79,7-103,0	108,3-152,5	89,3-144,0				
LV EDV, %	Me	98,3	119,0	111,0	0,080	-	-	-
	IQR	74,7-122,3	100,9-136,0	102,0-119,0				
LVEF,%	Me	72,0	67,0	73,0	0,003	0,015	0,606	0,004
	IQR	65,0-79,5	56,5-72,0	69,5-76,5				

Abbreviations: LA — left atrium, RA — right atrium, LV EDV — left ventricle end-diastolic volume, LVEF — left ventricular ejection fraction.

accompanied by unstable SVT or VT) to subnormal values (<1000 per day) with the elimination of grouped extrasystoles and episodes of unstable tachycardia.

2. Partially effective therapy:

2.1. The decrease in the frequency of tachycardia paroxysms ⩾50% of the baseline, extension of a period without paroxisms to 3-6 months.

2.2. The decrease in mean HR ⩾20% of the baseline.

2.3. Ectopic activity decrease in premature heart beat ⩾50% of the baseline.

Table 4

The AAT efficiency predictors based on univariate logistic regression analysis

Parameter	P	OR	95% CI		Match rate (%)
			Lower limit	Upper limit	
Age	0,001	0,513	0,349	0,754	75,0
ACM	0,003	4,608	1,703	12,467	72,7
LA volume	0,012	0,971	0,949	0,994	80,9
RA volume	0,001	0,661	0,524	0,835	85,7
LA	<0,001	0,763	0,661	0,882	74,4
LA1	0,001	0,781	0,676	0,903	85,3
LA2	0,001	0,731	0,606	0,881	82,4
RA1	<0,001	0,751	0,652	0,866	82,5
RA2	<0,001	0,734	0,628	0,859	81,3

Abbreviations: ACM — signs of arrhythmogenic cardiomyopathy, LA volume — volume of the left atrium (ml), RA volume — volume of the right atrium (ml), LA — anterior posterior dimension of the left atrium (mm), LA1 — lateral-medial dimension of the left atrium (mm), LA2 — superior-inferior dimension of the left atrium (mm), RA1 — lateral-medial dimension of the right atrium (mm), RA2 — superior-inferior dimension of the right atrium (mm), OS — odds ratio, CI — confidence interval.

2.4. Partially effective therapy also included cases when in the first days and weeks the criteria for effective therapy were achieved and then efficiency was decreased, which in most cases required AAT modification. Therapy was considered ineffective if it did not meet any of the above criteria.

3. At the beginning, we were guided by the trial and error method. Firstly, agent with the shortest half-life and lowest risk of side effects was prescribed. If one agent was ineffective, another was prescribed after five half-lives of the previous one.

Over the entire follow-up, 50 (50%) children received 1 agent, 33 (33%) — 2 agents, 8 (8%) — 3 and 4 agents, and 1 (1%) — 6 agents in sequence. With resistance to antiarrhythmic monotherapy in 19 patients, combination therapy was prescribed — in 16 children 1 combination was used, in 3 children — 2 combinations in sequence.

Children receiving amiodarone were evaluated every 3 months for liver and thyroid function.

We assessed HM and echo parameters initially, at 5-8 days after the effective therapy criteria were reached, and 6 months after the AAT discontinuation.

The mean follow-up period for patients with effective therapy was 5,3±2,1 years (2 to 8 years).

Statistical analysis. Statistical processing of the results was carried out using R 3.0.2 software. Description of quantitative characters is presented as median and interquartile range — Me (Q1; Q3). Comparison of two independent samples was performed using the Mann-Whitney test, three or more — Kruskal-Wallis test. When conducting multiple pairwise comparisons of the samples, the significance level achieved in the study was adjusted with Bonferroni correction. The quantitative changes were evaluated using the Wilcoxon test.

The assessment of unfavorable prognosis probability and the identification of significant predictors of an adverse outcome were performed using multivariate logistic regression analysis. The creation of a forecast model for the AAT effectiveness was carried out using discriminant analysis. The statistical significance of the model was evaluated by the Wilks's

Table 5

CLDF values in centroids of effective and ineffective AAT groups

Parameter	Function
Effective therapy	-1,276
Ineffective therapy	0,300

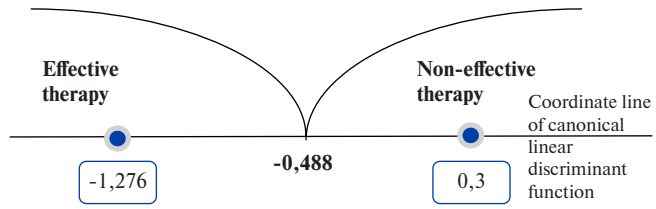

Fig. 1. Graphical representation of the discriminant function.

lambda distribution. Goodness of fit of the real observation distribution and the forecast, the Percentage Correct method was used, and the sensitivity and specificity of the model were evaluated. The quality of the model was also evaluated using ROC analysis with the determination of the area under the ROC curve (AUC). Statistical significance was considered as $p<0,05$.

The study was conducted in accordance with Good Clinical Practice guidelines and the principles of Declaration of Helsinki; the study protocol was approved by local independent ethics committees. All legal representatives of patients completed the informed consent.

Results

The effectiveness and duration of antiarrhythmic therapy are presented in Table 2. The criteria for effective therapy were obtained using amiodarone, propafenone, propranolol and verapamil, as well as AAT combinations: amiodarone+propranolol, amiodarone+digoxin.

A proarrhythmic effect was obtained in 1 patient, who, against the background of amiodarone taking, underwent parenteral esmolol administration to suppress tachycardia paroxysm. As a result of this combination, the patient had the symptomatic bradycardia, which required resuscitation. There were no cases of proarrhythmia in other patients.

The main reasons for discontinuation were inefficiency and delayed resistance of agents after the initial effect.

Absolute effectiveness criteria were achieved in 26 (26%) of 100 patients receiving prolonged AAT, partial effectiveness — in 12 (12%) patients. Therapy was ineffective in 62 (62%) patients.

When comparing the AAT effectiveness in patients with various electrophysiological types of arrhythmias, there were no statistically significant differences between the variants of tachycardia and the clinical manifestations of heart failure (class I-IV according to NYHA classification).

During effective therapy, reducing clinical symptoms of heart failure was noted in 11 patients was observed.

A comparative analysis of patients with effective, ineffective, and partially effective therapy by age and intracardiac hemodynamic parameters is presented in Table 3. Among patients with effective AAT, there were more children under the age of 1 year ($F=20,713$; $p<0,001$) without ACM ($\chi^2=11,618$; $p=0,003$). Echo results showed that in the effective therapy group, the median values of initial atrial volume were in normal range. In patients with an initial atrial volume increase, AAT was ineffective. LV ejection fraction (EF) in patients with effective AAT was statistically significantly higher compared to patients with ineffective AAT.

Univariate logistic regression analysis showed that the age, atrial dimension and volume, as well as a qualitative character of ACM signs, are independent predictors of the AAT effectiveness (Table 4).

The results of the analysis indicate that with an increase in age by 1 year, the probability of effective therapy decrease by 48,7%. The presence of ACM signs reduces the chance of effective results by 4,6 times. With an increase in the volume of the right (RA) and left atria (LA) by 1 ml, the probability of high AAT effectiveness decrease by 33,9% and 2,9%, respectively. With an increase in atrial dimensions by 1 mm, the chances of an effective results are reduced by 21,9-26,9%.

Discriminant analysis allowed us to develop a multidimensional model for predicting the effectiveness of continuous therapy (Patent № 2611954 of 03.17.2017). As a criterion for dividing into groups, a sign of the AAT effectiveness was used.

During the analysis, predictors of the AAT effectiveness were determined — patient's age, RA and LA volumes as a percentage, LVEF, mean and maximum HR according to the HM.

Equation for calculating canonical linear discriminant function (CLDF) is built:

CLDF = -3,359 + 0,017 * RA volume (%) + 0,001 * LA volume (%) — 0,001 * LVEF — 0,013 * mean HR + 0,009 * max HR according to HM + 0,296 * age, years.

CLDF values in group centroids are presented in Table 5:

The decision rule for the classification of objects is formulated as follows: the object will be assigned to the class closer to the centroid of which is the calculated CLDF value (Fig. 1).

The model is statistically significant (Wilks's lambda distribution 0,716, p=0004). The total percentage of correctly classified cases is 81%, sensitivity — 78,4%, specificity — 91,7%.

The high quality classification using the proposed model is also confirmed by the ROC analysis: the area under the ROC curve was 0,895 (95% CI 0,814-0,977, $p<0,001$).

The proposed method for predicting the AAT effectiveness is demonstrated in the following clinical observations.

Clinical example 1. Patient M., age of 22 days. There are complaints from parents about tachycardia

episodes accompanied by lassitude, refusal to feed. It is known that the first episode of tachycardia occurred during delivery. After this, tachycardia paroxysms up to 4 hours; it stopped after intravenous bolus infusion of an adenosine solution (0,1 mg/kg), as well as a bolus infusion of amiodarone (5 mg/kg for 30 min). Follow-up control showed a tendency toward an increase in tachycardia episodes, which began to occur daily and became continuously recurring. Based on the history data, physical examination, survey including ECG monitoring during and outside tachycardia episodes, HM, transesophageal electrophysiological study (TEEPS), and echo, the following diagnosis was established: Latent WPW syndrome. Paroxysmal orthodromic tachycardia. Class II heart failure (according to NYHA classification).

The markers for constructing an AAT effectiveness model are as follows:

Age: 0,08 years (1 month)
RA volume, %: 72,5%
LA volume, %: 71,8%
EF, %: 87%
Mean HR according to HM: 137 bpm
Maximum HR according to HM: 199 bpm
Forecast for the AAT effectiveness:

CLDF = -3,359 + 0,017 * 72,5 + 0,001 * 71,8 — 0,001 * 87 — 0,013 * 137 + 0,009 * 199 + 0,296 * 0,08.

CLDF = -2,11

This value indicates a high probability of the effective AAT.

As a result of the AAT selection, the patient was prescribed amiodarone powder at a loading dose of 10 mg/kg/day for 15 days, followed by 5 mg/kg/day. During the administration of loading dose, frequency of tachycardia episodes decreased and starting from the 16th day of therapy, it did not relapsed. In order to prevent tachycardia, the patient was prescribed prolonged therapy with amiodarone at a dose of 5 mg/kg/day. Given the normal state of health and the absence of tachycardia paroxysms, amiodarone was discontinued after 4 months of therapy. There were no tachycardia episodes over the next 5 years of follow-up.

Clinical example 2. Patient I., 11 months of age, was admitted to the Division of Pediatric Cardiology with complaints from his parents about tachycardia, sweating, lassitude, fatigue, loss of appetite. After the examination, including ECG, HM, echo, the following diagnosis was established: Continuously recurring atrial tachycardia. Class III heart failure.

The markers for constructing an AAT effectiveness model are as follows:

Age: 0,92 years (11 months)
RA volume, %: 159 %
LA volume, %: 199%
EF, %: 32%
Mean HR according to HM: 194 bpm
Maximum HR according to HM: 277 bpm
Forecast for the AAT effectiveness:

CLDF = -3,359 + 0,017 * 159 + 0,001 * 199 — 0,001 * 32 — 0,013 * 194 + 0,009 * 277 + 0,296 * 0,92.

CLDF = -0,25

This value indicates a high probability of the ineffective AAT.

Given that the first-line treatment of arrhythmia in early childhood is AAT, in the department, there was agent selection including digoxin, propafenone, propranolol, amiodarone. Therapy was ineffective. Against the background of continuously recurring tachycardia with a high mean HR according to HM, ACM according to echo, and circulatory failure increase, the patient underwent RFA of the right atrial ectopic foci.

Discussion

The clinical and prognostic value of arrhythmias is determined by the hemodynamic manifestations of arrhythmia — the ACM development [14-16]. Children of the first years of life constitute a risk group for the ACM development due to high HR during tachycardia, its tendency to chronization, and drug resistance [17-19]. Atrial tachycardia is the most common cause of ACM in children. In addition, the ACM is susceptible to both children with SVT due to accessory atrioventricular connections and ventricular arrhythmias, which are characterized by a tendency to chronization, and drug resistance [8, 9, 17, 20].

As regards the management strategy, there is no universal approach. A number of researchers report high efficacy of medication in infants and toddlers and recommend treatment regimens that include combinations of two or even three antiarrhythmic agents [21-25]. However, a large number of publications indicate the limited effectiveness and safety of AAT for the management of arrhythmias in children [2-6, 25]. Despite the fact that various combinations of AAT can increase its effectiveness, it increases the risk of side effects, including mortality, in particular, with a combination of classes I and III agents [18].

In a multicenter retrospective study by Seslar SP, et al. it has been shown that AAT during hospitalization is effective and safe in children under the age of 1 year with idiopathic SVT. It should be noted that the average hospital stay for patients was 4 days. It depended on the number of drugs taken and the need

for patients to stay in the intensive care unit. However, this study has significant limitations — there were only assessment of therapy beginning and no prospective follow-up [21]. The authors of another retrospective cohort study, evaluating the effectiveness of AAT in children hospitalized in the intensive care unit, indicate the lack of data on further outpatient monitoring, changes in treatment regimens, side effects of therapy, recurrence of arrhythmia after drug withdrawal [13]. Whereas precisely these data specify the expediency and prospects of the therapy, the initial effectiveness of AAT with its subsequent loss and arrhythmia recurrence is well known. Most publications on AAT in children have limitations associated with small sample sizes, the retrospective design of the study, and the lack of data on long-term outcomes [26, 27]. According to Maid G, et al., basic principles of AAT in pediatric practice, dosages and intervals for AAT administration are taken from "adult" arrhythmology without taking into account the physiological features of children. Therefore, many authors point to the need for multicenter, randomized, placebo-controlled clinical trials. [6].

The results of our study show that children under the age of 1 year without ACM signs are more likely to have an effective AAT results. Factors that increase the risk of ineffective AAT include older children, severe ACM manifestations according to echo. Similar results are presented in the study by Ge H, et al., where the predictors of the AAT effectiveness are early age and the paroxysmal tachycardia, which usually does not lead to the ACM formation [28]. Our data are consistent with the paper by Sanatani S, et al., where 44 patients under the age of 6 months were studied. Authors revealed that reduced LVEF was a predictor of refractory tachycardia, while the nosologic unit of arrhythmia did not significantly affect the result of therapy [29]. It is noteworthy that, according to the results of the above study, early manifestation of arrhythmia was not the key to successful therapy. On the contrary, the present study showed that the early age of the patient is an independent predictor of the effective AAT. Similar data were obtained by Salerno JC, et al. Authors reported a high probability of spontaneous resolution of atrial ectopic tachycardia after successful drug therapy if it occurs in the first year of life, but this trend rarely remain at an older age [22].

Based on the data obtained, a multivariate model for predicting the effectiveness of a prolonged AAT has been developed to determine individual management of children with arrhythmias. This model will allow avoiding prolonged therapy and timely using other treatment methods in case of predicting an ineffective AAT.

Conclusion

Factors affecting the AAT efficiency are age and state of intracardiac hemodynamic parameters. Prolonged AAT is indicated for young children with tachyarrhythmias not accompanied by structural changes in the heart. It should be noted that this category of children has a high chance of spontaneous resolution of arrhythmias, and after the discontinuation of effective therapy, arrhythmia may not relapse during further follow-up. In patients of any age, and especially after 1 year of life with echocardiographic signs of ACM, an ineffective AAT should be assumed and RFA should be planned.

Conflicts of Interest: nothing to declare.

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