Indian Pacing and Electrophysiology Journal 19 (2019) 57–62

Contents lists available at ScienceDirect

Indian Pacing and Electrophysiology Journal

journal homepage: www.elsevier.com/locate/IPEJ

Ventricular tachycardia prediction in patients with implantable cardioverter-defibrillators for primary prevention of sudden cardiac death

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ARTICLE INFO

Article history:
Received 20 July 2018
Received in revised form
24 November 2018
Accepted 25 November 2018
Available online 25 November 2018

ABSTRACT

Clinical data analysis of 83 patients with implantable cardioverter-defibrillators (ICDs) for sudden cardiac death (SCD) primary prevention has been done. We revealed 5 parameters associated with the detection of life-threatening ventricular arrhythmias. These parameters formed the basis for constructing a logistic regression model. The model makes it possible to obtain the probability of occurrence of a specific event depending on the severity of the predictive parameters and the degree of its influence (risk of true ventricular arrhythmias detection). Estimating the potential risk of the life-threatening arrhythmias, individual programming options are required in implantable cardioverter-defibrillators (ICDs) to reduce the amount of unnecessary electrotherapy, as well as more accurate monitoring of the patient's drug therapy.

1. Introduction

Implantable cardioverter-defibrillators (ICD) reduce mortality caused by ventricular arrhythmias in sudden cardiac death (SCD) primary prevention patients [1–4]. However, unnecessary electrotherapy is performed in 13–29% of cases, despite the current discrimination algorithms used in devices [5,6]. Inappropriate shocks for atrial arrhythmias with rapid ventricular conduction or for abnormal sensing result in multiple well-documented adverse effects, including, but not limited to, two-fold increased risk of overall mortality due to mechanical and hemodynamic side effects [7], as well as a potentially fatal pro-arrhythmic effect [8–10]. It is therefore critical to better understandi of the ways to reduce unnecessary ICD electrotherapy.

Use of tachycardia discrimination algorithms in patients with unnecessary electrotherapy has been evaluated previously. It is noted that the efficiency of most of these algorithms is reduced when the detectable tachycardia exceeds 170 bpm [11]. The DETECT SVT trial demonstrated a decrease in proportion of supraventricular tachycardia (SVT) inappropriately detected as a ventricular tachycardia (VT) with dual-chamber ICDs, compared to single-chamber ICDs (30.9% vs. 39.5%) [12]. Nevertheless, almost a third of SVT episodes are classified incorrectly, despite the presence of both the atrial and ventricular pace/sense channels. The total amount of unnecessary electrotherapy remains high [13]. Therefore, further improvements of the ventricular and supraventricular rhythm discriminators are needed in order to reduce the amount of unnecessary electrotherapy [14–18].

The indication for electrotherapy in any ICD is the tachycardia detection in the programmed VT zone, and the classification of the detected episode with the application of all established discriminators. Thus, as more episodes are detected and classified as VT, the electrotherapy amount increases as well. However, ICD detection parameters can be programmed individually, accounting for individual risk modifiers of true life-threatening arrhythmia, potentially reducing the unnecessary electrotherapy.

In this study, we emphasize the role of mathematical modeling in clinical practice. An easy-to-use predictive model makes it possible to obtain the risk of true ventricular rhythm disturbances in patients with ICDs for sudden cardiac death primary prevention. Thus, it is possible to individually program the ICD detection parameters to reduce the amount of unnecessary electrotherapy.

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Peer review under responsibility of Indian Heart Rhythm Society.

https://doi.org/10.1016/j.ipej.2018.11.011

2. Materials and methods

2.1. Study design

There is a retrospective observational single-centre study with data analyses, designed to test the hypothesis that predictive logistic model for the true VT detection in patients with ICDs for SCD primary prevention reduces the incidence of the inappropriate electrotherapy due to SVTs or abnormal sensing compared with conventional ICD therapy programming. Following baseline assessment, eligible subjects were implanted with an ICD system. The type of system was determined in accordance with clinical indications: single chamber, dual chamber ICD, or CRT-D.

Inappropriate electrotherapy was determined retrospectively by a team of clinical experts: two electrophysiologists and clinical support specialist of the relevant ICD producer. The data for the manual arrhythmia analyses included: a complete intracardiac electrogram, an evaluation of the rhythm onset and stability, the atrial and ventricular electrogram ratio, surface ECG and electrogram ratio, and the patient clinical conditions.

The study complied with the Declaration of Helsinki and was approved by the Internal Ethics Committee of the National Almazov Medical Research Centre.

2.2. Baseline patient characteristics

We analyzed the data of 83 patients with ICD for SCD primary prevention who had sustained VT episodes after implantation. Data collection started immediately after device implantation. Arrhythmia parameters were collected and summarized at each follow-up (FU) visit. Baseline patient characteristics are listed in Table 1.

The most frequent type of implantable devices was cardiac resynchronization therapy (CRT-D), n = 45, followed by two-chamber ICDs (n = 20), and single-chamber ICDs (n = 18). The mean average FU time from ICD implantation to the detection of ventricular arrhythmia was 10.75 (ranging from 2.3 to 24.5) months. We were particularly interested in the analyses of the life-threatening arrhythmias, and a patient group at high risk of detecting true VT/VF.

Table 1
Baseline patient characteristics.

Parameters	Value;
All patients, n	83
Age, years (M ± SD)	61.1 ± 4.4
Male gender, n	61
Coronary artery disease, n	48
Dilated cardiomyopathy, n	35
NYHA class II, n	34
NYHA class III and ambulatory IV, n	49
1° atrioventricular block, n	14
2° atrioventricular block, n	2
3° atrioventricular block, n	3
Heart rate, bpm (M ± SD)	67.8 ± 10.4
QRS width, ms (M ± SD)	149.4 ± 16.7
Clinical VT rate, bpm (M ± SD)	168.7 ± 20.2
Left atrium, mm (M ± SD)	42.2 ± 8.4
LVEDd, mm (M ± SD)	71.5 ± 14.2
LVEF, Simpson, % (M ± SD)	24.4 ± 11.7
Left bundle branch block, n	42
Right bundle branch block, n	9
Paroxysmal atrial fibrillation, n	10
Persistent atrial fibrillation, n	34
Paroxysmal atrial flutter, n	11
Beta-blockers, n (%)	78 (93.9)
Amiodaron, n (%)	26 (31.3)
ACE inhibitors/ARB, n (%)	71 (85.5)
Loop diuretics, n (%)	74 (89.2)

VT – ventricular tachycardia.
LVEDd – left ventricle end diastolic diameter.
LVEF - left ventricle ejection fraction.
ACE/ARB - Angiotensin Converting Enzyme/Angiotensin Receptor Blocker.
M ± SD - mean ± SD (Standard Deviation).

2.3. ICD programming protocol

ICD programming was performed during implantation procedure, then 3 days after ICD implantation and further every 12 months. The pacing parameters were chosen based on the need to treat bradycardia and CHF in accordance with current clinical guidelines. Two separate zones of ventricular arrhythmia detection were exposed: 1 – the ventricular tachycardia zone (160 [155; 175] bpm), 2 - the ventricular fibrillation – VF – zone (200 [200; 214] bpm). Electrotherapy in each zone was established separately. Two series of different antitachycardia pacing (ATP) types were programmed in the VT zone, followed by a single cardioversion attempt, and by shock therapy upon failure of previous types of electrotherapy. In the VF zone, the electrotherapy was programmed according to the proven efficacy of ATP in the fast VT zone, specifically one attempt of ATP burst stimulation with the subsequent shock application. Nominal SVT discriminators were fully used in accordance with implanted device manufacturer. There was electrotherapy correction after revealed true VT/VF paroxysms during the dynamic observation. Individual programming of the device corresponding parameters was also performed in case of inappropriate VT/VF detection.

2.4. SVT/VT episode assessment

SVT/VT episode assessment was made by a clinical expert team: two electrophysiologists and clinical support specialist of the relevant ICD Company. The main data for the manual arrhythmia analysis included: a complete recording of the intracardiac electrogram (IEGM), an evaluation of the rhythm onset and stability, the atrial and ventricular electrogram ratio, surface ECG and electrogram ratio, physical parameters of the ICD, patient clinical conditions.

The events detected by the device were classified as non-sustained VT (episode with a cycle length entering the detection zone but less than the detection interval), sustained VT (episode meeting the criteria of the cycle length and the detection interval), or VF episode (arrhythmia entering the VF detection zone and the corresponding detection interval). Depending on the ICD program, appropriate electrotherapy was used according to the arrhythmia detection conditions and the discrimination algorithms application. The detailed characteristics of all episodes were recorded and stored in the database.

2.5. Statistical analysis

The analyses were carried out using a standard statistical software (STATISTICA, StatSoft Inc., version 10.0.228.8, Oklahoma, USA). The data were presented as mean ± SD, and numbers and percentages, respectively. The χ^2 test, Fisher's exact method (categorical variables) were used to determine differences between two groups. Nonparametric Mann-Whitney, Kolmogorov-Smirnov, and median χ^2 tests were used for quantitative variables since the distribution of variables did not meet the requirements of normality. After univariate analysis calculation and P value calculation, a multivariate logistic regression analysis was carried out. The decision tree classification method was used for predictor importance estimation. A generalized estimation of the selected

parameters totality in the probabilistic risk format for detecting true/false VT/VF was obtained based on logistic regression analysis. We used classification trees as one of the data mining methods and threshold value for heart rate was obtained for split selection method CART and by stopping rule FACT. In two-tailed *t*-test, P values of <0.05 were considered significant.

3. Results

3.1. FU visits description

We analyzed the clinical data from all study population (83 patients), including baseline demographic and clinical characteristics, laboratory and instrumental parameters, including 370 FU visits with different types of arrhythmias (Table 2). The following parameters were evaluated: chronic heart failure (CHF), etiology, detailed diagnosis, concomitant diseases, medicines therapy of the underlying disease and concomitant pathology, rhythm features (type, rate and intervals at the FU visit time), echocardiography data in dynamics.

At one FU visit, there were up to 31 episodes of ventricular tachycardia or up to 121 VF episodes. In total ATP electrotherapy was applied 464 times, shocks were applied 255 times. False detection of ventricular arrhythmias was established at 73 FU visits. False detection of ventricular arrhythmia was considered as an event when the ICD regarded a rhythm disturbances episode as VT or VF, but there was no true ventricular arrhythmia. Nonsustained VT was called episode with a cycle length entering the detection zone but less than the detection interval, sustained VT was called episode meeting the criteria of the cycle length and the detection interval, VF episode - arrhythmia entering the VF detection zone and the corresponding detection interval.

IEGM analysis of the recorded VT/VF episodes showed that 181 times (from 1 to 32 times per visit) shock therapy was unnecessary. ATP was unnecessary in 22 out of 108 times. The most common cause of false VT/VF detection was atrial fibrillation (AF) with rapid ventricular conduction (58.9%). T-wave was detected in 12 cases (14.5%), sinus tachycardia in VT detection zone – in 5 cases (6.1%), atrial flutter with a high ventricular rate – in 4 cases (4.8%). The other cases were due to a double counting (2), noise on the right ventricular lead (2), combination of AF and T-wave detection (2). Thus, the total supraventricular arrhythmias caused false detection of ventricular arrhythmia in patient study population in 47.4% of all detections.

3.2. Probability model description

Mathematical analysis was performed to identify the most significant and repeatable variables accompanying the fact of ventricular event detection. Using the decision tree model for predictor importance, five indicators with the highest rank of prognostic significance were identified for patient group with and without true VT/VF detection:

1. Diagnosis of AF at the time of ICD implantation;
2. A history of atrial flutter at the time of ICD implantation;
3. Presence of persistent AF at the FU visit;
4. Registered paroxysmal AF according to ICD statistics or directly at the FU visit;
5. The heart rate (bpm) at the FU visit.

Differences in the resting heart rates between two groups of patients are summarized in Table 3.

Using the decision tree classification, the heart rate threshold value of 70 bpm was obtained, which was significant for assessing the risk of true VT/VF detection. The values of the selected variables in the groups with false and true VT/VF detection for the different categories of qualitative parameters are shown in Table 4.

The generalized estimation of the selected parameters totality in the probabilistic risk format for detecting true/false VT/VF was obtained based on logistic regression analysis. An important aspect is the odds ratio (OR) for the parameters on which the models are based, listed in Table 5. This ratio shows how many times the risk of detecting a true VT/VF episode increases compared to the minimal parameter value. The logistic regression equation was obtained with the following 5 factors: AF diagnosis, atrial flutter diagnosis, persistent AF on FU visit, paroxysmal AF on FU visit, heart rate.

The logistic regression model allows obtaining the probability of the phenomenon depending on the degree of the specific predictive characteristics severity (the positive effect forecast is given for $y > 0.5$, the negative effect forecast for $y \leq 0.5$). Additionally, the logistic regression model allows estimation the influence degree of one or several predictive factors on the likelihood of event (risk of true VT/VF detection). The logistic function parameters for the optimal model are shown in Table 6.

The logistic function is defined as:

Ψ A1*X1 + A2*X2 + A3*X3 + A4*X4 + A5*X5 + B, where A1, A2, A3, A4, A5, B are the logistic equation coefficients calculated in the process of constructing the model, and obtained using the logistic regression module in STATISTICA (StatSoft Inc., version 10.0.228.8). X1, X2, X3, X4, X5 are exact values of the variables included in the model and described in Table 6. Substituting the coefficients from the table, we obtain the function Ψ to estimate the risk of the true VT/VF detection:

Ψ 3.81–1.65*X1 – 57.37*X2 – 0.39*X3 – 51.01*X4 – 0.03*X5

Each of the regression coefficients describes the severity of the corresponding factor contribution. A positive regression coefficient indicates that this factor increases the overall risk (i.e., increases the analyzed outcome likelihood), while a negative coefficient means that this factor reduces the risk. The magnitude of the regression coefficients determines the impact on total risk, as well as in the case of multiscale variables, i.e. measured in different units, this magnitude aligns the scale.

In our study all coefficients are negative, and if each of them is larger, then the risk of detecting the true VT/VF is lower. The ranks (predictive significance) in the calculation of risks do not apply. The

Table 2
Arrhythmia events in FU visits.

Type of arrhythmia	Number FU
Nonsustained VT	256
Sustained VT	23
Sustained VT and VF	21
Sustained VF	70
Total	370

VT - ventricular tachycardia.
VF – ventricular fibrillation.

Table 3
The differences in the heart rate at rest.

	Patients with false VT/VF detection		Patients with true VT/VF detection		P-value
	M ± SD	min ÷ max	M ± SD	min ÷max	
bpm	81.8 ± 22.1	45÷147	63.6 ± 26.6	69÷148	<0.001

M ± SD - mean ± SD (Standard Deviation).
min ÷ max – minimum and maximum values of the heart rate at rest.

Table 4
Frequency of false and true ventricular arrhythmias detection for different parameter values.

Parameters	Parameter value	Groups				
		False VT/VF detection		True VT/VF detection		Total
		Abs.[a]	%	Abs.[a]	%	
Diagnosis AF (P<0.001)[b]	Paroxysmal AF	9	81.8	2	18.2	11
	Persistent AF	38	64.4	21	35.6	59
	No AF history	9	18.0	41	82.0	50
	Total	56	46.7	64	53.3	120
Atrial flutter history (P<0.05)	Yes	4	100.0	0	0	4
	No	52	44.3	64	55.2	116
	Total	56	46.7	64	53.3	120
Persistent AF on FU visit (P<0.05)	Yes	24	64.9	13	35.1	37
	No	29	40.3	43	59.7	72
	Total	53	48.6	56	51.4	109
Paroxysmal AF on FU visit (P<0.001)	Yes	14	93.3	1	6.7	15
	No	37	40.2	55	59.8	92
	Total	51	47.7	56	52.3	107
Heart rate (P<0.001)	Greater than or equal to 70	36	61.0	23	39.0	59
	Less than 70	12	27.3	32	72.7	44
	Total	48	46.6	55	53.4	103

[a] Abs. - Absolute values.
[b] The values for calculating the logistic function Ψ

Table 5
The risk ratio for the model.

Parameters	Parameter value	Risk ratio (OR)
Diagnosis AF	Paroxysmal AF	Minimal risk
	Persistent AF	2.49
	No AF history	20.50
Diagnosis atrial flutter	Yes	Minimal risk
	No	11.06
Persistent AF on FU visit	Yes	Minimal risk
	No	2.74
Paroxysmal AF on FU visit	Yes	Minimal risk
	No	20.81
Heart rate	Greater than or equal to 70	Minimal risk
	Less than 70	4.17

ranks indicate in which order each parameter are situated for the risk significance. Prognostic significance is the “collateral” result of the model construction. Of note, the predictive significance evaluation of indicators composition shows an almost completely coinciding order of indicators significance except for the two last ranks that were swapped places. At the same time, it was revealed that the model has a high quality rate, with $\chi^2 = 46.6$; $p < 0{,}001$; $OR = 33.3$.

The main properties of this model are summarized in Table 7.

The comprehensive risk assessment of true VT/VF detection for a particular patient depends on the values of all parameters included in the logistic regression equation. Namely, unfavorable levels of some parameters are compensated by other parameters. To use this model and accurately to assess the risk, it is necessary to calculate Ψ (abscissa axis), and then, by the logistic curve: $Y = \exp(\psi)/(1 + \exp(\psi))$, determine the probability of detecting a true VT/VF episode (ordinate axis). The logistic curve is standard, so it can be

Table 7
The model properties, in percents.

Properties	%
Sensitivity	90.0
Specificity	78.7
Forecast of positive result	81.8
Forecast of negative result	88.1
Diagnostic accuracy	84.5

used as the key values of Ψ for risk assessment:

Ψ - 2.94 – Risk less than 5%
Ψ 0 – Risk less than 50%
Ψ 0 – Risk more than 50%
Ψ 2.94 – Risk more than 95%

3.3. Examples of the predictive model calculation

Patient 1, without AF history at the time of ICD implantation, has atrial flutter. AF paroxysms were recorded at one of the FU visits according to the ICD statistics. The heart rate at the time of the visit was 74 bpm. These values are shown in Table 8.

The following values are substituted into the formula:

$$\Psi = 3.81 - 1.65 * X1 - 57.37 * X2 - 0.39 * X3 - 51.01 * X4 - 0.03 * X5$$

$$\Psi = 3.81 - 1.65 * 0 - 57.37 * 1 - 0.39 * 0 - 51.01 * 1 - 0.03 * 74 = -106.8$$

Therefore, the risk of true VT/VF detection is less than 5%. If, during the observation period, this patient develops tachycardia

Table 6
Characteristics of the model for assessing the risk of true ventricular arrhythmia detection through logistic regression.

Model parameters	Variables name	Value of coefficients	Rank of predictive significance
Diagnosis AF	X1	−1.65	3
Diagnosis atrial flutter	X2	−57.37	5
Persistent AF on FU visit	X3	−0.39	4
Paroxysmal AF on FU visit	X4	−51.01	2
Heart rate	X5	−0.03	1
Absolute term	B	3.81	

Table 8
Clinical example for model calculations.

Parameters	Parameter value	Value for Ψ function
Diagnosis AF (X1)	Paroxysmal AF	–
	Persistent AF	–
	No AF history	0
Diagnosis atrial flutter (X2)	Yes	1
	No	–
Persistent AF on FU visit (X3)	Yes	–
	No	0
Paroxysmal AF on FU visit (X4)	Yes	1
	No	–
Heart rate (X5)	74	74

that falls into ICD detection zone, it will be most likely to be supraventricular tachycardia.

Patient 2, does not have AF history and atrial flutter history; AF has not been recorded during FU visits, and the heart rate at the time of examination was 55 bpm:

$$\Psi = 3.81 - 1.65*0 - 57.37*0 - 0.39*0 - 51.01*0 - 0.03*55 = 2.16$$

A logistic curve estimate gives a risk of positive VT/VF detection of more than 50%, but less than 95%. For accurate risk calculation, the following formula applies:

$$Y = \exp(\psi) / (1 + \exp(\psi)) = 0{,}8966$$

Therefore, an arrhythmia in the VT detection zone is most likely ventricular tachycardia.

3.4. Model validation

To validate our predictive model, a second group of 40 patients with ICD for SCD primary prevention was enrolled in the study. The baseline demographic and clinical characteristics matched the main patient group (Table 9). The validation group was prospectively evaluated during two FU visits, at 6 and 12 months after ICD implantation. During first FU visit we calculated the probabilities of true ventricular tachycardia based on the proposed prognostic model for each patient. Then we increased the VT detection zone from 160 to 175 bpm, and the VF detection zone from 200 to 210 bpm, to reduce the risk of unnecessary electrotherapy for patients in whom the calculated probability of true VT/VF was less than 5%.

At 12 month FU visit, the numbers of true and false ventricular arrhythmia episodes were calculated. It was found that 12 patients with a low risk of true ventricular tachycardia had mostly SVTs, and the most common SVT type was atrial fibrillation, n = 10, 2 patients had the atrial flutter. Conversely of the seven patients at high risk of true ventricular tachycardia according to our model, five presented paroxysms of ventricular tachycardia, with mean VT rate 173 ± 5.6 bpm. As predicted from to the calculated probabilities of arrhythmias in 21 individuals with the intermediate risk of the true VT for 12 months after ICD implantation, no rhythm disturbances were revealed (Table 10), validating our model.

Table 9
Model validation: comparison of baseline patient characteristics.

Parameters	Model group	Validation group	P-value
Patients, n	83	40	–
Age, years (M ± SD)	61.1 ± 4.4	58.4 ± 6.2	0.127
Male gender, n	61	31	0.301
Coronary artery disease, n	48	27	0.210
Dilated cardiomyopathy, n	35	13	0.094
NYHA class II, n	34	14	0.147
NYHA class III and ambulatory IV, n	49	26	0.211
Heart rate, bpm (M ± SD)	67.8 ± 10.4	63.4 ± 12.3	0.341
QRS width, ms (M ± SD)	149.4 ± 16.7	137.8 ± 14.8	0.104
Left atrium, mm (M ± SD)	42.2 ± 8.4	40.4 ± 5.4	0.258
LVEDd, mm (M ± SD)	71.5 ± 14.2	68.2 ± 16.2	0.141
LVEF, Simpson, % (M ± SD)	24.4 ± 11.7	25.6 ± 10.7	0.208
Left bundle branch block, n	42	23	0.084

LVEDd – left ventricle end diastolic diameter.
LVEF - left ventricle ejection fraction.
M ± SD - mean ± SD (Standard Deviation).

4. Discussion

The application of electrotherapy to AF with a high ventricular rate is not uncommon. The ICD rhythm discriminators with recognition ventricular arrhythmia algorithms are based primarily on the occurrence of tachycardia in the detection zone. Some ICD auto programmed steps include ventricular rhythm onset, rhythm stability and changes in the cycle length, the analysis of the ventricular and atrial rhythm ratio. But AF without proper rate control could have very high ventricular rate and the cycle length could be stable. The ICD then identifies the life-threatening arrhythmia episode and applies electrotherapy, which may not be warranted [19].

Our data verify the importance for more careful AF rate control, setting higher ventricular arrhythmia detection zones and delayed electrotherapy application in patients with ICDs [20]. The use of additional zones with diagnostic algorithms at lower VT detection can lead to a false sense of tranquility for the patient. Such ICD program parameters provide electrotherapy at low tachycardia rates, in which most of tachycardia is supraventricular arrhythmias. This unnecessary electrotherapy usage for SVTs occurs in up to 24% of cases. In such cases it's advisable to use electrotherapy with more stable and long tachycardia paroxysms with a high rate, that will help to avoid unnecessary ATPs and shocks [21]. Pre-calculated risks of true and false life-threatening tachycardia detection in patients with SCD primary prevention can facilitate correct individual programming of ICD detection parameters.

We validated our model in practice. In particular, in the group of 40 patients with a history of paroxysmal atrial fibrillation, the ICD for primary SCD prevention programming of the ventricular fibrillation zone at a higher level (210 bpm) led to decrease the probability of unnecessary shocks due to supraventricular tachycardia at 6 months FU. At the same time, this model clearly describes the likelihood of true ventricular tachycardia onset. Thus, the application of this model is useful in routine practice.

4.1. Study limitations

This was a single-centre observational study and consequently, we have no reliable information about dependence of all discriminatory algorithms and the number of unmotivated ICD electrotherapy. Each ICD and pacemaker manufacturer has its own discriminatory algorithms. In our study, patients carried ICDs from

Table 10
Model validation results.

Patients, n	12 month FU	Ψ logistic function value[a]
Patients with SVT	12	- 53.4 ± 17.6
Patients with VT	7	16.9 ± 11.4
Patients without events	21	1.8 ± 1.2
Total	40	- 11.6 ± 6.1

SVT - supraventricular tachycardia.
VT - ventricular tachycardia.
[a] M ± SD - mean ± SD (Standard Deviation).

three different companies. Our predictive model is yet unable to predict events by type of T wave detection, double counter and lead noise.

However, this study was designed with adequate power to test the predictive role of this mathematical model in clinical practice. A more accurate prospective data analysis with long-time follow-up, larger sample size, and sufficient power to evaluate clinical outcomes between patients with and without usage of this proposed model are warranted.

5. Conclusions

Estimating the potential risk of true life-threatening arrhythmia occurrence with usage of the proposed model, it is possible to individually program the ICD detection parameters to reduce the amount of unnecessary electrotherapy, optimizing management recommendations for patients with SCD primary prevention.

Funding

The study was supported by Council on grants of the Russian Federation President, Grant number MK-6328.2018.7.

Conflicts of interest

None declared.

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