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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Risk stratification personalised model for prediction of life-threatening ventricular tachyarrhythmias in patients with chronic heart failure

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Abstract

Background: The development of prognostic factors of life-threatening ventricular tachyarrhythmias (VTA) and sudden cardiac death (SCD) continues to maintain its priority and relevance in cardiology. The development of a method of personalised prognosis based on multifactorial analysis of the risk factors associated with life-threatening heart rhythm disturbances is considered a key research and clinical task.

Aim: To design a prognostic and mathematical model to define personalised risk for life-threatening VTA in patients with chronic heart failure (CHF).

Methods: The study included 240 patients with CHF (mean-age of 50.5 ± 12.1 years; left ventricular ejection fraction 32.8 ± 10.9%; follow-up period 36.8 ± 5.7 months). The participants received basic therapy for heart failure. The electrocardiogram (ECG) markers of myocardial electrical instability were assessed including microvolt T-wave alternans, heart rate turbulence, heart rate deceleration, and QT dispersion. Additionally, echocardiography and Holter monitoring (HM) were performed. The cardiovascular events were considered as primary endpoints, including SCD, paroxysmal ventricular tachycardia/ventricular fibrillation (VT/VF) based on HM-ECG data, and data obtained from implantable device interrogation (CRT-D, ICD) as well as appropriated shocks.

Results: During the follow-up period, 66 (27.5%) subjects with CHF showed adverse arrhythmic events, including nine SCD events and 57 VTAs. Data from a stepwise discriminant analysis of cumulative ECG-markers of myocardial electrical instability were used to make a mathematical model of preliminary VTA risk stratification. Uni- and multivariate Cox logistic regression analysis were performed to define an individualised risk stratification model of SCD/VTA. A binary logistic regression model demonstrated a high prognostic significance of discriminant function with a classification sensitivity of 80.8% and specificity of 99.1% ($F = 31.2$; $\chi^2 = 143.2$; $p < 0.0001$).

Conclusions: The method of personalised risk stratification using Cox logistic regression allows correct classification of more than 93.9% of CHF cases. A robust body of evidence concerning logistic regression prognostic significance to define VTA risk allows inclusion of this method into the algorithm of subsequent control and selection of the optimal treatment modality to treat patients with CHF.

Key words: myocardial electrical instability, electrocardiography, heart failure, sudden cardiac death, tachyarrhythmias, risk stratification

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INTRODUCTION

The study of prognostic factors of life-threatening tachyarrhythmias and closely related sudden cardiac death (SCD) remains a cornerstone issue in cardiology today. About 80% of SCD cases result from ischaemic heart disease, including 65% of cases due to acute coronary flow disorders, and 20% of SCDs are of non-coronary origin, including dilated cardiomyopathy (DCM), arrhythmogenic right ventricular dysplasia, hypertrophic cardiomyopathy, isolated left ventricular (LV) myocardial non-compaction, and genetically determined ion channel dysfunctions. The predominant mechanisms responsible for the circulatory arrest include heart rhythm disturbance with ventricular tachyarrhythmias (VTA) that is approximately 90% of SCD cases. Therefore, it is not unexpected that prognostic risk stratification models result from multifaceted randomised trials combined with the results obtained from meta-analyses of known, and a variety of new, risk factors of SCD and VTA [1–5]. The principal limitation of such prognostic models is that they are population and not individual based.

Markers functionally associated with the life-threatening arrhythmias reflect myocardial electrical instability. They include microvolt T-wave alternans, QT/JT interval dispersion, heart rate turbulence, fragmented QRS, heart rhythm acceleration/deceleration, early repolarisation syndrome, etc. The above-mentioned electrocardiogram (ECG) markers reflect heterogeneity of processes of myocardial de- and repolarisation, and vegetative dysfunction. Individually, they have a certain prognostic significance related to life-threatening VTA and SCD [6–10]. Prognostic properties of ECG myocardial electrical instability markers are based on the use of the non-linear dynamics method, which is not yet medically standardised and is more suitable for the analysis of complex dynamic objects such as human cardiovascular system rather than conventional statistical methods [11].

In the presence of some nosological condition, the identification of subjects with high risk of cardiovascular events, and the selection of the most adequate treatment strategy including surgery, is a key factor. However, the potential of myocardial electrical instability markers to resolve this issue has not been fully studied; this is especially true for patients with chronic heart failure (CHF) and decreased LV ejection fraction (EF).

The purpose of the present study was to develop a mathematical model of individualised risk stratification of life-threatening VTA in patients with CHF using a combination of myocardial electrical instability markers.

METHODS

The study included 240 subjects with CHF (New York Heart Association [NYHA] class II–III). 179 subjects fulfilled the diagnostic criteria for non-coronary DCM (45/25.1% women, 134/74.9% men, mean age 47.2 ± 11.7 years), and ischaemic cardiomyopathy (ICM) due to coronary heart disease was present in 61 subjects (60/98.4% men, mean age 54.4 ± 5.4 years). A sinus rhythm was registered in 176/73.3% subjects, atrial fibrillation was present in 64/26.7%, average QRS duration was 123 ± 27 ms, complete left bundle branch block with QRS duration of 167 ± 30 ms was present in 63/26.2% subjects, and the follow-up period was 36.8 ± 5.7 months. All patients received standard medical therapy for heart failure, including beta-blockers, angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, aldosterone antagonists, and diuretics. The study was approved by the Local Ethics Committee. Demographics and characteristics of patients with CHF included in the trial are presented in Table 1.

Table 1. Demographics and characteristics of subjects with chronic heart failure (n = 240)

Demographics and characteristics	Mean ± SD, n (%)
Age [years]	50.5 ± 12.1
Men	194 (80.8%)
NYHA functional class: II/III	48 (20%)/192 (80%)
Six-minute walk test [m]	387 ± 106
Sinus rhythm/atrial fibrillation	176 (73.3%)/64 (26.7%)
Complete left bundle-branch block	63 (26.3%)
LV end-systolic volume [mL]	179 ± 56
LV end-diastolic volume [mL]	268 ± 89
LV ejection fraction [%]	32.8 ± 10.9
Heart rate [bpm]	94 ± 19
Systolic BP [mm Hg]	109.4 ± 14.8
Diastolic BP [mm Hg]	67.4 ± 10.1
Selective coronary angiography	240 (100%)
Ventricular tachyarrhythmias (VT/VF, ICD/CRT-D discharge)	57 (23.8%)
Heart failure medical therapy:	
Beta-blockers	237 (98.8%)
ACE inhibitors or AIIRA	238 (99.2%)
Aldosterone antagonists	227 (94.6%)
Diuretics	216 (90.0%)
ICD	22 (9.2%)
ICD-capable CRT (CRT-D)	27 (11.3%)

AIIRA — angiotensin II receptor antagonists; ACE — angiotensin converting enzyme; BP — blood pressure; CRT — cardiac resynchronisation therapy; ICD — implanted cardioverter defibrillators; LV — left ventricular; NYHA — New York Heart Association; SD — standard deviation; VF — ventricular fibrillation; VT — ventricular tachycardia

All patients received a complete physical investigation including echocardiography (ECHO), based on the common protocol (Vivid 7, GE, USA), 24-h ECG Holter monitoring (HM-ECG), six-minute walk test, seven-minute 12-lead ECG (5 min of at rest and 2 min of at moderate-intensity physical activity with 25 Watt level).

Table 2. Operating features and coefficients included in the discrimination model, which preliminarily classifies the risk of life-threatening ventricular tachyarrhythmic (VTA) events in patients with chronic heart failure

Parameter	VTA (Y_1)	Non-VTA (Y_2)	Wilks-Lambda	F-criterion	P-level
T-wave alternans	6.34914	0.71013	0.664261	76.36031	< 0.0001
Heart rate turbulence	6.19380	0.92788	0.662329	75.67274	< 0.0001
Heart rate deceleration	2.41755	1.38960	0.459755	3.59184	0.046
QT dispersion	1.92062	1.85872	0.449703	2.01514	0.047
Constant	–5.62736	–1.08851	–	–	–

The analysis of ECG markers of myocardial electrical instability was performed. A microvolt T-wave alternans (mTWA), which reflects myocardial repolarisation temporary heterogeneity of myocardial repolarisation processes, was measured in accordance with international standards [12]. In the presence of mTWA > 47 mcV, alternans was considered high. The spatial heterogeneity of myocardial repolarisation processes was assessed using QT interval duration/dispersion (QT and dQT) [13]. In the presence of dQT > 70 ms, dispersion was considered high. Heart rate turbulence (HRT) evaluates dysfunction of the baroreceptor control of haemodynamics, and was assessed in accordance with the standards developed by the Working Group and edited by Bauer et al. [14]. If turbulence onset (TO) was > 0% and/or the turbulence slope (TS) was < 2.5 ms/RR, HRT was considered abnormal. To define vegetative dysfunction, heart rhythm acceleration/deceleration (AC/DC) using standard methods was applied [15]. In cases when DC < 4.5 ms, vagal dysfunction was registered. The original 'Intecard 77' software was applied (Centre of Cardiology, Belarus).

Statistical analysis

Methods of parametric and nonparametric statistics, Cox multifactorial analysis, and binary logistic regression method were used and processed using Statistics 8 package (Stat Soft Inc., USA). A critical significance level of $p = 0.05$ was adopted in the analysis of statistical hypotheses.

RESULTS

In the follow-up period of 36.8 ± 5.4 months, VTA events were registered in 66 subjects with CHF. SCD was registered in nine cases. VTA events were detected by HM-ECG (24 h) and interrogation of implanted devices in 57 CHF patients, including seven subjects with syncope episodes. For clinical indications, 22 subjects received implantable cardioverter defibrillators (ICD), and 27 subjects received ICD-capable resynchronisation devices (CRT-D).

The events of SCD or paroxysmal sustained ventricular tachycardia/ventricular fibrillation (VT/VF) based on HM-ECG and implantable device interrogation or episodes of device shock therapy of ventricular tachyarrhythmia (ICD, CPT-D) were chosen as the primary endpoints.

Stepwise discriminate analysis showed a number of independent ECG-markers including mTWA, HRT, dQT, and heart rate deceleration. For a primary VTA risk stratification using a 'high-low' category, a discriminate model was developed, which combined independent ECG predictors of myocardial electrical instability. Table 2 contains results obtained from the discriminant analysis of ECG markers of myocardial electric instability. Reported VTA events are denoted as Y1, and non-VTA events are denoted as Y2.

Discriminators Y1 and Y2 are calculated as follows:

$$Y_1 = 6.35 \cdot \chi_1 + 6.19 \cdot \chi_2 + 2.42 \cdot \chi_3 + 1.92 \cdot \chi_4 - 5.63$$
$$Y_2 = 0.71 \cdot \chi_1 + 0.93 \cdot \chi_2 + 1.39 \cdot \chi_3 + 1.86 \cdot \chi_4 - 1.09, \quad (1)$$

where

x_1=1, if mTWA > 47 mcV, otherwise 0;
x_2=1, if TO > 0% and/or TS slope < 2.5 ms/RR, otherwise 0 (not detected also);
x_3=1, if DC < 4.5 ms, otherwise 0;
x_4= 1, if dQT > 70 ms, otherwise 0.

Y1 > Y2 suggests that the risk of life-threatening VTAs is high, whereas Y2 > Y1 suggests that it is low. Such preliminary ECG-screening of the risk is feasible at each visit of a CHF patient and during the follow-up period.

Cox regression analysis included ECG myocardial electrical instability markers, HM-ECG data, and ECHO parameters. Analysis showed prognostic signs that maximally affect the risk of monitored endpoints SCD/sustained VT/VF: paroxysmal unstable fast VT (≥ 5 complexes with heart rhythm ≥ 150 bpm, $p = 0.001$); positive test mTWA (more than 25% of abnormal mTWA ≥ 47 mcV, $p = 0.011$); abnormal HRT (TO ≥ 0%, $p = 0.017$); low EF (EF ≤ 21%, $p = 0.02$); abnormal ventricular ectopy according to HM-ECG (≥ 1500 PVCs/24 h, $p = 0.032$); high QT dispersion (dQT ≥ 70 ms, $p = 0.018$). Independent parameters with the statistical significance of $p \leq 0.047$ were incorporated into Cox multivariate analysis to define independent predictors of SCD risk. The results of uni- and multivariate Cox regression analysis are presented in Table 3.

Cox multivariate regression analysis showed highly predictive hazard ratio (HR) values for the following independent

Table 3. Results obtained from the analysis of primary endpoints in Cox regression model

Parameters	Univariate Cox analysis			Multivariate Cox analysis		
	Hazard ratio	95% CI	p	Hazard ratio	95% CI	p
nsVT (nsVT ≥ 5 complexes with HR ≥ 150 bpm)	5.88	2.82–13.9	0.001	3.24	1.29–9.25	0.007
Abnormal mTWA (≥ 25% mTWA ≥ 47 mcV)	2.76	1.26–6.08	0.011	1.79	1.06–4.89	0.011
HRT, TO ≥ 0%	2.67	1.19–5.16	0.017	1.13	0.85–1.61	0.051
LVEF ≤ 21%	2.43	1.21–5.02	0.020	1.32	1.01–3.03	0.045
≥ 1500 PVC/24 h	1.91	1.10–3.98	0.032	1.93	1.03–3.12	0.045
dQT ≥ 70 ms	2.99	1.57–5.73	0.018	1.79	1.25–3.57	0.033
nsVT (> 3 complexes with HR > 120 bpm)	2.11	1.00–4.45	0.047	2.28	0.99–3.68	0.051
QRS width > 122 ms in any lead V1–V3	1.73	0.94–3.96	0.046	1.54	0.74–3.01	0.053
Deceleration DC < 4.5 ms	1.63	0.84–2.31	0.051	–	–	–

CI — confidence interval; DC — heart rate deceleration; dQT — QT dispersion; HR — heart rate; HRT — heart rate turbulence; LVEF — left ventricular ejection fraction; mTWA — microvolt T-wave alternans; nsVT — non-sustained ventricular tachycardia; PVC — premature ventricular contractions; TO — turbulence onset

Table 4. Binary logistic regression model assessment (F = 31.2; χ^2 = 143.2; p < 0.0001)

Parameters	Constant (b_0)	LVEF ≤ 21% (b_1)	PVC > 1500/24 h (b_2)	nsVT* (b_3)	dQT (b_4)	HRT** (b_5)	mTWA*** (b_6)
Coefficients	7.25	–0.38	–0.76	–4.35	–1.46	–4.28	–5.03
χ^2	1414.5	0.68	0.47	0.01	0.23	0.01	0.01

*nsVT if ≥ 5 complexes of VT are with HR ≥ 150 bpm; **TO ≥ 0% and/or TS < 2.5 ms/RR; ***≥ 25% of abnormal mTWA > 47 mcV; TS — turbulence slope; other abbreviations as in Table 3.

predictors of fatal VTAs in patients with CHF: paroxysmal non-sustained VT (nsVT): HR 3.24, 95% confidence interval (CI) 1.29–9.25, p = 0.007; positive test mTWA: HR 1.79, 95% CI 1.06–4.89, p = 0.011; high QT dispersion: HR 1.79, 95% CI 1.25–3.57, p = 0.033; LV dysfunction: HR 1.32, 95% CI 1,01–3,03, p = 0.045; abnormal ventricular ectopias: HR 1.93, 95% CI 1.03–3.12, p = 0.045. For individualised SCD/VTA risk assessment model, binary logistic regression analysis was performed incorporating all independent predictors of VTA events. The binary regression mathematical model showed high predicative value of the classifying binary function. The coefficients for all independent predictors included in the binary logistic regression are present in Table 4.

As a result, we can use Cox model proportional hazard to assess the probability (*P*) of the SCD/VTA risk stratification:

$$P = \frac{1}{1 + e^{-Z}}, \text{ where } Z = \sum_{i=0}^{6} b_i \cdot \chi_i \text{ — linear weighted function, (2)}$$

— $x_1 = 1$ in LVEF < 21%, otherwise 0; $x_2 = 1$ in PVC > 1500 daily, otherwise 0; $x_3 = 1$ in the presence of non-sustained VT > 5 complexes and heart rhythm > 150 bpm, otherwise 0; $x_4 = 1$ in dQT > 70 ms, otherwise 0; $x_5 = 1$ in TO > 0% and/or TS < 2.5 ms/RR, otherwise 0 (and not detected also); $x_6 = 1$ in mTWA > 47 mcV, otherwise 0;

— $b_0 = 7.25$; $b_1 = -0.38$; $b_2 = -0.76$; $b_3 = -4.35$; $b_4 = -1.46$; $b_5 = -4.28$; $b_6 = -5.03$.

The range of probability of *P* was divided into the risk level quintiles: from 0.5 to 0.6 for relatively low risk; from 0.61 to 0.7 for medium risk; from 0.71 to 0.8 for high risk; from 0.81 to 0.9 for very high risk; and more than 0.91 for critical risk. The risk grading is presented in Figure 1.

Classification model sensitivity was 80.8%, and specificity was 99.1%. Thus, the individual risk assessment method using Cox logistic regression allowed the correct classification of 93.9% of CHF cases.

Therefore, the robust prognostic significance of Cox logistic regression for VTA risk stratification allowed inclusion of the method into the diagnosis algorithm of subsequent assessment of risk for life-threatening arrhythmias. The algorithm shown in Figure 2 is a two-step approach to stratify the risk:

— the initial step based on exact ECG data to assess VTA risk;
— the final step of risk stratification combined with ECG, HM-ECG, and ECHO data assessment.

DISCUSSION

In multiple randomised multicentre trials, the search for a unified index was made for the reliable prediction of VTA/SCD risk, but it produced no results. For more than two decades, severe LV dysfunction has been used as a criterion

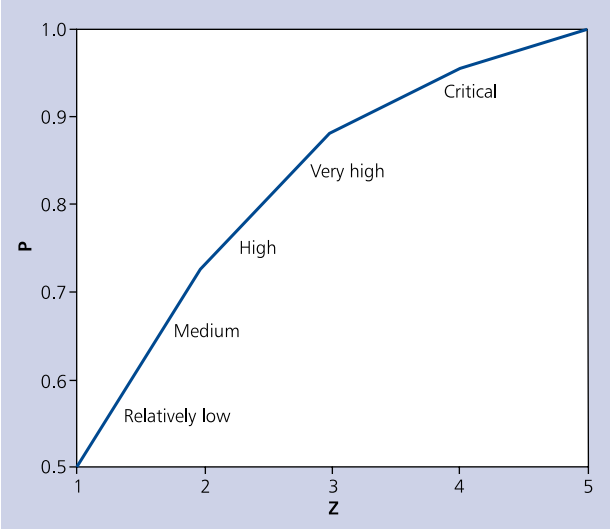

Figure 1. Probability values of adverse cardiovascular events **P** depending on logistic function **Z**

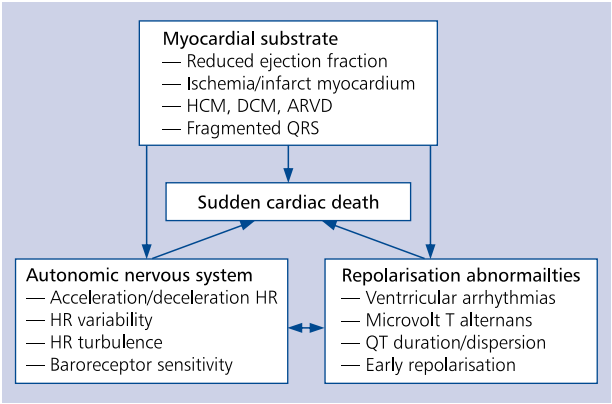

Figure 3. A totality of cause-effected relationships contributing to sudden cardiac death; ARVD — arrhythmogenic right ventricular dysplasia; HCM — hypertrophic cardiomyopathy; HR — heart rhythm; DCM — dilated cardiomyopathy

and key prognostic marker of SCD in a variety of prospective randomised trials [13–16]. However, Dagres and Hindrics [17] showed that six from seven SCD cases are registered in individuals with normal or moderately reduced LVEF, and vice versa, in subjects with LVEF < 30%, who received implantable ICD, shock therapy charges are frequently not established.

We believe that to stratify risk, predictive models should incorporate additional data functionally associated with VTA. Figure 3 shows a totality of cause-effect relationships contributing to SCD events. These are myocardial abnormal changes (the anatomic substrate), myocardial repolarisation abnormalities, and heart function vegetative regulation disorder. The risk stratification considering low LVEF and high NYHA functional class is currently used in clinical practice. This approach has poor prognostic power.

A comprehensive assessment of the underlying mechanisms of the dysfunction forming the individual risk of SCD may be reliable in determining the 'weak spot' in the pathologic matrix of the disease. This is especially true in CHF patients with reduced EF. The above-mentioned model to stratify

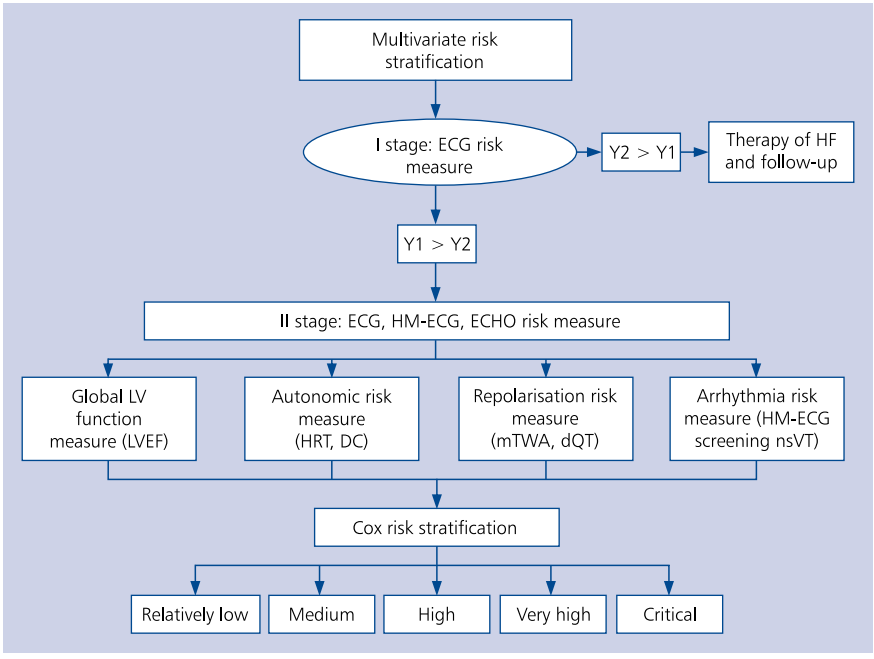

Figure 2. Two-step algorithm for personalised risk stratification of life-threating tachyarrhythmia in patients with chronic heart failure (HF); ECG — electrocardiogram; ECHO — echocardiogram; HM — Holter monitoring; other abbreviations as in Table 3

risk facilitates decision-making regarding ICD implantation. On the one hand, the model helps to identify patients with high risk of SCD requiring preventive ICD implantation, and on the other hand, the patients who will not benefit from the ICD, but rather, it would reduce patients' life quality and demand substantial financial expenditure [18]. This has been shown by a highly informative negative myocardial electrical instability marker test (99%).

The authors declare that the study was mono-centre, non-randomised, and limited by inclusion of CHF patients only. In addition, exclusion criteria are atrial fibrillation and ventricular pacing because mTWA, AC/DC cannot be measured in these conditions. More trials are needed to test the given technology for risk stratification, not only in respect to CHF nosology but also on a population level.

It is expected that the proposed mechanism to assess the risk of life-threatening VTAs using fourth-generation digital electrocardiography and tests of myocardial electrical instability markers, as well as HM-ECG and ECHO, will be extensively used in clinical practice.

CONCLUSIONS

1. Based on the results of the study, a new two-step model of the individualised risk stratification in patients with CHF has been developed. The preliminary VTA risk assessment as shown by ECG allows primary screening. When a high risk of VTA is initially defined, an in-depth examination is feasible by including the markers of myocardial electrical instability, as well as HM-ECG and ECHO data, into the Cox proportional risk model. The classification model has a sensitivity of 80.8% and specificity of 99.1%. The algorithm of the individualised risk assessment using logistic regression model allowed correct classification of 93.9% of CHF cases.
2. The proposed risk assessment model in patients with CHF is a non-invasive, individualised, and applicable technology to stratify subjects with high risk of life-threatening VTAs using standardised clinical and instrumental investigations (12-lead ECG, HM-ECG, and ECHO).

Conflict of interest: *none declared*

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Spersonalizowany model stratyfikacji ryzyka do prognozowania zagrażających życiu tachyarytmii komorowych u pacjentów z przewlekłą niewydolnością serca

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Streszczenie

Wstęp: Określenie czynników prognostycznych zagrażających życiu tachyarytmii komorowych (VTA) i nagłego zgonu sercowego (SCD) wciąż pozostaje priorytetowym celem w kardiologii. Opracowanie metod spersonalizowanego prognozowania na podstawie analizy wieloczynnikowej czynników ryzyka związanych z zagrażającymi życiu zaburzeniami rytmu uznaje się obecnie za zagadnienie o podstawowym znaczeniu zarówno z naukowego, jak i klinicznego punktu widzenia.

Cel: Celem badania było zaprojektowanie prognostycznego i matematycznego modelu służącego do definiowania spersonalizowanego ryzyka zagrażających życiu VTA u pacjentów z przewlekłą niewydolnością serca (CHF).

Metody: Badanie obejmowało 240 chorych z CHF (średnie wartości: wiek 50,5 ± 12,1 roku; frakcja wyrzutowa lewej komory 32,8 ± 10,9%; okres obserwacji 36,8 ± 5,7 miesiąca). Chorzy byli poddani podstawowemu leczeniu niewydolności serca. Oceniano wskaźniki elektrokardiograficzne (EKG) niestabilności elektrycznej miokardium, w tym zmienność kształtu i wysokości załamka T (*microvolt T-wave alternans*), zaburzenia rytmu serca, deceleracje rytmu serca i dyspersję odstępu QT. Ponadto chorych poddano badaniu echokardiograficznemu i monitorowaniu holterowskiemu EKG. Punktami końcowymi badania były zdarzenia sercowo-naczyniowe, w tym SCD, napadowy częstoskurcz komorowy/napadowe migotanie komór (VT/VF) stwierdzone w zapisie holterowskiego EKG oraz odpowiednie dane pobrane z wszczepionego urządzenia (CRT-D, ICD), a także historia podanych wyładowań.

Wyniki: W okresie obserwacji u 66 (27,5%) osób z CHF wystąpiły zdarzenia niepożądane w postaci zaburzeń rytmu, w tym 9 przypadków SCD i 57 epizodów VTA. Dane uzyskane w krokowej analizie dyskryminacyjnej skumulowanych wskaźników EKG niestabilności elektrycznej miokardium wykorzystano do opracowania matematycznego modelu wstępnej stratyfikacji ryzyka VTA. Ponadto przeprowadzono jedno- i wieloczynnikową analizę regresji logistycznej Coxa w celu określenia modelu zindywidualizowanej stratyfikacji ryzyka SCD/VTA. Stosując binarny model regresji logistycznej, wykazano wysoką istotność prognostyczną funkcji dyskryminacyjnej tej metody, a czułość i swoistość klasyfikacji wynosiły odpowiednio 80,8% i 99,1% ($F = 31$; $\chi^2 = 143{,}2$; $p < 0{,}0001$).

Wnioski: Metoda spersonalizowanej klasyfikacji ryzyka z zastosowaniem modelu regresji logistycznej Coxa pozwala prawidłowo sklasyfikować ponad 93,9% przypadków CHF. Liczne dane naukowe potwierdzające skuteczność prognozowania ryzyka VTA przy użyciu metody regresji logistycznej uzasadnia włączenie tej metody do algorytmu monitorowania i wyboru właściwego sposobu leczenia u pacjentów z CHF.

Słowa kluczowe: niestabilność elektryczna miokardium, elektrokardiografia, niewydolność serca, nagły zgon sercowy, tachyarytmie, stratyfikacja ryzyka

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