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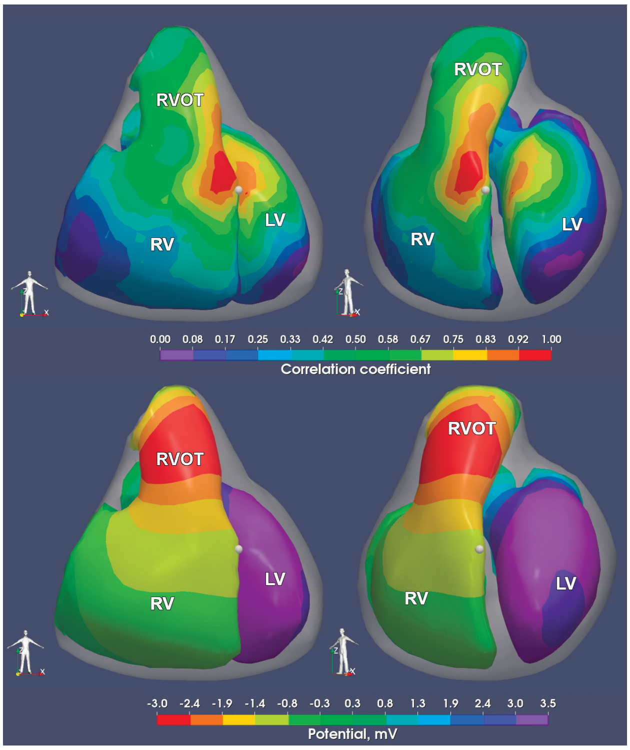

Figure from the article by M.P.Chmelevsky, D.A.Potyagaylo, S.V.Zubarev et al.

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CONTENT

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REMOTE MONITORING FOR THE EARLY DETECTION OF CHANGES IN PATIENT STATUS USING THE HOME MONITORING TECHNOLOGY

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Aims: To perform the analysis of adverse events (AE) rate and trends of physiologically meaningful parameters in patients with cardiac implantable electronic devices (CIEDs) with the mobile remote monitoring option.

Methods: In 9 clinical centers of the Russian Federation and 2 clinical centers of the Republic of Kazakhstan, 126 patients with an implantable cardioverter-defibrillator (ICD) or a pacemaker (PM) equipped with the Home Monitoring (HM) technology (BIOTRONIK, Berlin, Germany) were enrolled. Based on the daily data transmission, all alarm alerts, all HM options changes and all AE were recorded with dated alert content and undertaken measures.

Results: The study patients, followed up at least for one year, experienced 42 adverse events (AE), of which 26 were serious AE (SAE) and 3 SAE were defined as device-related (SAED). ICD patients (N=90) with concomitant coronary artery disease (CAD) had a statistically significantly higher SAE prevalence (p=0.0249). Patients with CRT-D had a lower SAE rate than patients with dual- or single-chamber ICD (p=0.046). Downloads of Home Monitoring parameters for retrospective mathematical analysis were available for 60 ICD patients, of which 47 had episodes of ventricular tachycardia (VT), ventricular fibrillation (VF) and/or atrial tachyarrhythmia (AT). Machine learning analysis of the trends of the physiologically meaningful parameters revealed correlations between changes and arrhythmia episodes, with the random forest and gradient boosting methods demonstrating the random effect of the results.

Conclusion: Home Monitoring of CIED patients enables the evaluation of different devices applications and their clinical advantages. This might implement the prevention of adverse events and iatrogenic effects of pacing. Based on daily transmission of physiologically meaningful Home Monitoring parameters, the study results demonstrate the feasibility of developing a prediction algorithm for adverse events.

Key words: electrotherapy of heart; Home Monitoring; adverse events; trends of physiological parameters

Conflict of Interests: nothing to declare
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Remote monitoring (RM) of patients with cardiac implantable electronic devices (CIEDs) has been in use for more than 20 years [1]. Currently, RM is recommended for patients with pacemakers (PMs), implantable cardioverter-defibrillators (ICDs) and systems for cardiac resynchronization therapy (CRT) as a part of standard follow-up (FU) strategies [2, 3].

Numerous clinical trials as well as randomized, have been performed with the Biotronik Home Monitoring (HM) systems. The TRUST study [4] has demonstrated statistically that relevant clinical events can be revealed in patients followed-up by RM much earlier than for patients, followed-up only by ambulatory visits. Clinical outcome can be improved through early diagnostics of important cardiac events, prone to serious complications (e.g. stroke as a consequence of persistent atrial fibrillation) [4-6], better patients' compliance [7] and satisfaction of therapy procedures [8].

On one hand, the COMPAS [6] and OEDIPE [9] clinical trials have shown that RM can significantly shorten time to necessary physician's intervention and, on the other hand, reduce greatly the number of unnecessary FUs, - approximately 50% of patients not needing a scheduled FU [10] as no changes in their therapy or their implant's program are necessary [11]. According to the "TRUST" [4] and "COMPAS" [6] trials, the related clinical burden can be reduced, both for physicians and patients, by 45% and 56%, respectively.

The "ECOST" study showed [12] that HM can reduce the number of inadequate shocks by 52% and the number of related hospitalizations - by 72%. The appropriate implant reprogramming enabled for reduction of the number of shock charges by 76%, and of delivered shock discharges - by 71%, with a significant positive effect on the battery longevity.

The most important clinical result have been reported in the "IN-TIME" trial [13], with a more than two-fold reduction of the overall and cardiovascular mortality in congestive heart failure (CHF) patients monitored remotely, in comparison to patients, followed-up only by scheduled ambulatory FUs.

The Russian Scientific Society of Arrhythmology, Electrophysiology and Cardiac Pacing has sponsored the "ReHoming" (Registry Home Monitoring) clinical trial with the goal to evaluate the clinical results of patient's remote monitoring FU in the Russian Federation and the Republic of Kazakhstan. The Home Monitoring generated alerts of relevant clinical events have been recorded in case report forms (CRF). Trends of physiologically meaningful parameters have been used by physicians to decide whether to intervene with an unscheduled FU. Serious adverse events including hospitalizations and cardiovascular complications have been recorded, as well as undertaken measures, like therapy or implant program changes.

METHODS

Patient enrollment and study protocol

Patients of both sexes older than 18 years were eligible to enroll in the study if they had an ICD or a PM with the mobile RM option (Home Monitoring BIOTRONIK, Germany). Exclusion criteria were:

- Post cardiac surgery or post infarction < 1 month,
- More than two cardioversion shocks within last 6 months (for ICD patients),
- Lead dislodgement, and/or impedance, threshold, or sensing failure, loss of capture and inadequate ICD therapy,
- Implant-related infection,
- Inability to handle the "Home Monitoring" system correctly,
- Participation in another clinical study,
- Insufficient GSM coverage at patient's home,
- Pregnancy or nursing.

Study design

The Rehoming trial was designed as an open, multi-center and observational study. In addition to an ICD or a PM the enrolled patients received (or already had) a RM transmitting device (Cardiomessenger II-S, BIOTRONIK) with both the patient and the transmitter registered at the Home Monitoring Service Center (HMSC).

Regular patient's FUs were scheduled by the study investigators according to the guidelines intervals starting from the enrollment procedure: 3 months for ICD patients, and 6 months for PM patients (Fig. 1).

All FU results were documented in the patient's health record and then entered into the CRF. Russian Internet platform rehoming.dicoming.com was developed [14], with the downloaded Home Monitoring data, offering a possibility to fill in the CRF protocols online.

Study parameters

Continuous patient RM was aimed to register all alarming HM alerts with the "red" (urgent) and with the

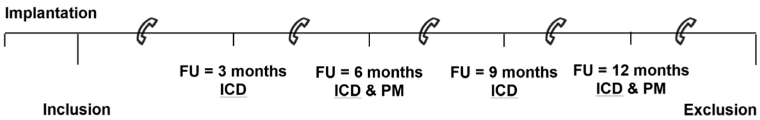

Figure 1. ReHoming study design. From the inclusion point the patient is followed up by "Home Monitoring". Besides regular ambulatory follow-ups (every 3 months for the ICD, every 6 months for the pacemaker) the investigator has to perform additional follow-up in the case of a relevant "Home Monitoring" alert, indicating a serious adverse event probability.

Table 1.

Patient characteristics

	TP (n=119)		ICD (n=89)		PM (n=30)	
	%	n	%	n	%	n
AH	50.4%	60	56.2%	50	33.3%	10
CAD	51.3%	61	52.8%	47	46.7%	14
CHD	2.5%	3	1.1%	1	6.7%	2
VHD	10.9%	13	9.0%	8	16.7%	5
CMP	47.9%	57	62.9%	56	3.3%	1
DM	13.4%	16	13.5%	12	13.3%	4
HF Class I	13.4%	16	4.5%	4	40.0%	12
HF Class II	28.6%	34	25.8%	23	36.7%	11
HF Class III	44.5%	53	55.1%	49	10.0%	3
HF Class IV	2.5%	3	3.4%	3	0.0%	0
No HF	3.4%	4	4.5%	4	0.0%	0
Not investigated	7.6%	9	6.7%	6		4
Mean HF Class	2.14		2.35		1.43	

Here, and after on: TP - total population, ICD - implantable cardioverter-defibrillator population, PM - pacemaker population, AH - arterial hypertension, CAD - coronary artery disease, CHD - congenital heart disease, VHD - valvular heart disease, CMP - cardiomyopathy, DM - diabetes mellitus, HF - heart failure.

”yellow“ (attention) status, and to register all resultant changes of the HM options. If necessary, based on the physician’s decision and/or patient’s need and in view of received HM alert, FU was scheduled, to prevent an anticipated a serious adverse event (SAE). An EchoCG was recommended in case of the following patient‘s status changes: dramatic increase of atrial arrhythmia burden, dramatic increase of the ventricular paced events ratio Vp, rapid worsening of the Heart Failure Monitor (HFM, Biotronik) parameters.

Ambulatory FUs of patients with ICDs or CRT-D systems were scheduled 3, 6, 9 and 12 months after enrollment, and the following data were recorded:

- Implant printout of device parameters and statistical data (paroxysms of atrial tachyarrhythmia - AT, ventricular tachycardia - VT, mean ventricular rhythm, also, at rest, patient activity, number of ventricular extrasystoles (VES) per hour);

Table 2.

Patient medication

	TP (n=119)		ICD (n=89)	
	%	n	%	n
Class I antiarrhythmics	0.9	1	1.2	1
Beta blockers	59.5	66	70.6	60
Class III antiarrhythmics	16.2	18	18.8	16
Ca-antagonists	8.1	9	4.7	4
Cardiac glycosides	7.2	8	9.4	8
ACE inhibitors	54.1	60	60.0	51
Diuretics	56.8	63	64.7	55
Nitrovasodilators	2.7	3	2.4	2
Anticoagulants	46.0	51	43.5	37
Other	64.9	72	61.2	52
On medication totally	93.3	111	95.5	85

Table 3.

Ventricular arrhythmias, documented in ICD and CRT-D patients as indication for the device implantation

		ICD (n=59)		CRT-D (n=30)	
		%	n	%	n
Ventricular fibrillation (VF)		0.0	0	0.0	0
Ventricular tachycardia (VT)		42.4	25	16.7	5
VT type	Monomorphic	30.5	18	13.3	4
	Polymorphic	11.9	7	3.3	1
Consciousness loss	Pre-Syncope	20.3	12	10.0	3
	Syncope	3.4	2	0.0	0
	Clinical death	5.1	3	0.0	0
Cryptogenic syncope		1.7	1	0.0	0
Primary prophylaxis of SCD		57.6	34	83.3	25
Secondary prophylaxis of SCD		42.4	25	16.7	5
Congestive heart failure		32.2	19	100	30

Here and after on: CRT-D - cardiac resynchronization therapy with defibrillator population, SCD - sudden cardiac death.

- Necessity of the EchoCG procedure;
- Implant reprogramming;
- Changes of drug therapy;
- Events revealed by Home Monitoring.

Statistical Analysis

Study data were analyzed with the SAS software package (SAS Institute, USA), version 9.4. Mean value and standard square deviation (SD) are stated for parameter sets with normal distribution, median and quartiles for the other parameters. For categorical data, absolute and relative frequencies are given.

Metric study parameter sets were compared using the Student’s t-test or the Wilcoxon-Mann-Whitney test (if the parametric test assumption was not fulfilled). Binary and categorical parameters were analyzed using the χ^2-test and the Fisher exact test. Critical double-sided level of significance for all tests was 0.05.

Internet platform

Besides the HMSC portal, investigators were offered to use the ReHoming portal [14] developed as a part of the universal HELTERBOOK™ [15] Internet platform. The portal enabled for comprehensive HM data mirroring and continuous study monitoring. Automatic options of statistical analysis were available with different filtering parameters, allowing analysis of study data in different patient sampling groups.

Study endpoints

The primary endpoint was the occurrence of a serious adverse event (SAE), including patient’s death or hospitalization, complications from cardiovascular disease and the implanted device failure.

Secondary endpoints were the efficiency of the “Home Monitoring“ technology to reveal the AEs and the clinical benefit of RM application within the country healthcare structure.

Retrospective analysis of the Home Monitoring database

To reveal possible correlation between the changes of the daily RM parameters and the probability of certain arrhythmia events, the trends of the physiologically meaningful parameters that could be used to develop a predictor of patient’s status worsening were retrospectively analyzed [16]:

- Mean heart rate (HR) over 24 hours,
- HR at rest,
- Patients activity,
- VES per hour averaged over 24 hours,
- HR variability (HRV),
- Right ventricle lead impedance,
- Shock lead impedance,
- Ratio of atrial paced events Ap.

To evaluate the feasibility to develop a predictor algorithm, the events that are automatically recorded by Home Monitoring for ICD were chosen (i.e. episodes of AT, VT and ventricular fibrillation (VF)).

RESULTS

Patient population

In 9 research centers of the Russian Federation and 2 research center of the Republic of Kazakhstan, 126 patients were enrolled, 114 of which completed the trial and 12 - dropping out. The database contains the complete data of 119 patients, included in the study efficacy analysis population: 89 patients with ICDs, 30 with PM. Data for ICD patient were partly available and used for appropriate results analysis. Therefore, the total population size was 120 patients and the ICD population size was 90 patients.

For the total population of 119 patients, 88 (73.9%) were male and, for the ICD population (n=89), 69 (77.5%) were male. Mean ages were 57.5±11.4 and 56.8±11.4, respectively. The main comorbidities were cardiovascular disease (mostly CHF) and diabetes mellitus (Table 1).

The majority of patients, 111 (93.3%) and 85 (95.5%) of the total and the ICD groups, respectively, received cardiovascular medications (Table 2). 59 patients of the total population (49.6%) and 48 patients of the ICD population (53.9%) were surgically treated due to coronary artery disease (CAD), congenital (CHD) or valvular heart disease (VHD), or arrhythmias. 30 patients of the ICD population (n=89) had an ICD for cardiac resynchronization therapy (CRT-D systems).

Ventricular arrhythmia was the indication for the ICD or the CRT-D implantation in all ICD patients (n=89), mostly for primary SCD prophylaxis - 59 patients, 66.3% (Table 3).

Study safety analysis

Safety analysis included 120 patients with a total 42 adverse events (AE), of which 4 were evidently related to the implantable device (AED) and 4 - possibly related. In total, 26 serious AE (SAE) were reported, of which 3 were SAED (related or probably related to the device). During the course of the study there were 2 patient deaths not related to the implant. The other 24 SAE included patient hospitalizations due to different reasons: CHF worsening (n=8, 19.0% of all AE), VT (n=7, 17%), CAD (n=2), gastritis (n=2), acute myocardial infarction (n=1), ischemic stroke (n=1), permanent atrial fibrillation (n=1), cardiac transplant rejection (n=1) and lead dislodgement (n=1).

Fisher exact double-sided test of ICD patients' data (n=90) demonstrated statistically significant differences in SAE rate for patients with and without CAD, p=0.0249 (Table 4).

For some other cardiac diseases, no statistically significant difference were observed other than a trend for higher SAE rate was seen: for VHD - p=0.1473, and for diabetes mellitus (DM) - p=0.2151.

Fisher exact double-sided test demonstrated a statistically significant lower SAE rate in patients with CRT-D than in patients with dual-chamber ICD, p=0.046 (Table 4).

Study efficacy analysis

Upon CIED implantation and RM activation, 120 patients were followed-up according to the study protocol for an average of 28.3±10.1 months (2÷43 months). Mean annual number of HM messages was 43.6±35.6 messages per year for the total population (n=120), (5÷221). Home Monitoring of the ICD population (n=90) documented ventricular arrhythmias in 52 patients: VF episodes - in 43, and VT - in 21 (Table 5).

Thirty four ICD patients (n=89) received on the average 4 [1;11.5] defibrillation shocks per patient (maximum - 127), with an efficiency of 100[60.7;100]%. Forty five (50.6%) patients received anti-tachycardia pacing (ATP) therapy with an efficiency of 40 [10.5;78.1] % in the VT zone (n=29) and of 54.5 [14.3;99] % in the VF zone (n=30).

Of clinical interest was to reveal any correlation between the disease etiology and the rate of arrhythmias, registered by the implant. The most significant correlation in the ICD population (n=90) was VT prevalence in patients with supraventricular tachycardia (SVT), p = 0.0107. VT episodes rates were statistically significantly lower in ICD patients with CHF in anamnesis lonely (Fisher test p=0.0320), and with comorbidity of CHF and VHD, p = 0.0327 (Table 6). CAD did not increase in a statistically significantly manner the rate of VT detection, p = 0.6706.

Clinical patient load

According to the study protocol, investigators recorded different aspects of the clinical load related to patients' FU and also based on VT presence (Table 7). The total number of patients' visits to clinic was 240 for an average of 0.97±0.56 per patient per year. Medical care was requested by 41 patients. Patients with VT needed emergency help twice more often than patients without VT, while the mean number of hospitalization and unproductive days per year were approximately the same for both subgroups.

Clinical load was analyzed based on patients' etiology. Among the ICD population (n=90), CHD patients created higher clinical load than VHD patients: days to first therapy - 213 and 354 days, unproductive days - 8.9 and 8.3, hospitalization days - 6.8 and 5.7, respectively. Efficacy of different ICD therapy types for CHD and VHD patients showed non significant statistical trends: ATP in VF zone (56.6% vs 52.3%) and cardioversion shocks (81.7% vs75.0%) were more efficient in CHD patients, but ATP in

Table 4.

Serious adverse events (SAE) in ICD and CRT-D patients with and without CAD

	SAE - Yes	SAE - No	Total
CAD			
Yes	13	35	48
No	3	39	42
Total	16	74	90
Implantable device type			
ICD	14	42	56
CRT-D	2	28	30
Total	16	70	86

Table 5.

Ventricular arrhythmias in ICD and CRT-D patients (n=90)

	Number of episodes			
	ICD		CRT-D	
	Total (n)	Mean*	Total (n)	Mean*
VA	52	10 [2; 32.7]	13	11 [2; 30]
VT	21	9 [2; 54]	5	7 [3; 24]
VF	43	7 [2; 20.5]	12	5.5 [1; 16.2]
PS	51 (56.7%)		13 (14.4%)	

* - per patient, VA - ventricular arrhythmias, PS - patient sample

the VT zone was more efficient in VHD patients (47.9% vs 41.9%).

In accordance with the study protocol, investigators rated different aspects of the Home Monitoring technology for patients' FU with a 5-point scale (5 - highest rating). The mean ratings were: HMSC performance - 4.7, "traffic light" concept - 4.7, "IEGM online" option - 4.7 and sufficiency of HM data - 4.6.

Analysis of physiological parameters' trends

For 60 ICD patients, long-term trends of daily recorded parameters were downloaded from the HMSC portal. Data for retrospective mathematical analysis were chosen according to the criteria of possible correlation analysis between the RM parameters' trends and the event onset probability. Therefore, the episodes with monitoring data available for at least 7 days and with no more than 2 successive blank days were selected. After trends review, 47 patients with events of the VT, VF and SVT type were selected. In order to build analytical models on the available dataset, we selected the following number of independent events: SVT - 200, VT - 27, VF - 38.

We used the cross validation technique to evaluate accuracy of possible correlations [17]:

- The dataset was randomly divided into five subgroups so that the number of records with and without the specific event were approximately similar in different subgroups;
- The data of four subgroups were used to determine which correlations (training sets) could predict the onset of a specific event;
- The models were validated on the retained data of the fifth subgroup.

To evaluate the models quality, a ROC-analysis (Receiver Operating Characteristic) was performed with the ROC_AUC (area under the curve) metrics [18]. The choice was due to the relatively low number of specific events in the dataset (VF, VT) and large time intervals with no events. The ROC_AUC metric does not depend on the number of specific events and, in general, reflects the ratio of truly classified cases of event occurring or not, with 1 meaning ideally correct prediction, and 0.5 - a random guess.

Search for correlations and predictor modelling

The search for correlations was performed with the following algorithms of machine learning:

- Decision tree - random forest classifier (search of parameters' values that could be the symptoms of the target event and splitting data trends in groups according to the parameters' values) [19];
- Support-vector networks with linear and radial kernels (values separation by hyperplanes in multi-dimensional space of parameters) [20];
- Nearest neighbors algorithm [21];
- Logistic regression (based on correlation of events and parameters) [22];
- Gradient boosting method [23].

These algorithms revealed significant deviations of ROC-curves from the diagonal demonstrating the possibility of the available parameters' set to predict specific events with a probability, significantly exceeding a random guess.

The best result for AT (with the largest dataset) was shown by the gradient boosting method with a ROC_AUC = 0.79624, min = 0.73510. Overall, owing to the relatively large number of samples, this event type was the best predicted. The following parameters were the most relevant for the modelled predictors (in order of importance): mean heart rate (HR), HR at rest, impedance of the right ventricular (RV) lead, mean number of ventricular extrasystoles (VES) per hour and patient activity.

Comparatively good intermediate results for VF (38 event samples) were achieved by the random forest (ROC_AUC = 0.71819, min = 0.55398) and gradient boosting methods (ROC_AUC = 0.66753, min = 0.53420576). Even the worst case result was exceeding a random guess (though much weaker than for the AT event type). The

Table 6.

Rate of VT detection in ICD patients (n=90) and comorbidities: SVT, CHF and VHD

	VT detection		
	Yes	No	Total
Supraventricular tachycardia			
Yes	31	12	43
No	21	26	47
Total	52	38	90
Congestive HF			
Yes	23	26	49
No	29	12	41
Total	52	38	90
Congestive HF & valvular heart disease			
Yes	23	19	42
No	33	15	48
Total	56	34	90

Table 7.

Clinical load for ICD patients in dependence on VT presence

	VT detection		
	Yes (n=54)	No (n=36)	Total (n=90)
Number of messages*	17.3 [11.2; 30.7]	10.6 [6.7; 14.5]	14.9 [8.4; 29.4]
Days to first therapy	199 [61; 485]	-	199 [61; 485]
Number of patients with inability days*	12 (22.2%)	8 (22.2%)	20 (22.2%)
Number of patients with emergency help*	9 (16.7%)	3 (8.3%)	12 (13.3%)
Days of hospitalization*	0 [0; 8.5]	0 [0; 7.9]	0 [0; 8.6]

* - per year

most relevant parameters for the modelled predictor were as follow: PP-interval variability (HRV), RV-lead impedance, shock lead impedance, mean HR, number of high HRV intervals, ratio of cardiac cycles with atrial pacing Ap, patient activity, mean VES per hour and number of «mode switching» per day.

For the VT events (27 event samples), we were not able to define statistically reliable correlations though the result of the gradient boosting method were found to be slightly better than a random guess (ROC_AUC = 0.68984, min = 0.51504). The most relevant parameters for the modelled predictors were as follow: mean HR, RV-lead impedance, presence of blanking monitoring data and mean atrial rate.

DISCUSSION

During the course of the ReHoming study we have developed a Russian portal to conduct remote follow-up of patients with CIEDs. As opposed to other similar portal, and in addition to the CIED compiled data, our portal also enables us to record other clinical data for their processing. The integrated automatic system for statistical analysis of the data allows for the processing of all recorded patients‘ data as well as specific groups pooling according to different clinical feature of the investigator’s choice (e.g. ICD or PM patients, CAD patients, etc.). These options give unlimited possibilities for research and management of clinical studies of any scale.

The newly developed study RM center has proven its efficacy and advantages that could be used in the future as an additional service to gather RM of patients of different clinics. It could be especially relevant for medical institutions with small number of patients, where additional personnel workload would be not cost-effective.

Strengthening the preventive aspect of this medical service is one of the priorities of healthcare development. Interventional arrhythmology and, especially CIED therapy, are currently leading innovative fields in the broad use of the RM technology. The “ReHoming” project is an example of the “Home Monitoring” technology localization in the healthcare structure that facilitates the development of guidelines for patients’ FU with mobile RM. This clinical study demonstrates the potential of medical data integration and the machine learning methods for complex data analysis of large population cohorts to develop a predictor of patient’s status worsening.

It must be outlined that the predictor models, presented in this paper use essentially nonlinear methods, and therefore, there is no direct linear relationship between the parameters’ values and the probability of the event onset. Importantly, the implants record automatically both the parameters’ trends and the predictable events, without any physician’s or patient’s intervention. This will become an important factor as the data volume will increase due to greater patient and physiological parameters number.

STUDY LIMITATIONS

Results of the ReHoming study are largely aligned with other studies on remote monitoring of CIED patients. However, our study is a registry with no control group for comparative analysis. It is advisable to organize a larger national trial including a control group in order to reveal the influence of the specific national healthcare system, and to verify statistically the clinical and economic advantages of CIED patients’ remote monitoring.

CONCLUSION

Follow-up of the CIED patients with the RM technology enabled the evaluation of the clinical aspects of different implants‘ use and how to avoid iatrogenic pacing effects. The SAE rate was significantly lower in CRT-D patients than in patients with single- and dual-chamber ICDs.

Comparative analysis of the arrhythmias rate based on the diseases etiology showed statistically significant correlations between the VT number and SVT, CHF and VHD comorbidity.

Despite the limitations due to the small amount of statistical data, the study results demonstrate the possibility to develop a predictor of disease complications based on daily transmission of trends of physiologically meaningful parameters recorded by the implant. Machine learning algorithms, such as the random forest and gradient boosting methods, revealed results that were strongly exceeding a random guess.

The Internet portal developed in the context of the ReHoming project and the built-in automatic system of data statistical analysis provide a framework for the implementation of machine learning methods. CIED therapy has therefore become one of the clinically relevant fields of artificial intelligence development and application.

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NONINVASIVE EPI-ENDOCARDIAL ELECTROCARDIOGRAPHIC IMAGING OF VENTRICULAR SEPTAL PACING

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Noninvasive epi-endocardial ElectroCardioGraphic Imaging (ECGI) allows reconstruction of electrograms and high-resolution visualization of various isoparametric maps based on multichannel ECG recordings and tomography. We aimed to verify the ECGI accuracy during septal ventricular pacing in patients with pre-implanted pacemakers using the new ECGI algorithm.

Methods. Ten patients underwent epi-endocardial ECGI mapping (Amycard 01C EP Lab, Amycard LLC, Russia - EP Solutions SA, Switzerland). The iterative Equal Single Layer algorithm (ESL-iterative) and a new Fast Route algorithm in combination with the vector approach (FRA-V) were used to reconstruct isopotential and correlation similarity maps. Geodesic distance between noninvasively reconstructed early activation zone and RV reference pacing sites were measured to evaluate the ECGI accuracy.

Results. The mean (SD) geodesic distance between noninvasively identified sites and reference pacing sites was 22 (15) mm for the ESL-iterative and 12 (7) for FRA-V algorithms, median (25-75% IQR) - 23 (8-29) mm and 10 (8-14) mm, respectively. The accuracy of ECGI mapping based on the FRA-V algorithm was significantly better than ESL-iterative algorithm (p=0,01). A detailed visual analysis of correlation similarity and isopotential maps showed significantly more accurate localization of early activation zones using the new FRA-V algorithm.

Conclusions. Our study showed the feasibility and accuracy of a novel epi-endocardial ECGI mapping approach to identify early activation zones during septal ventricular pacing using the new FRA-V algorithm. The FRA-V algorithm is significantly better for epi-endocardial ECGI mapping and shows a significant advantage of this technique compared to other non-invasive methods of topical diagnostics. Moreover, simultaneous beat-to-beat mapping of entire ventricular septum allows using this technique for pre-ablation evaluation of unstable and polymorphic ventricular arrhythmia exit sites.

Key words: noninvasive epi-endocardial electrocardiographic imaging; inverse ECG problem; ventricular septal pacing

Conflict of Interest: Mikhail Chmelevsky and Danila Potyagaylo are specialists at EP Solutions SA, Stepan Zubarev and Margarita Budanova are consultants at EP Solutions SA; in other cases nothing to declare.

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Non-invasive epi-endocardial ElectroCardioGraphic Imaging (ECGI) of the heart allows the reconstruction of electrograms and high-resolution visualization of different isoparametric maps based on multichannel ECG recording and tomography. The significant potential of this methodology was confirmed by several publications devoted to the analysis of the ECGI use in clinical practice for the diagnosis of various arrhythmias [1, 2]. In connection with the possibility of panoramic mapping of the epicardial and endocardial surface of the heart during one cardiac cycle the detailed topical and electrophysiological diagnostics before the catheter ablation procedure represents the most prospective area for the ECGI. It enables mapping of unstable and polymorphic ventricular arrhythmias with an analysis of the depth of the ectopic source and electrical propagation.

Despite the promising prospects of this methodology, lack of information on detailed quantitative analysis of the accuracy of ECGI until recently was one of the key factors limiting its use in clinical practice. In this regard studies with a detailed quantitative verification of ECGI and a thorough analysis of possible contributing factors on used algorithms for solving the inverse problem of electrocardiography allowed us to estimate its accuracy along with the facilities in topical diagnosis of focal arrhythmias [3, 4]. In particular, it was shown that the accuracy of ECGI in the area of interventricular septum (IVS) was relatively low (median value 23 mm), and the clinical implementation of ECGI for preoperative diagnostics of ventricular arrhythmias was significantly limited.

We have to note that from a mathematical point of view non-invasive mapping of the IVS seems to be associated with some difficulty considering incorrect solving of the ECG inverse problem. In addition, it is necessary to consider the position of the IVS that is in fact covered by the free walls of the cardiac ventricles. Currently used algorithms have been described in detail previously and tested on various data, but it did not allow to solve this problem [5, 6].

Proposed in several recent papers new mathematical methods for solving the inverse problem of ECG suggest a significant improvement in ECGI resolution of IVS [7, 8]. The first results looked promising while new technologies demonstrated the accuracy of ECGI in the region of IVS up to 10 mm [8].

Within this context, the aim of the study was to investigate a new algorithm for solving the inverse problem of ECG and to verify the accuracy of ECGI during septal ventricular pacing in patients with pre-implanted pacemakers.

MATERIALS AND METHODS

The study included 10 patients with previously implanted pacemakers where right ventricular (RV) electrode was located in different segments of IVS. All patients were screened for contraindications to computed tomography (CT) and signed informed consents to participate in the study. Multichannel ECG recordings was performed in all patients using the "Amycard 01C" system («Amycard» LLC, Russia - EP Solutions SA, Switzerland). This clinical study was conducted in accordance with the standards of good clinical practice (Good Clinical Practice) and the principles of the Helsinki Declaration; it was also approved by the Ethics Committee of the Almazov National Medical Research Centre.

During multichannel ECG registration the pacemakers were switched in the mode of the isolated mono - or bipolar stimulation from the RV tip electrode (RV tip) with a frequency of 90 in 1 min for the period of 10 seconds and subsequent restoration of the initial parameters. Further analysis included evaluation of typical morphology of paced QRS complex. All other stages of registration of multichannel surface ECG, CT and processing of non-invasive imaging data were identical to those previously published in our recent work [3,4]. Export of three-dimensional polygonal models in the VTK format and original multichannel ECG recordings in the specific text format was performed using software "Amycard 01C".

An iterative Equal Single Layer algorithm (ESL-iterative) was used initially for solving the inverse problem of ECG with subsequent visualization of the isopotential maps [5]. Then new Fast Route algorithm in combination with vector approach were used to identify the most likely area of early activation of focal sources (FRA-V) with subsequent visualization of correlation similarity maps [8].

Based on ESL-iterative algorithm the early activation zone was evaluated by visual determining the area of the earliest sustained negative potential (assigned by physician-researcher on the isopotential maps with an accuracy of 1 ms), concentrically propagating along the endocardial surface of the heart. According to the new FRA-V algorithm, the area of early activation was determined automatically on the three-dimensional polygonal model of the ventricles as the point with the highest value of the correlation coefficient of the similarity maps (Figures 1, 2). In the same way to previous studies, the exact position of the pacing electrode in the IVS was evaluated during CT. Then the geodesic distance was measured (along the surface) between the tip of the RV electrode and the center of the early activation zone that were marked with a tag [3,4]. All study measurements were performed only on the endocardium of the epi-endocardial three-dimensional polygonal model (endo epi-endo model) in each patient.

The obtained values were exported for further statistical analysis. For interactive reconstruction of isopotential and correlation similarity maps on three-dimensional polygonal models of the cardiac ventricles special software was used based on the open graphical cross-platform software package Paraview v.5.6.0 (Kitware Inc., USA).

Statistical analysis

Statistical analysis of the results was performed using the same methodology described in details in our previous publications [3]. Thorough analysis of patients' clinical data and the values characterizing the ECGI accuracy was carried out in the same way. The Wilcoxon sign rank test was used for comparison of accuracy values obtained by different algorithms. The variability of the compared values was estimated using one-dimensional box&whickers plot (Tukey) and categorized histograms. Considering a small sample of patients, all accuracy values were compared using linear plots for multiple variables.

In addition, to assess the variability parameters along with stability and reliability of the calculated statistical data compared to the initial characteristics as well as to ensure the validity of obtained results the analysis of ECGI accuracy was performed according to random selection of 1000 repeat samples. An accelerated non-parametric bootstrap analysis with 95% confidence intervals (CI) calculation was used as a method of numerical resampling [9]. The visual evaluation of the statistics for the obtained samples of accuracy values with different algorithms of solving the inverse problem was performed using violin plots [10].

Table 1.

Basic clinical characteristics and pacing parameters according to telemetry data of implanted devices in the study group

Characteristics	Value
Gender [мale], N (%)	5 (50)
Age [years]	61 (27; 54-66; 78)
CHD, N (%)	7 (70)
II/III FC NYHA, N (%)	5 (50)/2 (20)
MI, N (%)	2 (20)
Complete LBBB, N (%)	5 (50)
CRT, N (%)	5 (50)
Bipolar RV pacing, N (%)	4 (40)
Stimulus amplitude [mV]	2,0 (1,8-4,0)
Stimulus duration [ms]	0,4
Number of surface ECG electrodes, N	188 (130; 159-201; 234)
QRS complex duration, ms	178 (136; 152-204; 220)

Примечание. The values are expressed as median (min; 25-75%; max) or absolute numbers - N (%); CHD - coronary heart disease; FC - functional class of chronic heart failure; MI - history of myocardial infarction; LBBB - left bundle branch block; CRT - cardiac resynchronizing therapy; RV - right ventricle.

Considering relatively small number of patients in the selected group and therefore the necessity to evaluate the error of calculation of significance levels in our study the values of p ≤0.01 were considered as statistically significant according to the Bonferroni correction of the obtained values for multiple testing. Comprehensive statistical analysis was performed using statistical programs Statistica v.12 (Statsoft Inc., US), SPSS v.23 (IBM Corp., USA) and Statgraphics Centurion v.18.1.11 (Statgraphics Technologies, Inc., US).

RESULTS

Clinical characteristics of patients included in the study and pacing parameters of the implanted CRT devices

In the study group with 5 males (50%) the age of patients ranged from 27 to 78 years old (median value of 61; 25/75% quartiles, interquartile range (IQR) 54-66). In 5 (50%) patients ECG demonstrated the pattern of complete left bundle branch block (LBBB), 7 patients (70%) had coronary heart disease (CHD), among them 2 patients (20%) had prior myocardial infarction (MI). There were also 2 patients (20%) with chronic heart failure of class III (NYHA) and 5 patients (50%) - with class II. Cardiac resynchronization therapy (CRT) devices were implanted in 50% (5/10) of patients. The main clinical characteristics, device parameters and pacing modes are represented in Table 1. There were no statistical significant differences in all the above characteristics in the study group.

Exploratory analysis

During analysis of the ECGI accuracy using the ESL-iterative algorithm (according to preliminary results of recent studies), among all patients there were no outliers or extreme values data that could expect a mistake on any stage of the data collection. Considering this fact, patients' data were included in a further comparative accuracy analysis using two selected algorithms for solving the inverse ECG problem.

Accuracy of ECGI on epicardial and endocardial models

The average value (SD) was 22 (15) mm according to the ESL-iterative algorithm and 12 (7) mm using the FRA-V algorithm, while the median (25-75% IQR) was 23 (8-29) mm and 10 (8-14) mm, respectively. At the same time, in the 60% (6/10) of cases we obtained accuracy values less than 10 mm using the FRA-V algorithm, while similar results were observed only in 30% (3/10) of cases with the ESL-iterative algorithm. The results of the new FRA-V algorithm compared with the conventional ESL-iterative algorithm are represented by correlation similarity and isopotential maps as illustrated in Fig.1 and 2.

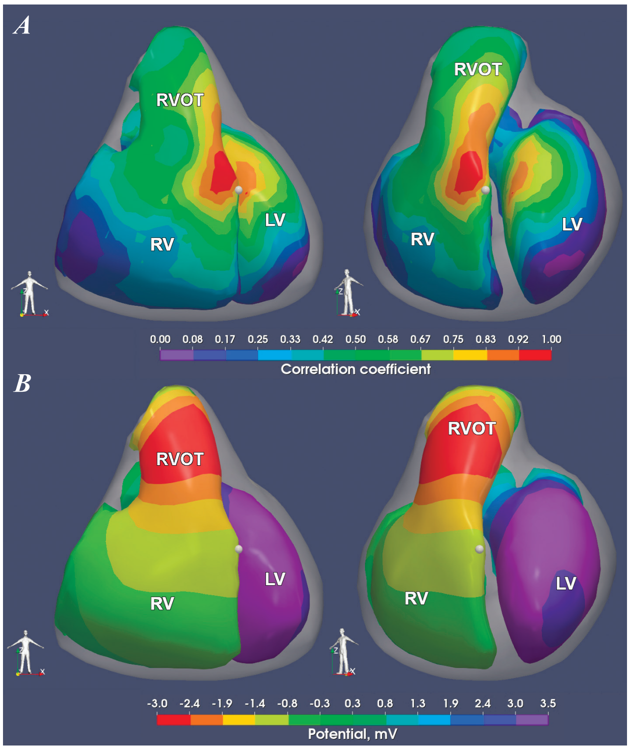

Figure 1. Semi-transparent three-dimensional epi-endocardial models of cardiac ventricles. The localization of the pacing electrode in the anterior-middle part of IVS is shown with a white marker. A (top). Correlation similarity maps based on new algorithm FRA-V. B (bottom). Isopotential map based on ESL-iterative algorithm. The zones of early activation are shown in red. Models of cardiac ventricles on the left side are shown in right anterior oblique (RAO) projection; models of cardiac ventricles on the right side are shown in left anterior oblique (LAO) projection.

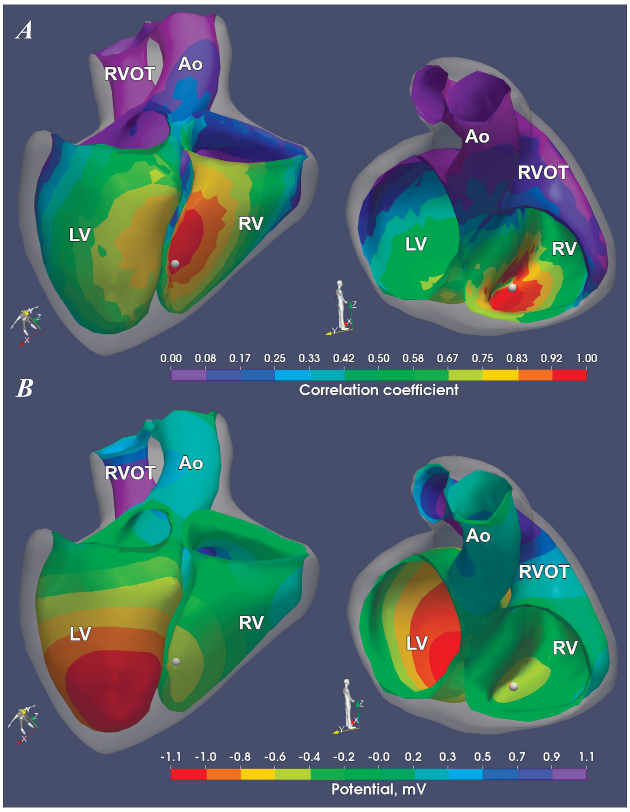

Figure 2. Semi-transparent three-dimensional epi-endocardial models of cardiac ventricles. The localization of the pacing electrode in the inferior-middle part of IVS is shown with a white marker. A (top). Correlation similarity maps based on new algorithm FRA-V. B (bottom). Isopotential map based on ESL-iterative algorithm. The zones of early activation are shown in red. Models of cardiac ventricles on the left side are shown in inferior (INF) projection; models of cardiac ventricles on the right side are shown in right lateral (INF-RAO) projection.

The main results of the ECGI accuracy are presented in Table 2. Distribution histograms of all obtained values using different algorithms are shown in Fig. 3. The comparative analysis of the results showed a statistically significant difference (p=0.01) in favor of a higher accuracy of FRA-V as compared to ESL-iterative (Fig. 4A) algorithm. Linear diagrams also demonstrated the advantage of the new algorithm over ESL-iterative in most of the cases (Fig. 4B).

Table 2.

Main characteristics of ECGI accuracy

Characteristics of accuracy, mm	Algorithm for solving inverse ECG problem			
	ESL-iterative		FRA-V	
	Value	95% CI	Value	95% CI
% of cases <5	10%	-	0%	-
% of cases <10	30%	-	60%	-
Mean value (m)	22	14-31	12	9-16
Standard deviation (SD)	15	8-20	7	2-9
Median (M)	23	8-30	10	8-14
Lower quartile (25%)	8	5-25	8	6-10
Higher quartile (75%)	29	22-53	14	9-28
Minimal value (min)	5	-	6	-
Maximal value (max)	53	-	28	-

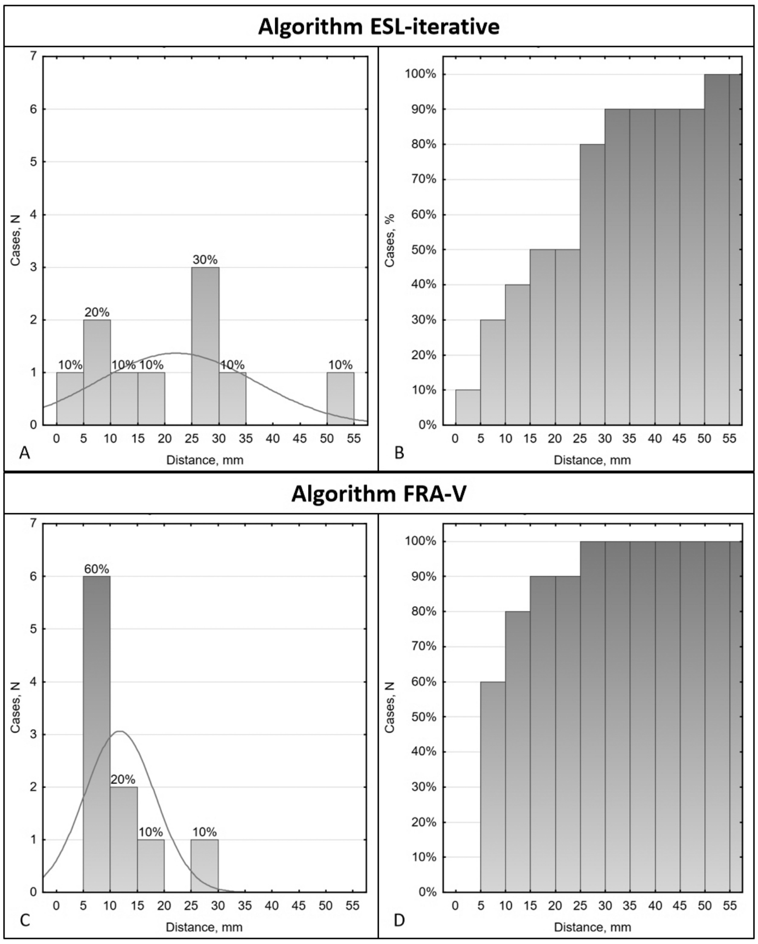

Figure 3: ECGI accuracy distribution histograms based on different algorithms for solving inverse ECG problem. X axis - distance between the pacing site and the early activation zone (Distance), Y axis - number (N) of observations (cases). On the left (A,C) - ECGI accuracy histograms, on the right (B,D) - cumulative histograms showing the accumulated percentage of cases (Y) for a certain value (X). A, B - ESL-iterative algorithm; C, D - FRA-V algorithm. The grey curve shows the approximation to the normal distribution.

Correlation of clinical characteristics of patients with ECGI accuracy

We evaluated possible correlation of basic clinical characteristics of the study group and ECGI accuracy but there were no significant interaction between these parameters. Statistical analysis also included the number of electrodes used for ECG recordings along with the duration of the selected ECG fragments (the results are presented in Table 1). In total, there were no also significant correlation with the accuracy of ECGI.

Evaluation of ECGI accuracy data based on the bootstrap analysis

The accuracy of ECGI based on the data of the bootstrap analysis (95% CI; 25 ÷ 75% IQR) was 8-30 (5-25 ÷ 22-53) mm using ESL-iterative compared to 8-14 (6-10 ÷ 9-28) mm using FRA-V algorithm (Table 2). The visual distribution of the obtained values is shown in Fig. 5. Therefore, comparative analysis of different algorithms based on the bootstrap also demonstrated a statistically significant difference between groups (p < 0.001).

DISCUSSION

Main results

Comparative analysis showed better ECGI accuracy in the localization of the early activation zone when using the new algorithm FRA-V (10 mm median) compared to the conventional ESL-iterative algorithm (23 mm median). Linear diagrams also demonstrated more accurate values in 80% of cases with the FRA-V algorithm. In addition, this observation was confirmed by the statistically significant difference between the obtained results in favor of a higher accuracy of the new algorithm. Detailed visual analysis of isopotential and correlation similarity maps showed much more precise localization of the early activation zones using the new FRA-V algorithm during ventricular pacing in the anterior and medial part of IVS (Fig. 1) and in the inferior and medial part of IVS (Fig. 2). In view of this, the implication of FRA-V algorithm contributes significantly to the improved diagnostic accuracy of ECGI.

It should also be noted that the new algorithm FRA-V is characterized by balanced localization error range (6-28 mm) compared to the ESL-iterative algorithm (5-53 mm) that demonstrates its higher robustness in solving the inverse ECG problem. All the above facts indicate that the combination of vector analysis methods and the new Fast Route algorithm of finding the most likely area of early activation of focal sources gives much better results compared to the ESL-iterative algorithms for solving the inverse ECG problem in terms of simple layer potential.

Therefore, the use of ECGI with the new algorithm FRA-V demonstrates its significant advantage in comparison with other non-invasive concepts in topical diagnostics. Moreover, the simultaneous mapping of the entire surface of the IVS during one heart cycle represents the promising approach for preoperative topical diagnostics of such complex rhythm disorders as nonsustained and polymorphic ventricular arrhythmias.

Evaluation of data distribution and impact on ECGI accuracy

A detailed analysis of ECGI accuracy histograms showed significant differences from the normal distribution (Fig. 3A, 3C). This confirms the need for non-parametric statistical methods to compare results because these methods do not depend on any particular distribution and do not use its properties. Moreover, it is almost impossible to predict the distribution of data in such cases because the study group usually represents a complex system consisting of large number of heterogeneous components. Any further conclusion could not be correct in case they are based on the assumption of normal distribution even with the increased sample size and actually will be useless to summarize the results of the study. Thus, taking into account a small sample size, we used non-parametric statistical methods to provide correct study conclusions. Besides that, the analysis of linear diagrams of ECGI accuracy also points to the high heterogeneity of the initial data (Fig. 4B). It could be explained not only by the using of specific algorithms for solving the inverse ECG problem but also by the high variability of electrical tissue conductivity values in different patients. At the same time, it is necessary to take into account the high heterogeneity between the relatively small sample of patients included in this study. It also implies that the new FRA-V algorithm is characterized by higher robustness in comparison with ESL-iterative algorithm. In addition, the results show that different algorithms can significantly alter the accuracy of ECGI. This fact may again indicate the need for more detailed study of the algorithms for solving the inverse ECG problem and further improvement of the ECGI technique.

Correlation of different characteristics of patients in the study group with ECGI accuracy

The lack of statistically significant differences between ECGI accuracy and other factors of non-invasive mapping (clinical characteristics, pacing parameters, number of surface ECG electrodes, etc.) in the study group may partly illustrate independence of the obtained values from these parameters when using different algorithms for solving the inverse ECG problem. At the same time, it is necessary to take into account a relatively small number of patients while further studies are required to verify the results.

Evaluation of bootstrap analysis results

In small studies despite the use of non-parametric methods even one discordant observation may lead to wrong estimation of the results. Moreover, in the absence of aprior accuracy characteristics of ECGI in the study group it is practically impossible to estimate the presence of outlying data or extreme values on any stage of the data collection. In this case, the calculated statistics appear to be irrelevant, and it becomes almost impossible to evaluate the representativeness of the study, so it is necessary to repeat it on other samples. But due to complexity of the ECGI procedure as well as the necessity to use contrast-enhanced CT in patients with initial low left ventricle ejection fraction (LV EF) it becomes practically impossible to increase the sample of the study group. Considering this fact, we decided to use the methods of random selection of repeat samples [11]. Furthermore, we used the accelerated non-parametric bootstrap analysis with the calculation of corresponding 95% confidence intervals (CI) because of the absence of aprior characteristics of the initial distribution type of the studied values. As a result, when using the bootstrap analysis there is a peculiar modeling of the empirical distribution of the studied values with different

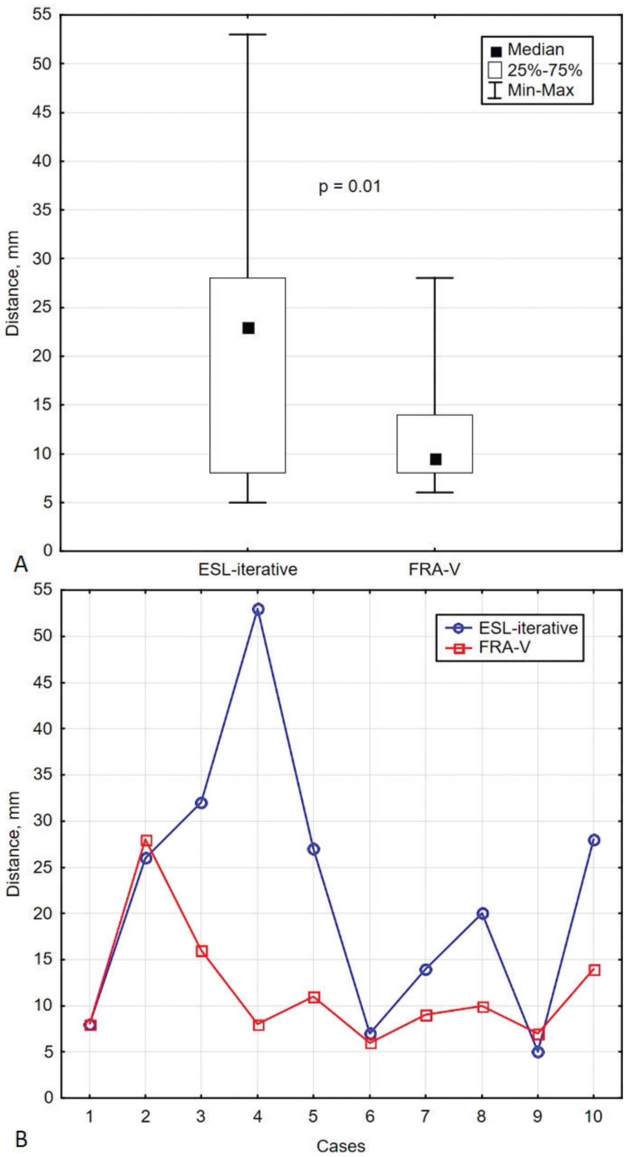

Figure 4. Comparative evaluation of ECGI accuracy using different algorithms for solving inverse ECG problem. A - Tukey box&whiskers plots Tukey of ECGI accuracy. X-axis - algorithm, Y-axis - the distance between the pacing site and the early activation zone (Distance); B - ECGI accuracy linear plot. X-axis - cases; Y-axis - distance between the pacing site and the early activation zone (Distance).

algorithms for solving the inverse problem that may significantly increase the stability and reduce the degree of uncertainty of the calculated data compared to baseline parameters [12]. Besides, it is shown that this method with sufficient number of repeated iterations (more than 1000) provides more accurate results than standard non-parameter comparison criteria [9].

Based on the results of the bootstrap analysis it was confirmed that the identification of early activation zone significantly improved when using the new algorithm FRA-V in comparison with the ESL-iterative algorithm. In addition, the calculated 95% CI were narrower with the new FRA-V algorithm. The presentation of the results using violin plots for each method of solving an inverse ECG problem also clearly demonstrates that there is significant variation in the calculated values with the ESL-iterative algorithm, while FRA-V algorithm is characterized by a compact values distribution without significant outliers. In addition, multimodal distribution of studied values in case of using ESL-iterative algorithm may indicate its less stability and robustness.

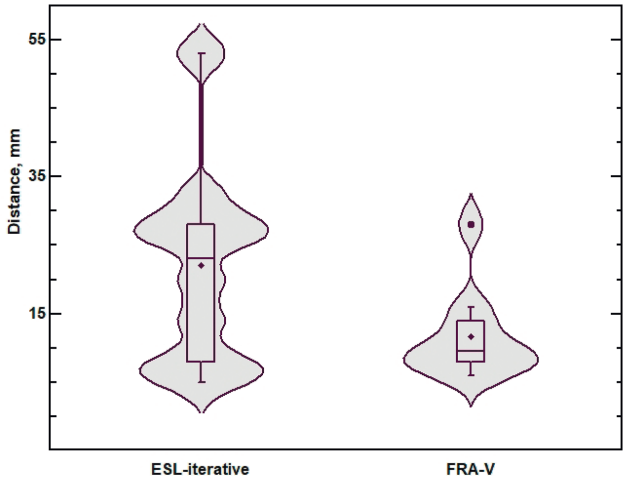

Figure 5. Violin plot of ECGI accuracy showing the distribution of values based on the bootstrap analysis method for different algorithms of solving the inverse ECG problem. Primary Tukey box&whiskers plot of ECGI accuracy used for generation of 1000 random repeated samples are located in the center of each violin plot. Additionally, an average value is shown inside as a solid rhombus. The X-axis is the algorithm for solving the inverse ECG problem, the Y-axis is the distance between the pacing site and the early activation zone (Distance). The configuration of the violin plot shows the distribution of the generated values data.

All the above-mentioned data clearly demonstrate the advantage of using the FRA-V algorithm for ECGI in routine clinical practice.

Evaluation of representativeness of the results and comparison with other studies

The study included relatively small group of patients, which certainly reduces the degree of representativity. At the same time, the use of resampling techniques reduces the probability of biased estimation and suggests that the calculated statistical results are rather stable in repeated studies.

However, it should be emphasized that a more accurate assessment of the validity and robustness of the obtained data could be available only after a major systematic review study on the accuracy of the ECGI.

It also worth noting that recent published data do not contain any clinical results of the ECGI accuracy study depending on different algorithms [13]. This underlines the role of obtained results for future studies on the algorithms for solving the inverse ECG problem along with the evolution of the ECGI technique.

The study limitations

The limitations of the study mainly include a relatively small sample size. This limitation is partially balanced by usage of resampling methods represented by accelerated bootstrap analysis. At the same time, it should be noted that none of the extremely intensive methods can guarantee the non-effect of undetermined factors or systematic errors.

Other specific limitations are listed in the recent published study on ECGI verification [3].

CONCLUSION

These results showed a possibility of novel epi-endocardial ECGI mapping to detect early activation zone during septal ventricular pacing with sufficient accuracy (median 10 mm) using new FRA-V algorithm. Therefore, FRA-V algorithm is significantly better for epi-endocardial ECGI mapping and shows a significant advantage of this technique compared to other non-invasive methods of topical diagnostics.

Considering the fact that the ECGI technique allows to perform mapping of the entire heart surface during one cardiac cycle it could provide preoperative topical and electrophysiological diagnostics of such complex rhythm disorders as non-sustained and polymorphic ventricular arrhythmias before catheter ablation procedure.

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ATRIAL FIBRILLATION CRYOBALLOON ABLATION IN PATIENTS WITH A COMMON PULMONARY VEIN TRUNK

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Objective: we aimed to assess the efficacy and safety of pulmonary vein (PV) cryoballoon ablation (CBA) in patients with a common trunk of the pulmonary veins (PVCT).

Materials and methods: We performed a retrospective analysis of 596 primary PV CBA procedures using the second-generation cryoballoon (CB) Arctic Front Advance (28 mm). PV anatomy was visualized using direct LA angiography during high-frequency right ventricular pacing. We included forty-nine patients in whom a PVCT was identified. The one-step and sequential ablation approaches with simultaneous recording of biophysical and electrophysiological parameters were used for PVCT isolation. During CBA in the right PVs, high-output (2000 ms, 25 mA) pacing of the right phrenic nerve was performed via a electrode placed in the superior vena cava, and amplitude of diaphragm movement was monitored. In the case of impairment/loss of the diaphragm contraction ablation was immediately stopped.

Results: 91.1% (543) patients had the normal drainage of PV. In 4 patients (0.67%), an additional right pulmonary vein was identified. The prevalence of PVCT was 8.2% (49 pts): a left common trunk (LCT) was observed in 43 patients (87.7%), a right common trunk (RCT) - in 6 patients (12.2%). Acute efficacy of PVCT isolation was 95.9% (47/79): in LCT - 95.3%, in RCT - 100%. The feasibility of the one-step antral isolation was 59.1% (n=29). During a median follow up of 12 (3-20) months, the clinical success rate of the procedure was 69.4%. A comparative analysis showed no significant difference between common trunk ablation approaches and clinical efficacy (p=0.346).

Conclusion: CBA has been shown effective and safe for symptomatic AF patients with PVCT. The simultaneous and sequential ablation approaches can be performed with comparable efficacy.

Keywords: atrial fibrillation, catheter isolation; cryoballoon ablation; pulmonary veins common trunk

Conflict of Interest: K.V.Davtyan is a proctor for Medtronic, Biosense Webster and Abbot
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Pulmonary vein isolation (PVI) with catheter ablation is the first-line therapy of symptomatic, antiarrhythmic drug (AAD) resistant atrial fibrillation (AF), including patients with variable anatomy of the pulmonary veins (PV) [1-3]. PV cryoballoon ablation (CBA) is a new option of the single-shot PVI [4, 5]. The comparable efficacy and safety of CBA to radiofrequency ablation (RFA) and steep learning curve have led to the widespread adoption of the cryoballoon technology [6, 4]. On the first view, CBA seems to be more dependent on PV anatomy, than RFA. The pattern of PV drainage, in particular, the presence of the common trunk, the length of the common trunk, PV ostium shape and size may compromise the contact stability between the cryocatheter and tissue, hence the PVI efficacy. The PV drainage pattern of with common trunk is more frequent on the left (8-32%). The additional PV is common on the right (16-35%) [8-12]. This study aimed to assess the safety and efficacy of the PV CBA in patients with the pulmonary vein common trunk (PVCT).

MATERIAL AND METHODS

We have performed a retrospective analysis on the procedural data of the five hundred and ninety-six PV CBA using the second-generation cryoballoon Arctic Front Advance (28 mm, Medtronic) in patients with drug-resistant, paroxysmal/persistent AF. The patients consequently underwent the primary PV CBA between November 2016 and November 2018 in National medical research centre

Figure 1. Angiography of the left atrium and pulmonary veins. The large and long pulmonary venous trunk is a limitation for cryoballoon ablation.

for preventive medicine. PV anatomy was visualised using a direct LA angiography on high-frequency right ventricular pacing. The evaluation of both large (≥26 mm) and long (≥10 mm) PVCT in three patients limited CBA performance (fig. 1). We enrolled forty-nine patients (8,2%) with evaluated PVCTs in the study. The minimum PVCT length was set to five mm.

Patients' clinico-demographic characteristics

The patients' median age was 61 yrs (interquartile range (IQR) 53-67), 49% (n=24) were females. The median age at the time of arrhythmia manifestation was 56 (50-62) yrs. The majority of the patients (91.8%) had paroxysmal AF with a median duration of AF history of 2 (1-5) years. The mean left atrium (LA) size was 40.5±4.6 mm, and the mean left ventricular ejection fraction 62.9±5.4%. The most frequent comorbidity was arterial hypertension (67.3%). Two patients (4.1%) had diabetes mellitus. The median CHA_2DS_2-VASc score was 1 (1-2).

Pulmonary vein cryoballoon ablation

The PV CBA was carried out under continuous intravenous sedation with propofol. The transseptal puncture was performed in the fossa ovalis under the intracardiac echocardiography (ICE) (Vivid I Safelock Cart, GE Healthcare, AcuNav 10-French, Siemens AG, Germany) using an 8 Fr. transseptal sheath (SR0, St. Jude Medical) with Brockenbrough needle. Intravenous heparin was administered

Table 1.

The set of cryoballoon isolation parameters, registered online during the procedure

CBA parameter		LSPV	LIPV	RIPV	RSPV
PV activity on Achieve catheter		yes	yes	no	yes
Applications number		1	1	1	1
Applications duration, sec.		240	240	240	240
Time to PVI, sec.	Entrance block	45	38	-	52
	Exit block	-	-	28	-
PV occlusion stability on the 30-th sec.		yes	yes	yes	yes
Cryoballon minimum temperature,°C		-46	-44	-51	-50
Acute PVI		yes	yes	yes	yes

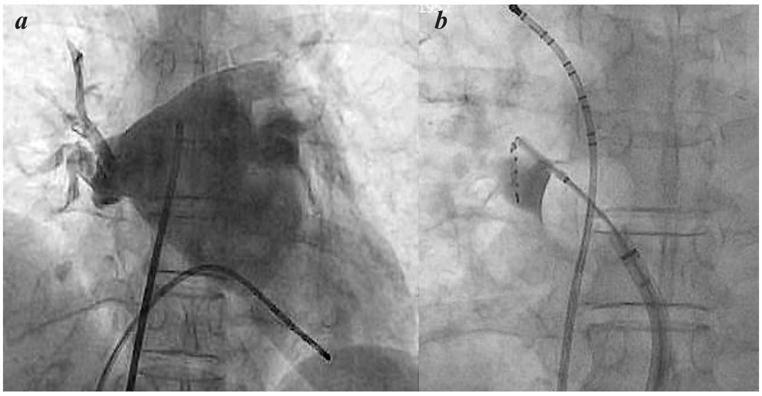

Figure 2. One-step cryoballoon ablation of the pulmonary veins' common trunk a) the visualisation of the right common pulmonary vein trunk on the left atrial angiogram, b) complete occlusion of the trunk by second-generation cryoballoon Arctic Front advance. We observed atrial fibrillation episode termination at the time of the right trunk isolation.

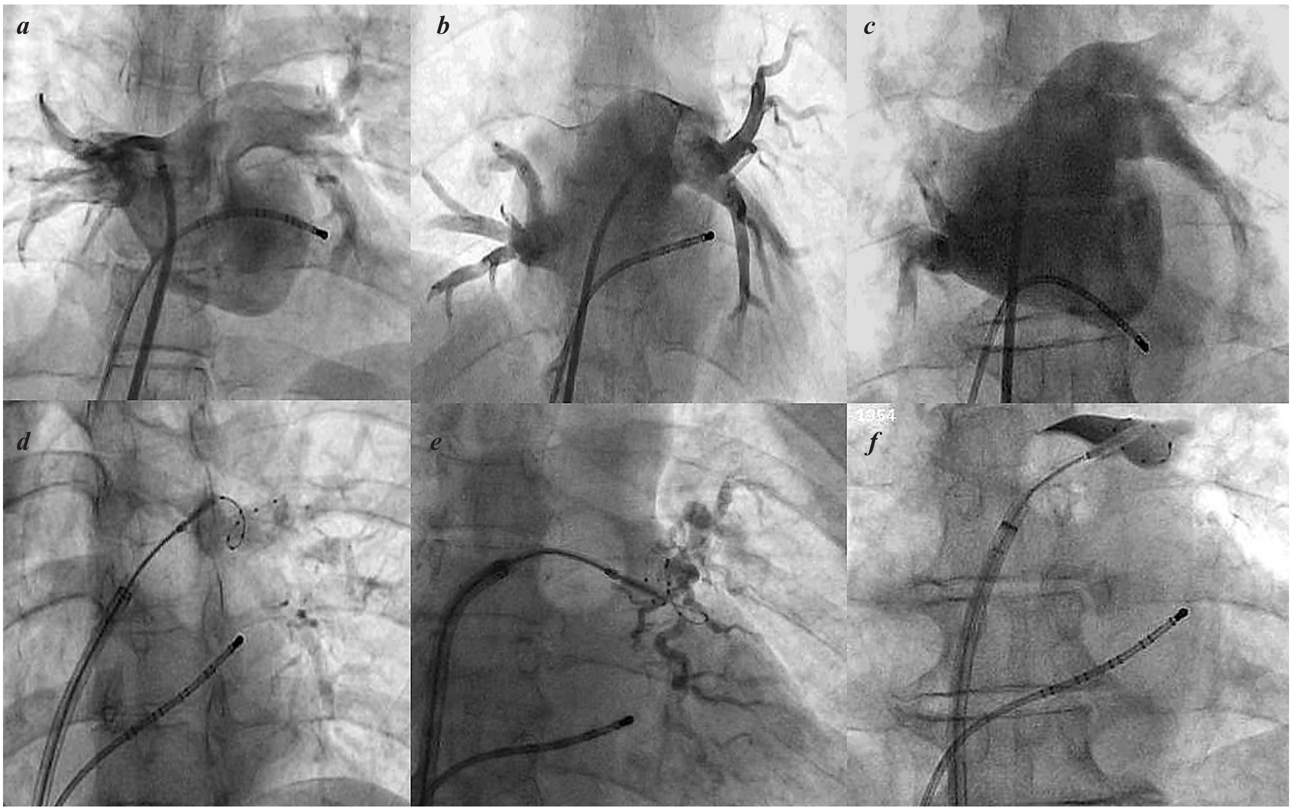

Figure 3. The variability of the left common trunk anatomy (a-c) and cryoballoon ablation approaches (d-f).

at the time of transseptal puncture (target activated clotting time ≥250 s) to prevent thromboembolic events. A decapolar diagnostic catheter (Webster Decapolar Deflectable Catheter, Biosense Webster, USA) was inserted into the right ventricle (RV). We performed a high rate RV pacing (cycle length 250 ms, MicroPace EPS 320, Micropace Inc., USA) to enhance the quality of LA anatomy visualisation. After LA angiography, we placed the diagnostic catheter into the coronary sinus (CS). The minimum length of the common trunk between common ostium and first branching was set to five mm. If no limitations for CBA were observed, the transseptal sheath was exchanged to cryoballoon delivery system FlexCath (Medtronic, USA, 12 Fr). The second-generation cryoballoon Arctic Front Advance with Achieve diagnostic catheter (Medtronic, USA) was advanced via the delivery system to the LA. The Achieve catheter was positioned to the PV ostium to map venous electrical activity. Then the catheter was inserted distally into the PV to support cryoballoon positioning. The cryoballoon was inflated in the PV and advanced to the PV ostium. PV angiography was performed to confirm the complete PV occlusion by the cryoballoon. We performed CBA in the clockwise direction (left superior PV, left inferior PV, right inferior PV, right superior PV). Initially, the application duration was 240 sec. Since March 2018, we have reduced the application duration to 180sec based on the results from the growing number of publications on efficacy and safety of shorter cryoapplication duration [13-15]. Ten patients underwent CBA with the application duration of 180sec. For PVCT isolation, we have used both one-step and sequential ablation approaches. If necessary additional applications were performed to complete PVI. Table 1 presents the example of CBA parameters set, registering during each PVI procedure.

We monitored diaphragmatic contraction by abdominal palpation during right phrenic nerve pacing (30 bpm, 24 mA) while performing CBA in the right PVs. In the case of diaphragm contraction weakening or disappearing the freezing was immediately discontinued, and the cryoballoon was deflated.

We have continuously monitored PV activity on Achieve catheter to verify PVI in real-time. If we could detect no PV activity, we paced the Achieve catheter (the dipole with stable conduction to LA) to verify the exit block. When necessary, we used the independent two-channel pacing in the right PVs to assess right phrenic nerve function and verify the exit block. After completing CBA, we remapped each PV and confirmed the exit block. In doubtful cases of LA capture, while pacing PV, we placed the decapolar diagnostic catheter on the possible closest part of the atrial myocardium to the paced PV. In the cases of atrial capture, the delay between stimulus artefact and atrial capture on the decapolar catheter was minimal (≤30 ms).

Postprocedural management

The patents restarted antithrombotic therapy in four hours after control echocardiography excluding pericardial effusion. Antiarrhythmic drugs for 3-6 months had been administered to five patients with persistent AF. Patients with paroxysmal AF did get no antiarrhythmic therapy. We have assessed the procedure clinical efficacy using results of rest ECG, 24-hours Holter monitoring and telephone survey, performed in 3, 6, 12 months after the procedure.

Table 2.

Comparative characteristics of PV common trunk ablation approaches

	Approach subgroup		P value
	One-step ablation	Sequential ablation	
PVCT number, n	29	20	-
Applications per vein, n	1.33	1.16	0.051
Applications duration, sec.	296.5	274.5	0.543
PVI in real time, %	64.4%	63.2%	0.878
PV complete occlusion by cryoballoon, %	88.75	91.5	0.566
Cryoballoon minimal temperature, ºC	49.6	49.3	0.813

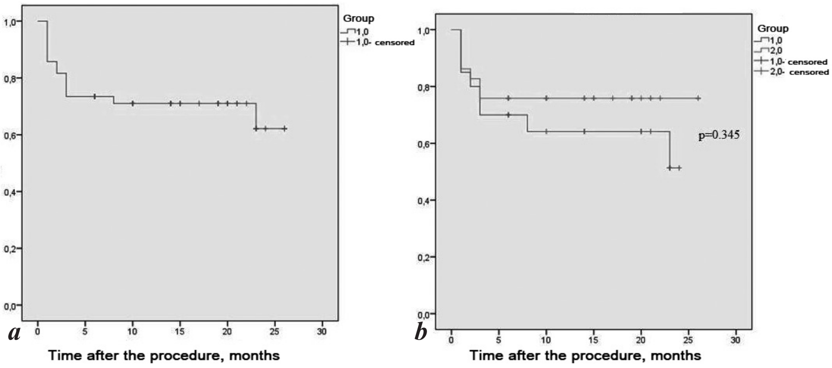

Figure 4. Clinical efficacy of cryoballoon ablation in patients with pulmonary veins' common trunk a) in the study population, b) in the subgroups of one-step and sequential ablation approaches (group 1 - sequential ablation, group 2 - one-step ablation).

Statistical analysis

We performed statistical analysis using Microsoft Excel 2016 (Microsoft Corporation, USA) and SPSS for Windows (IBM Corporation, USA). Normality was assessed using the Shapiro-Wilk test. Continuous variables were presented as mean ± standard deviation (SD) median (Me) and interquartile range (IQR). Comparisons between two groups were performed with the Mann Whitney U test and Student's T-test, as appropriate. We used Pearson's chi-squared test for categorical variables. A two-tailed p-value ≤ 0.05 was regarded to be significant.

RESULTS

Five hundred forty-three patients (91.1%) had the typical pattern of PV drainage (four PV ostia on the LA posterior wall). Four patients (0.67%) had an additional right PV (right middle PV). Forty-nine patients (8.2%) had a common PV trunk. Forty-three from forty-nine (87.7%) had a left common trunk, six patients (12,2%) - right common trunk. Procedural PVI success rate was 98.6%. We successfully isolated 95.9% (47 from 49) PV trunks and

100% right PVs. We performed one-step cryoablation in twenty-nine common trunks (59%) (fig. 2). For twenty PV trunks (41%), we used the sequential ablation approach (fig. 3. e-f).

The total number of PVI, using second-generation cryoballoon, was 147. The number of cryoapplication per vein was 1.4, application duration per vein - 284.2 sec. The complete PV occlusion by cryoballoon was achieved in 89.9% PV. The minimal cryoballoon temperature was 48.6±6.5ºC. Online PVI verification was possible in 64.9% PV; the median time to PVI was 42 (28-55) sec. Right phrenic nerve injury occurred in no patients. One patient (2.04%) developed a right femoral vein access site haematoma, managed surgically.

Table 2 presents the comparative analysis of procedural characteristics depending on the common trunk ablation approach (one-step and sequential). As the table shows, the ablation approach had no implications for biophysical and electrophysiological parameters of CBA.

Complications

One patient (2.04%) developed a large right femoral haematoma, requiring surgical intervention.

Clinical efficacy of the procedure

The procedure success rate (sinus rhythm maintenance) was 69.4% at the median follow-up time of 12 (3-20) months (fig. 4a). Fig. 4b presents the Kaplan-Meier curve of PVCT two ablation strategies, showing comparable efficacy of one-shot and sequential ablation strategies for PVCT (p=0.345).

DISCUSSION

Our study confirmed the high efficacy and safety of CBA in patients with PVCT. The freedom from arrhythmia was 69.4%, which correlated well with data from other trials [12,16].

Heeger et al. reported the comparable procedural and clinical success rate in patients with left common trunk and typical PV drainage pattern. The frequency of left common trunk, in this study, conducted in three high-volume centres, was 11%. All common trunks (100%) were successfully isolated. There were no statistical differences in applications per vein, time to PVI, cryoballoon minimum temperature between the groups. Khoueiry et al. demonstrated comparable clinical efficacy of CBA and RFA in patients with paroxysmal AF and variable PV anatomy [12]. The study, conducted by Tsyganov et al. [17], confirmed the universality of ballon technologies in variable PV anatomy. PVCT was not a predictor, too in the study, conducted by Huang et al. [18]. However, Chichkova et al. reported, that PVCT pattern was associated with higher procedure-related complications rate, in particular, pericarditis [19]. Indeed, the small sample size (n=7) suggests the sporadic character of the observed cases. Still, the authors' hypothesis of distally placed (outside the contour of the heart) cryoballoons damaging effect on epicardium seems to be logical. From this point of view, the strategy of our centre, limiting CBA in the cases of both large (>26 mm) and long (>10 mm) PVCT is justified in order to avoid such a grave complication as atrial-oesophagal fistula.

Interestingly the LA and PV computer tomography before catheter ablation has been performed rarer the recent years [16, 18]. Apart from the cost-efficacy, the growing experience of AF CA independent on PV anatomy is the possible explanation for this observation. Also, new mapping and ablation technologies have improved the feasibility of the catheter ablation. Probably that is the reason why data from the early studies, reporting catheter ablation dependence on PV anatomy, has not been confirmed in recent trials [11, 17, 20].

Nowadays, the main limitation to perform CBA is both large (≥26 mm) and long (>10 mm) PVCT (fig. 1). From this point of view, the results of the analysis of the three-dimensional PV ostium and antrum anatomy are impressive [21]. The distance between common ostium to first branching was 0-5 mm in forty-three patients from ninety-four (45.7%) and 5-15 mm in thirty-seven patients (39.4%). Only in fourteen patients (14.9%) the length of the common trunk was more than 15mm. Thus, the frequency of PVCT not feasible for CBA is low.

LIMITATIONS

The study is a retrospective analysis of the prospectively collected data. The likelihood of insufficient AF relapse evaluation, changes in cryoapplication duration (shift from 240 sec to 180 sec) are these study limitations. Further follow-up is necessary to assess the comparative procedure efficacy between patients with PVCT and typical PV drainage.

CONCLUSIONS

CBA of PVCT is efficient and safe in patients with symptomatic AF. One-shot and sequential ablation approaches can be used for PVCT isolation with comparable efficacy.

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EPICARDIAL VOLTAGE MAPPING IN PATIENTS WITH POSTINFARCTION VENTRICULAR TACHYCARDIA: A PILOT STUDY

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Introduction. Radiofrequency ablation (RFA) is an established treatment of post-myocardial infarction ventricular tachycardia (VT). Endocardial VT ablation can be insufficient for VT termination when the scar is intramural/epicardial.

Purpose: to assess the extent of epicardial electrophysiological VT substrate in patients with remote myocardial infarction.

Materials and methods. Thirteen patients with sustained postinfarction VT, who signed an informed consent, were included into the study. All patients underwent full clinical evaluation. Electroanatomical voltage bi- and unipolar mapping of endocardial and epicardial surfaces was performed. Maps were evaluated for the presence of low-voltage areas and local abnormal ventricular activity (LAVA). RFA was performed at LAVA sites. The end-point of the procedure was scar LAVA abolition and VT noninducibility (procedure success). VT recurrence was detected using an implantable cardioverter-defibrillator and/or ECG monitoring.

Results. Epicardial access was successful in 12 patients. Epicardial access was performed at a first procedure in 7 patients, 4 patients had a history of previous endocardial ablation. Epicardial LAVA sites were detected in 9 patients. Endocardial and epicardial arrhythmogenic substrate localization coincided in 8 patients. One patient had only epicardial scar, 1 patient had only septal endocardial scar. In one patient LAVA sites had different localizations on epicardial and endocardial maps. Acute ablation success was noted in 12 patients.

Conclusion. In our patient group transmural scar and epicardial electrophysiological arrhythmogenic substrate was detected in 82% of cases. Isolated endocardial ablation may be unsuccessful, in such cases epicardial mapping and ablation might be useful.

Key words: postinfarction cardiosclerosis; ventricular tachycardia; radiofrequency catheter ablation; endocardial access; epicardial access; scar tissue; late potentials; mapping

Conflicts of interest: E.N.Mikhaylov and D.S.Lebedev report receiving speaker and consultation honoraria from Biosense Webster; other authors report no conflicts of interest.

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Sustained ventricular tachycardia (VT) - is one of the most important causes of sudden cardiac death in patients with structural heart disease [1]. Antiarrhythmic drug therapy is frequently limited due to VT reccurence and side effects [2], whereas radiofrequency catheter ablation (RFA) demonstrates a higher efficacy in VT treatment in patients with remote myocardial infarction [3, 4].

Different RFA approaches have been proposed for VT substrate modification: mapping and ablation of critical isthmus of each induced VT, scar dechannelling, ablation of local abnormal ventricular activity (LAVA) sites [5-8], core scar isolation, and complete scar homogenization.

It should be acknowledged that acute VT non-inducibility and long-term freedom from VT recurrence cannot be achieved in all cases. Numerous observations have shown failure of RFA in case of intramural/subepicardial arrhythmogenic substrate location when ablation is performed endocardially via vascular access. RF energy penetration depth is about 4-6 mm, and generally it doesn't reach out subepicardial myocardial layers [9, 10]. Thereby a transcutaneous access has been proposed for epicardial mapping and ablation of VTs [11].

Most frequently, epicardial ablation is required for VT treatment in non-ischemic heart disease, when substrate is characterized by intramural or subepicardial location: arrhythmogenic right ventricle cardiomyopathy, dilated cardiomyopathy, hypertrophic cardiomyopathy (HCM), and other [12].

Regarding post-myocardial infarction VT, subepicardial localization of a critical isthmus has been located in 10% of patients, which might require an epicardial access for successful ablation. There have been few studies published that advised combined endo-epicardial ablation for successful VT treatment in patients with remote myocardial infarction [3, 11].

The prediction of arrythmogenic substrate subepicardial location is frequently limited. Magnetic resonance imaging (MRI) is a useful tool in delineation of the depth and extent of a scar, but its usability is limited in patients with an implanted ICD/CRT-D. Moreover, ECG criteria for epicardial VT exit site prediction have less accuracy in the presence of a postinfarction scar.

Theoretically, a combined endo-epicardial approach can improve the long-term efficacy of VT catheter ablation in some patients.

The aim of our pilot study was to evaluate the prevalence of electrophysiologically mapped epicardial VT arrhythmogenic substrate, and the necessity of epicardial ablation in patients with remote myocardial infarction.

MATERIAL AND METHODS

Between 2015 and 2018 165 patients with structural heart disease (coronary heart disease, dilated cardiomyopathy, arrhythmogenic right ventricle cardiomyopathy, infiltrative heart disease) were referred for VT catheter ablation at the Almazov Medical Centre, and 59 had remote myocardial infarction. The study group comprised patients who signed informed consent for epicardial access (study and agreement form were established by ethical committee of the Almazov NMRC, protocol №181 14.12.2015). One patient included into study group was operated in the Sukhanov Federal Centre for Cardiosurgery.

Inclusion criteria were the following: a postinfarction scar detected by transthoracic echocardiography or MRI and ECG-criteria of myocardial scar, the presence of sustained VT registered on ECG or during ICD follow-up, ineffective antiarrhythmic drug therapy, the absence of indications for revascularisation or it's impossibility, signed informed consent for epicardial access. Exclusion criteria: myocarditis, previous cardiothoracic surgery with pericardium dissection, other acute inflammatory disease, three component antithrombotic therapy without possibility to discontinue two of them, acute myocardial infarction <3 months ago, acute coronary syndrome during screening.

Standard clinical evaluation included: 12-lead rest ECG, TTE, 24-hour Holter monitoring, coronary angiography, ICD/CRT-D check-up. Heart MRI was performed in two patients before the procedure. In three patients VT manifested as VT storm, they were operated urgently.

Endocardial and epicardial accesses, electrophysiological study, catheter ablation

Procedure was provided in an EP laboratory under general anesthesia. Vascular accesses were performed using the Seldinger technique: to the right femoral artery and right femoral vein. Percutaneous pericardial access was obtained by a subxyphoid puncture. The access technique was described in detail previously [13]. The long Preface Multipurpose sheath (Cordis,USA) was introduced into the pericardial space. Then interatrial septum punctured under fluoroscopic guidance using the Brockenbrough needle (BKR-1, St. Jude Medical, USA). The transseptal sheath (Preface Multipurpose, Cordis, USA) was positioned in the left atrium and left ventricle. Therefore, a double endocardial access to LV was used. Heparin was administered as intravenously 80-100ME/kg with further ACT monitoring, with a target value >250 sec. A quadripolar diagnostic catheter (Webster, Biosense Webster, USA) was positioned in the RV apex. The procedure was performed under the guidance of the three-dimensional navigation system (Carto 3, Biosense Webster, USA). The NaviStar Thermocool or SmartTouch (Biosense Webster, USA) ablation catheters were used for mapping and ablation. The multipolar Pentaray catheter (Biosense Webster, USA) was used for epicardial mapping in two cases. Endocardial three-dimensional LV reconstruction and electroanatomical voltage mapping was performed in all patients (cut-off values 0.5-1.5 mV for bipolar signals), then epicardial electroanatomical mapping was performed with the same cut-off values. For unipolar maps cut off values 5.0-9.0 were used. Sites with local registration of late potentials, fragmented and double potentials were tagged on maps. When a scar was localized in the interventricular septum and VT remained inducible despite endocardial ablation, then RV mapping and substrate ablation was performed. Electroanatomical voltage mapping was performed during sinus rhythm or RV pacing. A scar was defined when myocardial signal amplitude was <0.5 mV, the intact myocardium was defined when myocardial signal amplitude was >1.5 mV.

The identification of VT exit site location was performed by both, activation and pace-mapping, and according to effective ablation. Arrhythmogenic substrate surface area was evaluated on bipolar and unipolar voltage maps. Protocol of EP study for VT induction included programmed stimulation up to three extrastimuli from the RV apex, RV ouflow tract, from LV, and overdrive burst pacing was performed when VT was not induced by programmed stimulation. Pace-mapping of conduction channels in the scar, entry and exit zones VT was performed. When induced VT was haemodynamically stable, entrainment-mapping performed. Selective coronary angiography used before epicardial ablation in order to de-

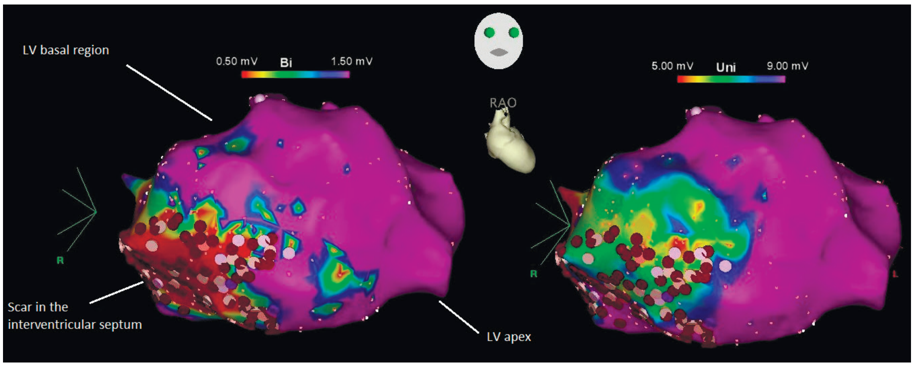

Figure 1. Patient №5. Electroanatomical voltage map with the endocardial scar only in the interventricular septum. RAO projection. The bipolar substrate area dominates over the unipolar map. Bipolar map cut off values 0.5-1.5 mV, unipolar cut off values 5.0-9.0 mV. Red color indicates the myocardial signal amplitude <0.5 mV, purple color indicates the myocardial signal amplitude >1.5 mV.

fine the proximity of coronary artery and to prevent their damage. Safety distance for ablation from the coronary artery was considered about 10 mm. RF energy was delivered at areas with late potentials, fragmented potentials until their abolishment or decreased amplitude by 85%. Entry and exit VT sites and conducting channels were ablated. When a VT cycle was mapped, the critical isthmus of tachycardia was ablated.

RF energy 40-50W was used, application duration - 10-40 sec, ablation catheter tip irrigation was 30 ml/min. Ablation was considered effective if late potentials and fragmented potentials vanished and loss of stimulation capture was achieved (amplitude of stimulation 10 V, time duration 1 ms, cycle length - 500 ms). After substrate ablation programmed stimulation for VT induction was performed. Acute procedure effectiveness was considered when VT was non-inducible.

The mean follow-up period was 20.2±16.1 months (from 2 to 46 months). VT recurrences were documented by ICD/CRT-D regular check-ups, and 24-hour Holter monitoring.

Statistical analysis

Continuous data with normal distribution were reported as mean ±s tandard deviation, compared by T-test. Categorical variables were expressed using non-parametric statistics, median with interquartile range (IQR). Mann-Whitney test and Fischer exact test were used for comparison non-parametric variables. Results were considered significant with a P-value <0.05. Statistical analysis was provided using STATISTICA 6,0 (StatSoft, Tulsa, USA).

RESULTS

Patient clinical characteristics

The study group included 13 patients, the mean age 58.1±9.8 years (12 men). Clinical characteristics are presented in table 1. Antiarrhythmic drug (AAD) therapy with a combination of amiodarone and beta-blockers was used in 9 patients, in 3 patients amiodarone was discontinued because of complications, and only beta-blockers were prescribed. In one patient without ICD AAD therapy was limited by symptomatic sinus bradycardia (nebivolol 2,5 mg per day). In nine patients the combined endo-epicardial access was used as a first-line approach. Endocardial ablation of postinfarction VT was previously performed in four patients, procedures were ineffective or with temporary effect (1-2 attempts). In one patient with two previous ineffective attempts of endocardial VT ablation three consecutive epicardial procedures were performed due to clinical VT recurrence. Final ablation was successfully performed using bipolar ablation because of intramural location of the tachycardia critical zone. Transmural postinfarction scar location was detected by cardiac MRI in two patients. Epicardial access was obtained in 12 of 13 patients, in one patient it was unsuccessful, presumably because of pericardial adhesions on diafragmatic surface of the heart. In one case comparative analysis of endocardial and epicardial electroanatomical voltage maps was not performed because of a technical failure. Thus, comparative analysis of endo - and epicardial voltage maps was performed in 11 patients.

Mapping and ablation

Electroanatomical voltage maps were created with the color threshold 5-10 mm (when an ablation catheter was used for mapping) and the color threshold 2 mm (when the multielectrode catheter was used for mapping). The mean epicardial mapped surface area prevailed above endocardial surface area because epicardial mapping included evaluation of both ventricles.

The prevalence of a median substrate surface area of unipolar voltage maps over bipolar voltage maps by 3.7 times was noted on the endocardial surface (45.8

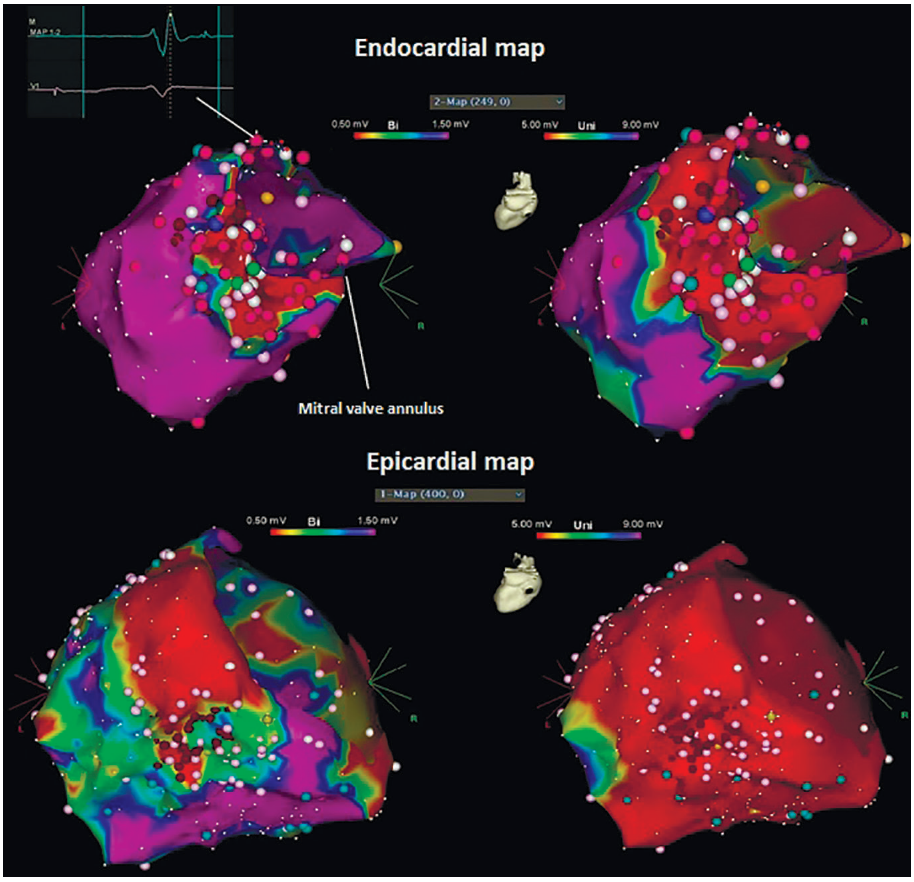

Figure 2. Patient №1. Endocardial and epicardial maps (bipolar and unipolar). Posterior projection. Bipolar map cut off values 0.5-1.5 mV, unipolar cut off values 5.0-9.0 mV. Pink tags represent sites with late potentials. The epicardial abnormal electrogram area prevails above the endocardial area. The unipolar low voltage area is more extensive than bipolar. The wide inferior myocadial involvement is seen on the unipolar map, while the bipolar map shows mainly lateral wall involvement.

(IQR:17.1;86.5) cm^2 vs 11,8 (IQR: 2.0;31.6) cm^2; p=0.035) (Table 2). Only in one patient the bipolar substrate area dominated over the endocardial unipolar map (by 2,5 times). There was no any abnormal electrical activity or low voltage signals registered on the epicardial surface. In one case there was no low-voltage substrate on the endocardial bipolar map, and was hardly represented on the unipolar map.

The median epicardial arrhythmogenic substrate area on the unipolar map prevailed over the same on the bipolar map by 2.3 times: 107.7 (IQR: 84.3; 168.9) cm^2 versus 46 (IQR: 15.9; 55.5): p=0.041 (Figure 1). Low-voltage areas were not found on the epicardial map in one patient (Figure 2); in two cases the endocardial substrate area was wider than epicardial arrhythmogenic substrate (table 2). We found no correlation between the substrate area on the endocardial and epicardial surfaces.

Table 1.

Patient clinical characteristics

Parameter	Value
Remote myocardial infarction, n (%)	13 (100)
Hypertension, n (%)	10 (76,9)
Diabetus melitus, n (%)	3 (23)
COPD, n (%)	1 (7,7)
Atrial fibrillation, n (%)	6 (46,2)
ICD, n (%)	9 (69,3)
CRT-D, n (%)	2 (15,4)
Patients with remote SCD, n (%)	10 (76,9)
ICD shock, n (%)	4 (30,8)
External shock, n (%)	7 (53,8)
Mean LV EF, %	38,8±10,6
Mean LV EDV, ml	193,8±73,7
Mean LV ESV, ml	125,3±54,9
Coronary angiography	
Without HSS, n (%)	9 (69,3)
PTCA and stenting, n (%)	5 (38,5)
Repeated PCI, n	2 of 5 patients
CABG, n (%)	0
TTE, scar localization	
Inferioir wall, n (%)	10 (76,9)
Lateral wall, n (%)	7 (53,8)
Apex, n (%)	2 (15,4)
Septum, n (%)	4 (30,8)
Anterior wall, n (%)	2 (15,4)

Description. COPD -chronic obstructive pulmonary disease, ICD - implantable cardioverter-defibrillator, CRT-D - cardiac resynchronization therapy defibrillator, LV EF - left ventricle ejection fraction, LV EDV - left ventricle end-diastolic volume, LV ESV - left ventricle end-systolic volume, HSS - hemodinamically significant stenosis, PTCA - percutaneous transluminal coronary angioplasty, PCI - percutaneous coronary intervention, SCD - sudden cardiac death, TTE - transthoracic echocardiography, CABG - coronary artery bypass grafting.

Late potentials and fragmented potentials were registered in nine patients: in seven cases - on the endocardial surface, and in six cases- on the epicardial surface. The areas of late potential registration in study patients is presented in table 2.

Two VT morphologies were induced before ablation in 4 patients, in 4 patients only one clinical VT morphology was induced, and in 4 patients VT was non-inducible.

Endocardial and epicardial scar location coincidence was noted in 8 cases. In one patient a scar was detected on the epicardial surface only. In one patient the postinfarction scar was identified endocardially only in the interventricular septum. In one case, there were different endocardial and epicardial scar localizations: an endocardial scar was identified on the inferior and septal walls, an epicardial low voltage activity was detected on the lateral RV wall.

Fragmented potentials and late potentials were detected in 9 patients, RF ablation was performed in these areas in all cases.

The mean procedure time duration was 228±62 minutes, the mean fluoroscopy time duration was 45±21 minutes. In 12 patients VT was non-inducible at the end of procedure, in two of them ventricular fibrillation was induced by an aggressive stimulation protocol. Thus, in 12 of 13 cases complete acute effect was achieved. In one patient the procedure was discontinued because of haemopericardium occurrence.

Complications

In one patient with unsuccessful epicardial access (there were adhesions on the inferior wall of LV), an attempt of transseptal puncture was performed with cardiac perforation and haemopericardium, which required surgical correction. There were no complications, associated with the epicardial access itself.

Long-term results

The mean follow-up period was 19.3±17.6 months. Two of 11 patients, who were operated using the epicardial access, were lost to follow-up. In three patients, the follow up period was less than 6 months; VT recurrence was not evident during this period of observation. In one patient with multiple ablation sessons (6 procedures in total) VT recurrence was not registered during 3-years follow-up. In one patient VT recurrence registered 1 year after the procedure: 11 VT paroxysms with ATP therapy registered and 1 shock because of acceleration VT to VF after ATP therapy at two years. Two of four patients with previous ineffective endocardial VT ablation were free from VT recurrence after combined endo-epicardial VT ablation.

DISCUSSION

VT substrate can be localized on both endocardial and epicardial surfaces in patients with remote myocardial infarction. In our pilot study among 11 patients with sustained postinfarction VT, electrophysiological VT substrate was identified epicardially in 82% of cases. Some patients with previous ineffective attempts endocardial ablation VT substrate epicardial mapping and ablation is an advisable approach, as it was noted in two of four patients.

In 2000 Sosa E. and colleagues published results of their study of epicardial mapping VT substrate in patients with remote inferior myocardial infarction. Subepicardial myocardium involvement in re-entry loop was demonstrated in 7 of 30 registered VT (23%) for 7 of 14 patients [11]. The presence of an epicardial substrate in patients with postinfarction VT was noted in the research published by Brugada J. and colleagues [3]. It has been demonstrated that unipolar scar surface area prevailed over the same on the bipolar map, that could be evidence of epicardial localization VT substrate [14]. In our research, we obtained similar findings.

The combined endo-epicardial approach demonstrates effectiveness in long-term period as a first-line approach, and after previous endocardial ablation as well. Recently, the application of the combined endo-epicardial access in patients with VT recurrence with previous ineffective endocardial VT substrate ablation was published [3, 15]. Nowadays, a multicenter randomized EPILOGUE clinical study is going, where patients with postinfarcton VT are allocated into the group of first-line combined access or into the group of sequential endocardial approach followed by epicardial ablation one a VT recurrence is detected [16].

The scar area is a target for radiofrequency ablation, it is defined on the bipolar map as myocardial signal <0.5 mV, zones with abnormal electrical activity (late potentials), as described by Nakahara S and Tung R and co-workers [17] for epicardial VT substrate in patients with ischemic cardiomyopathy. In this study late potentials were detected on both the epicardial surface and endocardial surfaces. Late potential elimination was associated with effective epicardial ablation.

Our findings comfirm previous results by Schmidt B et al. [18]. The authors demonstrated that 30% of patients with postinfarction VT, who were ablated repeatedly with the epicardial access, had both endocardial substrate and epicardial substrate, epicardial substrate only was detected in 30% of patients at the second procedure. In our study, 7 of 11 patients who underwent the combined endo-epicardial ablation had a coincidence arrhythmogenic substrate localization on the endocardial and epicardial surfaces. In four of 11 patients previous endocardial VT ablation was carried out.

The necesserity of epicardial access can be expected during the invasive procedure when an endocardial unipolar low-voltage area map prevails over bipolar low-voltage are; when ECG criteria of epicardial localization of induced VT are present; when there is a lack of low-voltage are on the endocardial map, or excessive endocardial ablation is ineffective despite appropriate exit site or isthmus mapping [19, 20].

CONCLUSIONS

In our patient group with remote myocardial infarction and indications to VT catheter ablation, 82% of cases demonstrated transmural scar with electrophysiological signs of arrhythmogenic substrate on the epicardial ventricular surface. Subepicardial myocardium involvement should be suspected during endocardial mapping, when there is a prevalence of local abnormal electrical activity area on the unipolar map over the area on the bipolar map, and in cases of endocardial ablation failure.

We suggest that epicardial mapping and ablation is useful/advisable in some patients with postinfarction VT, who should be referred to centers experienced with complex electrophysiological procedures and epicardial ablation.

Table 2.

Voltage mapping

Patient number	Endocardial surface					Epicardial surface				
	Bipolar signals			Unipolar signals		Bipolar signals			Unipolar signals	
	<0.5 mV	>0.5-<1.5 mV	LP	<0.5 mV	>0.5-<1.5 mV	<0.5 mV	>0.5-<1.5 mV	LP	<0.5 mV	>0.5-<1.5 mV
1	8.6	6.0	25.2	45.8	14.6	54.6	315.2	0	417.1	23.7
2	2.3	0	0	2.6	25.0	46.0	2.0	49.8	77.5	64.4
3	1.7	7.5	4.1	27.8	22.9	49.9	26.1	19.8	122.1	45.0
4	11.8	12	44.1	81.6	23.7	19.7	29.7	0	574.1	45.2
5	21.9	23.8	0.7	8.6	49.6	0	37.3	0	0	17.1
6	0	0	3.5	2.0	7.6	56.4	35.0	47.2	125.0	40.1
7	66.8	63.5	18.3	88.9	55.9	124.5	650.7	29.3	212.8	569.7
8	344.5	91.2	22.4	84.1	93	166.8	439.4	30.5	91.1	487.9
9	28.6	22.3	0	109.2	195.7	19.5	39.7	0	99.6	19.4
10	47.3	172.6	52.7	152.2	159	2.4	19.5	19.5	107.5	491.8
11	0	0	0	25.5	64.4	12.3	32.1	9.3	35.4	42.9
Median (1 и 3 quartile)	11.8 (2.0; 31.6) *	12.0 (3.0; 43.7)	4.1 (0.4; 23.8)	45.8 (17.1; 86.5) *	49.6 (23.3; 78.7)	19.6 (12.3; 53.8) *	36.2 (30.3; 236.4)	14.4 (0; 29.7)	95.4 (52.2; 120.6) *	54.8 (40.8; 460.5)

Description. LP - late potentials, * - p<0.05.

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NEW APPROACHES FOR PREDICTING OUTCOMES IN PATIENTS WITH ATRIAL FIBRILLATION

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Aim: we aimed to assess the capabilities of "machine learning" methods in predicting remote outcomes in patients with non-valvular atrial fi brillation (AF).

Methods. From 2015 to 2016 234 patients with non-valvular AF were included in the study (median age 72 (65; 79) years; 50.0% men). During the median follow-up of 2.9 (2.7; 3.2) years 42 patients died, 9 patients had non-fatal acute cerebral circulatory disorders and 3 patients had non-fatal myocardial infarction (MI). These events in 52 subjects (22.2% from all patients included) were combined into a combined endpoint (death and a nonfatal cardiovascular accident at the stage of remote observation). The first 184 patients comprised a "training" group. The next 50 patients formed the "test" group. The following methods of «machine learning» were used in the analysis: classifi cation trees, linear discriminant analysis, the k-nearest neighbor method, support vectors method, neural network.

Results. Long-term outcomes were influenced by age, known traditional risk factors for cardiovascular diseases, the presence of these diseases, changes in intracardiac hemodynamics and heart chambers as evaluated by echocardiography, the presence of concomitant anemia, advanced stages of chronic kidney disease, and the administration of drugs associated with a more severe cardiovascular disease progression (amiodarone, digoxin). The best prognosis was created using the model of linear discriminant analysis, the complex neural network model, and the support vector machine.

Conclusion. Modern methods aimed at prognosis estimation seem to be of importance in cardiology. These methods include big data analysis and machine learning technologies. The methods require further evaluation and confirmation, and in the future they may allow correcting cardiovascular risks, using data from real clinical practice and evidence-based medicine at the same time.

Key words: atrial fibrillation; mortality; ischemic stroke; myocardial infarction; prognosis; machine learning; discriminant analysis; complex neural network

Conflict of Interest: nothing to declare.
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Atrial fibrillation (AF) is among the most common cardiovascular diseases [1]. The management of AF is described in Russian and foreign clinical guidelines [2-3]. Numerous methods are known for assessing the risk of cardiovascular accidents and treatment complications in AF patients (CHA_2DS_2-VASc, HASBLED, ATRIA scores) [4-6].

Most of the available risk scales are designed to assess the likelihood of complications. However, few scales affect clinical and anamnestic, demographic indicators, concomitant diseases and the therapy taken. In recent years, novel methods for predicting risks associated with the use of so-called. «machine learning» [7]. The combination of these methods allows us to quickly analyze large amounts of data to assess the risk of a specific event in a particular patient. These methods are successfully used in genetics, oncology, endocrinology [8-10].

This article will describe several examples of the use of such methods in a small study evaluating long-term outcomes in patients with a non-valve form of atrial fibrillation.

MATERIALS AND METHODS

On the basis of the University Clinical Hospital №1 of I.M. Sechenov First Moscow State Medical University (Sechenov University) for the period 2015-2016 included 234 patients with non-valvular AF, median age 72 (65; 79) years, 50.0% of men and women. The median follow-up was 2.9 (2.7; 3.2) years, during which

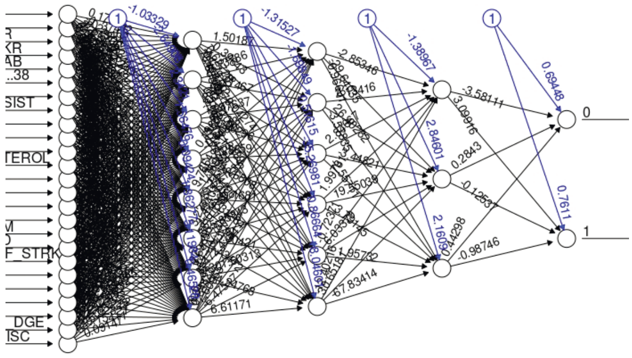

Figure 1. A multilayer perceptron with 13 "hidden" nodes used in this study.

time 42 patients died, 9 non-fatal acute cerebrovascular accidents and 3 non-fatal myocardial infarction (MI) occurred. These events in 52 patients (22.2% of all included) were summed into a combined endpoint (death and non-fatal cardiovascular catastrophes at the stage of remote observation).

The first 184 included patients formed a "training" group, the next 50 patients - the "test" group used for validation purposes. For the "training" group, regression analysis (Cox proportional risk model) was carried out to estimate the development of the combined.

Comparative analysis was carried out between the "training" and "test" groups (U - Mann-Whitney test for numerical data and Fisher's exact test for categorical data) to make sure that there are no significant intergroup differences.

Several "machine learning" methods were used for creating various predictive models. Factors, significant in Cox regression model, were used for model training. Afterwards, the models predicted outcomes for each patient of the "test" group, thus validating the models. Because the outcomes in the "test" group were known to researchers; a comparison was made of the true results and the results predicted by the models.

The accuracy, positive and negative predictive values, Cohen kappa were calculated to assess model quality. was calculated as an independent assessment of the quality of the model. ROC analysis was carried out for a number of models.

Modeling was performed using the R language v. 3.5.1 [11].

RESULTS

The study included 234 patients with a non-valvular form of atrial fibrillation, 50% of them were men. Median age was 72 (65; 79) years. A high prevalence of cardiovascular risk factors was noted: 11.5% were smokers, 92.7% diagnosed with arterial hypertension, 24.4% had type 2

Table 1
Comparative analysis between groups, assessment of factors significantly influencing on the "training" group prognosis (Cox regression analysis)

Factor	"Training" group, (n=184)	"Test" group, (n=50)	$p^{\#}$	Relative risk	95% CI	$p^{\$}$
Age	74 (66; 79)	70 (55; 78)	0.049*	1.1	1.0-1.2	<0.001
The presence of CHF	42.90%	34.00%	0.3	2.9	1.8-4.9	<0.001
The presence of vascular diseases	39.10%	34.00%	0.6	2.5	1.5-4.2	<0.001
Prior stroke history	12.50%	18.00%	0.4	2.8	1.6-4.9	<0.001
CHA_2DS_2-VASc, points	4 (3; 5)	3 (2; 5)	0.1	1.3	1.17-1.5	<0.001
Systolic blood pressure, mm Hg	135 (120; 155)	130 (115; 150)	0.4	0.9	0.8-0.99	0.027
Duration of QRS, ms	88 (84; 96)	96 (86; 110)	0.7	1.01	1.00-1.1	0.021
Left bundle branch block	13.60%	6.00%	0.2	2.4	1.3-4.4	0.006
Prior miocardial infarction	22.80%	14.00%	0.2	2.1	1.2-3.6	0.009
Total cholesterol, mmol/l	4.4 (3.6; 5.2)	4.6 (3.8; 5.6)	0.2	0.7	0.6-0.9	0.02
Indexed volume of the LA, ml/m^2	44 (39.7; 58.2)	41.6 (35.1; 54.4)	0.07	1.02	1.01-1.1	<0.001
Indexed volume of the RA, ml/m^2	36.9 (32.4; 44.7)	36.9 (28.3; 43.3)	0.56	1.02	1.01-1.1	<0.001
SPPA, mm Hg	33 (25; 36.5)	33 (33; 40)	0.7	1.02	1.01-1.3	0.005
GFR MDRD	60 (47; 71.4)	62 (51; 75)	0.3	0.97	0.96-1.3	<0.001
CKD stage	2 (2;3)	2 (2;3)	0.4	2.1	1.6-2.6	<0.001
Digoxin at discharge, %	7.10%	10.00%	0.5	2.5	1.2-5.4	0.02
HASBLED, points	2 (2; 2)	2 (1; 3)	0.2	1.8	1.4-2.4	<0.001
History of CVD , %	52.70%	52.00%	0.9	4.2	2.3-7.7	<0.001
Stable CAD, %	37.00%	24.00%	0.09	1.7	1.1-2.8	0.04
Local hypokinesis, %	15.20%	8.00%	0.2	2.3	1.3-4.2	0.006
Global contractility decrease, %	20.70%	20.00%	0.9	2.8	1.6-4.7	<0.001
Mitral regurgitation III, %	8.20%	4.00%	0.5	3.3	1.7-6.5	<0.001
Tricuspid regurgitation III, %	7.10%	6.00%	0.9	3.3	1.6-6.7	<0.001
Anemia, %	18.50%	16.00%	0.8	3.1	1.9-5.6	<0.001
Prior amiodarone intake, %	14.10%	4.00%	0.059	2	1.1-3.7	0.03

Description: $p^{\#}$ - significant differences between groups, CI - confidence interval, $p^{\$}$ - significant of prognosis, CAD - coronary artery disease, CHF - chronic heart failure, CKD - chronic kidney disease, CVD - cardiovascular disease, GFR - glomerular filtration rate, MDRD - Modification of Diet in Renal Disease Study, LA - left atrium, RA - right atrium, SPPA - pulmonary artery systolic pressure, * - at discharge diabetes mellitus. Dyslipidemia was detected in 61.5% of patients.

Among the whole group, cardiovascular risks and vascular catastrophes were widely recorded. A history of coronary heart disease (CHD) was diagnosed in 26.9% of patients, while 20.9% had a history of prior MI. In 41.0% of patients, symptoms of heart failure (HF) were noted, 13.7% previously had stroke, 5.1% had transient ischemic attack. Median score on CHA_2DS_2-VASc was 4 (3; 5) points, on the HASBLED - 2 (1; 2) points.

The first group consistently included 184 patients (78.6%) in the study group, the next 50 patients (21.4%) were included in the test group. Many works show the initial ratio of the data of «training» to the «test» data of 70.0% / 30.0% to 80.0% / 20.0% [7]. Also, the separation in accordance with the sequential switching time brings the experiment somewhat closer to real practice in the form of patients who are sequentially hospitalized or who came to see a doctor.

For the "training" group, a one-dimensional Cox regression analysis was performed to identify factors that significantly affect the development of the combined endpoint during remote observation. These factors, as well as the relative risk value, are presented in Table 1:

Long-term outcomes were influenced by age, changes in intracardiac hemodynamics by echocardiography, the presence of concomitant anemia and more severe stages of CKD, as well as prescriptions associated with more severe disease (prior amiodarone, digoxin on the long-term use at discharge).

According to these factors, a comparative analysis was carried out between the groups of «training» and «test», the results of which are given in table. 2:

Generally groups were comparable, with the exception of age (where differences were noted on the verge of significance). It is important to note that there were no significant differences either in the frequency of the combined endpoint or in the cardiovascular anamnesis.

Brief description of the methods used for "machine learning"

Classification trees

Trees combine regression and classification methods splitting of values and finding optimal threshold factor by factor. The result of numerous splitting is ultimately the classification of the object of interest Schemes of classification trees are quite clear and understandable both by researchers and doctors There are several algorithms for constructing classification trees (Random forest, building trees using boosting, and many others) [12].

Linear discriminant analysis

Methods underlying the linear discriminant analysis are somewhat similar to analysis of variance (ANOVA) and are associated with the search for best linear relationships between predictors. The analysis is sensitive to group size. The resulting linear interactions are somewhat reminiscent of linear regression analysis.

Table 2.

Evaluation methods predictive value classification

The method name	Accuracy	PPV	NPV	Cohen's Kappa
Classification Trees Random Forest, % (95% CI)	76.0 (61.8-86.9)	74.5 (59.7-86.1)	99.9 (37.3-99.9)	0.26
Classification tree C5.0 (with boosting), % (95% CI)	78.0 (64.4-88.5)	76.1 (61.2-87.4)	76.0 (39.8-99.9)	0.34
Simple 30-node neural network, % (95% CI)	78.0 (64.0-88.5)	80.0 (64.4-90.9)	70.0 (34.8-93.3)	0.42
Multilayer perceptron (3 layers of 17 neurons), % (95% CI)	82.0 (68.6-91.4)	79.6 (64.7-90.2)	99.9 (54.1-99.9)	0.48
Linear discriminant analysis, % (95% CI)	82.0 (68.6-91.4)	80.9 (65.9-91.3)	87.5 (47.3-99.7)	0.51
Reference vector meth, % (95% CI)	82.0 (68.6-91.4)	79.6 (64.7-90.2)	99.9 (54.1-99.9)	0.48
K-nearest-neighbours, % (95% CI)	76.0 (61.8-86.9)	74.5 (59.7-86.1)	99.9 (37.3-99.9)	0.28

Description: PPV - positive predictive value, NPV - negative predictive value, 95% CI - 95% confidence interval

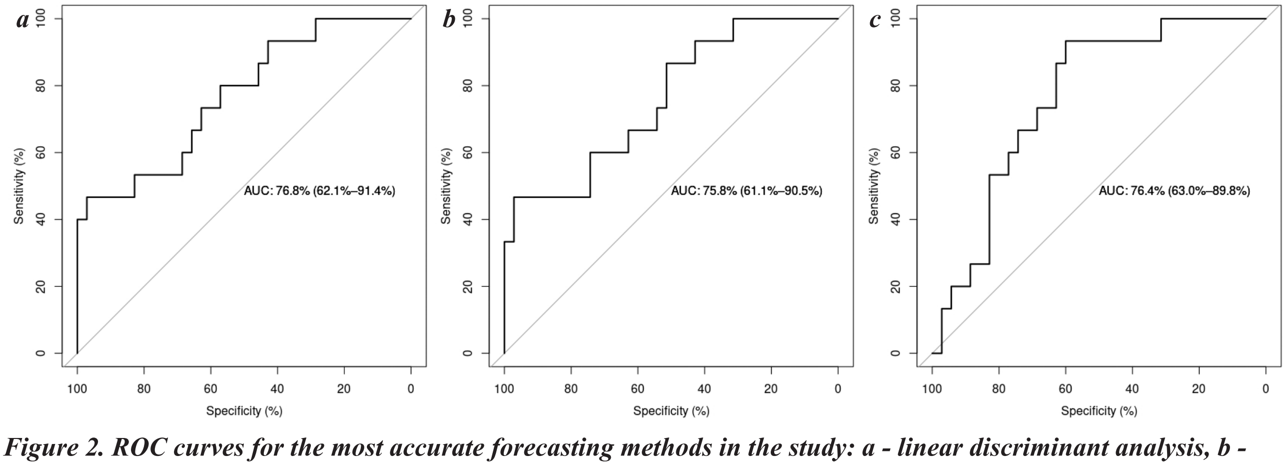

Figure 2. ROC curves for the most accurate forecasting methods in the study: a - linear discriminant analysis, b - support vector machines, c - multilayer perceptron.

The method of k-nearest neighbors

This method is close to cluster analysis when setting the number of outcome classes (in our case, there are two of them: the patient who has not reached the combined point and the patient who has reached the combined point). Each factor included in the analysis (for example, the age of the patients) is split according to the given class in terms of its average values and the distance between the average values in each class. Factors of interest are splitted thresholds are computed. Thresholds correlate with one of the predicted out come classes.

Support vector machines

The method is associated, on the contrary, with the maximum contrasts of 2 or more classes using linear and nonlinear methods. The method aims to find the largest possible separation between classes.

Neural networks

Neural networks are based on non-linear programming algorithms. The construction of neural networks occurs in analogy with the work of neurons of the nervous system, with the presence of signals, synapses, etc. The simplest neural networks solve classification problems (simplest option is a binary classification) of an object in accordance with its characteristics. Due to the logistic functions used, the "strong" and "weak" characteristics of an object can be equalized in terms of their influence on the classification decision. The size of the neural network determine the resource consumption for its creation and operation. Usually there are "hidden» nodes structures with complex nonlinear transformations. The construction of such a network is relatively slow.

Using several layers of «hidden» nodes, allow to use nonlinear methods for more flexible and complex classification problems.

A schematic representation of the neural network used in the trial is shown in Fig. 1. Fig. 2 on the left shows the input nodes with the main patient factors, on the right - the possible predicted outcomes - "1", when the patient is likely to develop a combined endpoint, and "0" when the patient's state does not change. In the middle we see 3 "layers" of 6, 4 and 3 neurons. These neurons are connected to each other by the so-called coefficients - "weights" (blue and black numbers), in some way reminiscent of coefficients in regression equations. The neuron itself is a complex non-linear function that calculates the probability of a particular outcome.

Assessment of the prognostic value of classification methods

Assessment is made on the predictive accuracy of the model, positive and negative predictive value, Cohen kappa coefficient. The results are presented in table. 3:

According to the value of 95% CI, the models of linear discriminant analysis, complex neural network, and support vector machines showed the best quality. Based on the Cohen's Kappa, the most accurate was the linear discriminant analysis model, followed by models using the support vector machines and a complex neural network.

To assess the sensitivity and specificity of the methods, ROC analysis was performed with the calculation of the area under the curve (AUC). In fig. Figure 2 shows some ROC curves of the most accurate methods:

Scientific and practical novelty

The aim of this trial was to demonstrate the possibilities of using machine learning methods in predicting long-term outcomes using typical clinical, medical, demographic characteristics of patients.

This approach will allow us to use routine examination data that the cardiologist enters in the electronic medical history, without the use of complex special scales and risk calculation techniques that require additional time from the doctor. An extremely important aspect is that the cardiologist receives information not about some abstract cardiovascular risks, but about the risk of a specific outcome or combination of outcomes in a given patient.

The scientific novelty lies in the fact that the forecasting methods are rarely used in the intersection of cardiology, epidemiology and practice. Classification prognostic models are usually built for a narrow specific problem [13]. At the same time, there can be wide perspectives for making prognosis in patients in "grey zones" of clinical guidelines. Of course, at the moment, comprehensive verification of machine learning in cardiology is needed.

DISCUSSION

Due to the fact that cardiovascular diseases are still among the three main causes of disability and mortality worldwide, the analysis of predicted outcomes is extremely important for the patient's life, physical condition and social activity. In articles where similar forecasting methods were used, it is carefully emphasized that the prognosis should be achieved by several independent modeling methods to reduce the likelihood of false results. Factors that influenced the risk of adverse long term outcomes in this study are not unexpected (for example, more than half of those included in the history of cardiovascular accidents), and have been described in modern clinical guidelines for many years.

The analysis above showed that machine learning methods show good results with respect to prognosis. The limiting factor was a small amount of the "training" group (184 patients), the choice of endpoints (mainly the combined point without analysis of the causes of mortality). Larger sample and shorter periods can theoretically increase the accuracy of the forecast.

Currently, the abilities of large medical centers and hospitals allow aggregating a large amount of patient data, introducing electronic document management, which can serve as a "playground" for testing and implementing such methods. An important aspect is the ability of the model to provide assessment of individual risks, taking into account many factors that significantly affect the forecast.

CONCLUSION

Evaluation of long-term outcomes in patients with AF appears to be an extremely important task due to the high prevalence of the disease and the severity of complications. Modern methods aimed at predictive assessment, using big data and machine learning technologies, represent great potential for cardiology. These methods require further critical confirmation, as in the long term, they can allow correcting cardiovascular risks, using both the data of real clinical practice and the concept of evidence-based medicine.

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ASSOCIATION OF HEMOLYSIS WITH THE INCIDENCE OF HEART RHYTHM DISTURBANCES FOLLOWING CORONARY ARTERY BYPASS GRAFT SURGERY

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Introduction: Coronary artery bypass grafting (CABG) might be associated with the development of heart rhythm disturbances.

We aimed at evaluating an association of intraoperative hemolysis (IOH) with the development of cardiac rhythm disturbances in patients with coronary artery disease after on-pump CABG.

Methods. The assessment of the degree of IOH was performed according to the level of plasma free hemoglobin [Hb] at baseline, immediately after the patient was connected to the cardiopulmonary bypass (CPB) device and 15 minutes before cessation of CPB. We included 123 patients, and they were divided into 3 groups (gr.) according to free [Hb] level: gr.1 - ≤0.1 g/l; gr.2 - > 0.1 g/l and <0,5 g/l; gr.3 - ≥0.5 g/l. A variety of ECG screening methods were applied for the detection of cardiac arrhythmia in the postoperative period. The follow-up period was 1 months.

Results. Arrhythmias were observed in 2.3% of patients in the 1st group, in 11.9% in the 2nd group, and in 52.6% in the 3rd group. The level of plasma free [Hb] in samples taken at the end of CPB was strongly associated with the arrhythmia detection (rs=0,70, p <0.001). Life-threatening and hemodynamically unstable arrhythmias were more frequently detected in the group with a higher degree of IOH (p <0.001), and accounted for about half of all arrhythmias.

Conclusions. On-pump CABG is associated with the development of cardiac arrhythmias in the postoperative period in 22% of patients. A significant proportion of these arrhythmias are potentially life-threatening. The highest proportion of patients with cardiac rhythm disturbances after CABG was observed when the level of plasma free hemoglobin was >0.5 g.

Kew words: ischemic heart disease; coronary artery bypass surgery; hemolysis; cardiac arrhythmias; ventricular tachycardia; atrial fibrillation; extrasystole; Holter monitoring

Conflicts of interest: nothing to declare
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Coronary artery bypass surgery (CB) in patients with coronary heart disease (CHD) can lead to the development of various complications in the postoperative period, among which arrhythmias are one of the leading ones [1-3]. Among one life-threatening arrhythmias - (ventricular fibrillation, ventricular tachycardia, atrioventricular block of the 3rd degree) and arrhythmias causing significant hemodynamic disturbances, or hemodynamically significant arrhythmias - paroxysms of atrial fibrillation, atrial fibrillation (AF), severe bradycardia and severe sinus tachycardia are distinguished [4]. AF is one of the most frequent and dangerous types of postoperative arrhythmias [5], which is referred to as hemodynamically significant arrhythmias and, according to various authors, is found in 25-65% of patients [6-8]. The effect of AF on long-term results has been shown, a connection is observed with the progression of heart failure and an increase in the frequency of thromboembolism, an increase in the length of hospitalization and mortality [2, 9, 10, 11]. In patients with AF after CB, an increase in mortality due to cerebrovascular accidents and myocardial infarction was noted [12]. The mechanisms of development of CB associated arrhythmias are complex, their pathogenesis is not complete understood. It has been shown that the occurrence of perioperative cardiac arrhythmias has a polyetiological character [10, 13, 14]. The development of arrhythmias in the perioperative and early postoperative periods is a reaction of the conducting system to the renewal of blood flow in the heart, which during the operation was under conditions of cold cardioplegia, and at the end of the operation it was exposed to heat in order to restore cardiac activity. Reoxygenation

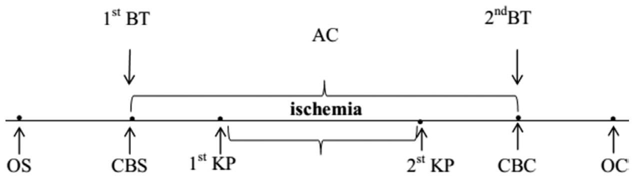

Figure 1. Diagram of the coronary bypass surgery operation. Note: CBS - cardiopulmonary bypass start, CBC - cardiopulmonary bypass completion, KP - cardioplegia, OS - operation start, OC - operation completion, 1st BT - first blood test, 2nd BT - second blood test.

during restoration of coronary blood flow leads to the development of oxidative stress, cellular and metabolic disorders, and contributes to the emergence of electrical myocardial heterogeneity [15]. It is assumed that the aggravation of these pathogenetic mechanisms can be caused by the destruction of red blood cells in the circuits of the cardiopulmonary bypass used during cardiac surgery to maintain blood circulation in organs and tissues and create optimal conditions for performing operations on a "dry" heart. The use of artificial circulation has a number of negative effects, among which there is a mechanical damage to blood cells [16, 17]. Hemolysis can affect the development of complications of the cardiovascular system, which can pose a threat to the life of patients after CB [18, 19]. However, in the literature there is no data about influence of intraoperative hemolysis (IOH) on the development of arrhythmias in patients with coronary artery bypass surgery. Purpose of the study to establish the connection of intraoperative hemolysis (IOH) with the development of cardiac rhythm disturbances in patients with coronary artery disease after coronary shunting in conditions of cardiopulmonary bypass (CB).

MATERIALS AND METHODS

A prospective study of 123 patients with coronary heart disease after the secondary school of the public health institution «Grodno Regional Clinical Cardiology Center» was performed. The study was consistent with the Helsinki Declaration of the World Medical Association «Ethical Principles for Conducting Scientific Medical Research with Human Participation» and was approved by the ethics committees of the Grodno State Medical University and the Grodno Regional Clinical Cardiology Center healthcare institution. All patients underwent CB surgery in a planned manner under IR conditions. According to the level of free hemoglobin [Hb] in blood plasma, which is a marker of the degree of IOH, patients are divided into three groups: group 1 - without IOH (Hb≤ 0.1 g/l), n=43, group 2 - with low IOH(lIOH) - with [Hb]>0.1g/l and <0.5 g/l, n=42, group 3 - with a high IOH (hIOH) corresponded to [Hb] ≥0.5 g/l, n=38 [19]. The degree of IOH was assessed by the level of free hemoglobin [Hb] in the blood plasma at the beginning of the operation, immediately after connecting the patient to the artificial device and 15 minutes before removal from the artificial device (Fig. 1), using a HemoCue Plasma / Low Hb analyzer, Sweden [20, 21].

Table 1.

Clinical characteristics and perioperative data

Indicator	Group 1 (n=43)	Group 2 (n=42)	Group 3 (n=38)
Age, years	60 (56; 63)	64 (58; 66)	66 (60; 68)
Gender (male), n (%)	36 (87.8%)	32 (78.0%)	31 (78.0%)
BMI, kg/m^2	27.8 (24.7; 29.2)	27.7 (24.8; 29.2)	29.1 (25.9; 32.2)
CHD duration, years	8.5 (4.2; 11.4)	8.9 (4.6; 10.8)	9.5 (6.2; 12.1)
Hyp, n (%)	36 (87.8%)	38 (90.2%)	38 (92.7%
Hyp duration, years	10 (6; 11)	8 (5; 10)	11.5 (9; 15)
Hyp FC II, n (%)	9 (20.1%)	11 (26.2%)	6 (15.8%)
Hyp FC III, n (%)	34 (79.9%)	31 (73.8%)	32 (84.2%)
PMICS, n (%)	37 (86.1%)	36 (85.7%)	33 (86.8%)
History MI, n (%)	16 (37.2%)	18 (42.8%)	13 (34.2%)
NYHA II, n (%)	36 (83.7%)	31 (73.8%)	33 (86.8%)
NYHA III, n (%)	7 (16.3%)	11 (26.2%)	5 (13.2%)
ICMP, n (%)	2 (0.86%)	3 (1.26%)	2 (0.76%)
Arrhythmias*, n (%)	7 (16.3%)	7 (16.6%)	6 (15.4%)
Paroxismal AF, n (%)	0 (9%)	1 (0.42)	1 (0.38%)
SVPB, n (%)	4 (1.72%)	2 (0.84)	2 (0.76%)
VPB, n (%)	1 (0.43%)	1 (0.42%)	1 (0.38%)
RBBB, n (%)	1 (0.43%)	1 (0.42%)	1 (0.38%)
LBBB, n (%)	1 (0.43%)	2 (0.42%)	2 (0.76%)
Chronic bronchitis, n (%)	7 (16.3%)	9 (21.4%)	12 (31.6%)
Gastropathy, n (%)	18 (41.9%)	17 (40.5%)	20 (52.6%)
Urolithiasis, n (%)	6 (13.9%)	9 (21.4%)	7 (18.4%)
Osteoarthritis, n (%)	0 (0%)	3 (7.1%)	1 (2.6%)
Excess BMI, n (%)	22 (51.2%)	18 (42.9%)	18 (47.4%)
Obesity, n (%)	14 (32.6%)	13 (31%)	15 (39.5%)
Total protein, g/l	69 (62; 71)	69 (58; 68)	66 (57; 67)
Glucose, mmol/l	5.0 (4.5; 5.6)	5.2 (4.4; 6.1)	5.3 (4.5; 6.2)
Cholesterol, mmol/l	4.1 (3.3; 5.0)	4.6 (3.2; 5.7)	5.0 (4.6; 5.6)
Urea, mmol/l	5.3 (4.8; 5.6)	6.0 (5.5; 7.6)	6.4 (5.5; 7.2)
Creatinine, mmol/l	99 (89; 104)	105 (98; 110)	106 (99; 112)
CRP, mg/ml	1.2 (0.8; 1.4)	1.1 (0.8; 1.3)	1.0 (0.6; 1.2)
IRT, min	69 (65; 89)	74 (68; 78)	80 (75; 94)
Ischemia time, min	46 (39; 64)	58 (56; 62)	59 (51; 68)

Description: quantitative data are presented as Me [LQ; UQ], where Me is the median, LQ and UQ are the values of the lower and upper quartiles, categorical values are presented in absolute and relative values. BMI - body mass index, CHD - coronary heart disease, Hyp - hypertension), FC - functional class, PMICS - postmyocardial infarction cardiosclerosis, MI - myocardial infarction, NYHA - New-York Heart Association, ICMP - ischemic cardiomyopathy, AF - atrial fibrillation, SVPB - supraventricular premature beats, VPB - ventricular premature beats, RBBB - right bundle branch block, LBBB - left bundle branch block, CRP - C-reactive protein, IRT - ischemia-reperfusion time.

Patients of all groups are comparable by age and gender (Table 1). All patients underwent surgical intervention using a standard anesthetic protocol under normothermic artificial sirculation conditions with a hemodilution level of hematocrit of 25-30%. The groups did not differ in the duration of artificial sirculation and the time of myocardial ischemia (p> 0.05), Table 2. Most patients (85%) underwent mammary-coronary bypass surgery in combination with aortic-coronary bypass surgery. Mammary-coronary bypass surgery was performed in 4% of patients (p <0.05), aortic-coronary bypass surgery - in 11% of patients (p <0.05). Groups were comparable in frequency (p> 0.05). More often, lesions of three or more coronary arteries, CA (63.1%) and significantly less often than one CA (7.1%) were revealed, Table 3.

Accordingly, with myocardial revascularization, three or more coronary arteries (CA) were shunted more often - 56.9% of patients. The most common lesions were observed in the anterior interventricular branch of left coronary artery(p <0.05), posterior interventricular branch of the of left circumflex artery (p <0.05) and the left marginal artery (p <0.05). Table 4 presents the nosological characteristics of patients.

Most patients had one previously suffered myocardial infarction, MI. Patient groups were comparable in the number of MI (p> 0.05), the presence of ischemic cardiomyopathy (p> 0.05) and a history of cardiac arrhythmias (A), p> 0.05. Table 4 presents the frequency and structure of cardiac arrhythmias in patients with varying degrees of intraoperative hemolysis before coronary artery bypass surgery. As you can see, before surgery, cardiac arrhythmias were found in 22 people (17.89%). Among cardiac arrhythmias, AF paroxysms, supraventricular and ventricular extrasystoles, as well as blockade of the right and left legs of the bundle of His were found. At the same time, AF paroxysms were observed in 2 (1.63%) patients, extrasystoles were found in 11 (8.94%), including supraventricular extrasystoles, and in 3 (2,44%) - ventricular extrasystoles were noted. Dysfunction of the conduction function was noted in 8 people (6.5%), including blockade of the left leg of the bundle of His was noted in 5 people (4.07%), blockade of the right leg of the bundle of His - in 3 people (2.44%). The groups were comparable in the frequency and nature of cardiac arrhythmias in the anamnesis (p>0.05).

Patients before CB (1-5 days) and after surgery (within 1-5 days) underwent daily ECG monitoring, as well as standard electrocardiography (ECG). In order to clarify the role of hemolysis in the development of postoperative arrhythmias in the studied groups of patients with different levels of IOH, we analyzed the incidence of cardiac arrhythmias in the perioperative (during the operation and during the first day after it) and in the early period (up to 1 month) and their structure [1].

The examined patients received standard therapy consisting of antiplatelet agents (79.7%), statins (76.4%), beta-blockers (84.6%), angiotensin-converting enzyme inhibitors (76.4%), antianginal drugs (79.7%), table 5.

The drug treatment among patients of the studied groups did not differ in the administration of aspicard and clopidogrel (χ^2 = 5.35; p = 0.069), β-blockers (χ^2 = 3.18; p = 0.204), but it differed in the reception of statins (χ^2 = 12.2; p = 0.006), inhibitors of the angiotensin-converting enzyme, ACE inhibitors (χ^2 = 7.13; p = 0.028) and antianginal drugs (χ^2 = 13.7; p<0.001). In particular, fewer patients in the third group took statins (57.9%, p <0.05), inhibitors (63.2%, p<0.001) and antianginal drugs (60.5%, p<0.001). Patients with a history of cardiac arrhythmias (paroxysmal AF) were treated with antiarrhythmic drugs 5-7 days before surgery.

To prevent arrhythmias during the operation, lidocaine was infused in a cardioplegic solution

Table 2.

Characterization of bypass grafts in patients with coronary heart disease in groups with different levels of IOH

	Group 1 (n=43)	Group 2 (n=42)	Group 3 (n=38)	p_{1-2}	p_{1-3}	p_{2-3}
1 bypass graft, %	9.9	7.5	10.8	0.412	0.510	0.314
2 bypass grafts, %	31.0	26.8	39.2	0.510	0.610	0.094
≥3 bypass grafts, %	59.1	65.7	50.0	0.462	0.130	0.318
LAD, %	87.8	100	100	0.21	0.31	0.31
CFX, %	4.9	7.3	19.5	0.644	0.420	0.105
PDA CFX, %	14.6	39.0	61.0	0.210	0.310	0.406
OM, %	56.1	65.9	80.5	0.172	0.22	0.324
RCA, %	24.4	58.5	61.0	0.231	0.341	0.821
PDA RCA, %	17.07	34.15	26.8	0.706	0.285	0.471

Description: LAD - left anterior descending, CFX - circumflex artery, PDA - posterior descending artery, OM - obtuse marginal branch, RCA - right coronary artery.

Table 3.

Characterization of drug therapy for examined patients with coronary artery disease before coronary artery bypass surgery with varying degrees of IOH

	Group 1 (n=43)	Group 2 (n=42)	Group 3 (n=38)	All (n=123)	χ^2	p
Beta blockers,%	86.0	90.5	76.3	84.6	3.18	0.204
ACE inhibitors, %	88.4	76.2	63.2*	76.4	7.13	0.028
Statins, %	90.7	78.6	57.9*#	76.4	12.2	0.006
Antianginal, %	93.0	83.3	60.5*#	79.7	13.7	0.0001
Antiplatelet agents, %	88.4	81.0	68.4	79.7	5.35	0.069

Description: ACE - angiotensin-converting enzyme, * - p <0.05 - statistical differences with the group without IOH, # - p<0.05 - with the group with lIOH.

(1-1.5 mg / kg /min). After the operation, antiarrhythmic drugs were administered to arrest AF paroxysm (AF - 5 mg /kg intravenously dropwise for 60 min). Patients after CB took β-blockers (atenolol 25-50 mg / day, metoprolol at a dose of 25-50 mg / day, bisoprolol at a dose of 2.5-5 mg / day) depending on the level of blood pressure. In patients with atrial flutter and ventricular tachycardia in the perioperative period, temporary atrial pacemaker was performed, which was maintained for 72 hours with a frequency of 10 beats / min more than their own heart rate.

Statistical data processing was carried out using the program Statistica 10.0 for Windows (StatSoft, Inc., USA). Given the abnormality of the distribution of attributes, nonparametric methods of descriptive statistics were used for processing: quantitative data are presented in the form Me [LQ; UQ], where Me is the median, LQ is the value of the lower quartile; UQ is the value of the upper quartile; categorical data are presented in the form of absolute and relative frequencies. When comparing the medians of quantitative variables of several independent groups, the Kruskell-Wallis test was used, to compare categorical data, the exact Fisher test, the $\chi 2$ criterion, with the Yeats correction at low frequencies were used. The strength of the relationship between the indicators was estimated using a correlation analysis based on the association coefficient (Kendall criterion) by its value (rs ≤0.25 - weak; 0.25 <rs <0.75 - moderate and ≥0.75 - strong). In order to check the dependence of the incidence of arrhythmias on the degree of IOG, determined by the level of free hemoglobin, a logistic regression analysis and ROC analysis were performed in the statistical program SPSS Statistics 21.0 (SPSS, USA). Differences were considered significant at p <0.05.

RESULTS

Of the 123 examined with CB, 29 (23.6%; p<0.001) patients had cardiovascular complications. Moreover, complications in the perioperative period were noted in 17 people (13.8%, p> 0.05), in the early period - in 13 people (10.6%, p> 0.05). More often, in the operated patients, arrhythmias were revealed in 27 patients (21.95%, p <0.001), less often - heart failure progression - in 12 patients (9.8%, p<0.001), 5-person CB-associated myocardial infarction developed (4.1%; p = 0.003), and stroke in 2 patients (1.6%, p = 0.323).

The most common complications of CB during myocardial revascularization in patients with coronary artery disease were various types of arrhythmias, which were observed both in the perioperative period and during the month of observation - an early period (Table 6).

After surgery, arrhythmias developed in 27 (21.95%) patients. At the same time, 5 (4.9%) patients had life-threatening arrhythmias (ventricular fibrillation, ventricular tachycardia), 7 (5.7%) patients had hemodynamically significant arrhythmias - atrial fibrillation and flutter, supraventricular tachycardia. Atrial fibrillation was the most common type of postoperative arrhythmias (5.7%, p<0.001), which is consistent with the literature [5]. In 11 (8.9%) patients after CB, other types of arrhythmias (supraventricular extrasystoles and ventricular extrasystoles of I-II classes (according to the classification of Myerburg RJ, 1984), as well as AV blockade of the 1st or 2nd degree) were observed, accounting for about half of the occurring during and after surgery arrhythmias.

Most often, arrhythmias were observed in patients with a high degree of IOH (Table 7). In the group with high IOH, the frequency of arrhythmias was 52.6%, which is higher than in the group with low IOH - 11.9%, p <0.001 and in the group without IOH - 2.32%, p<0.001 (table 8).

As can be seen from the table, in patients of the second (lIOH) and third (hIOH) groups, arrhythmias were more common than in the first group (without IOH), p<0.001, and in patients of the 3rd group more often than in the second group, p <0.001. Moreover, a significant part of arrhythmias (10.5%) in patients of the third group belonged to life-threatening arrhythmias and hemodynamically significant arrhythmias (13.2%). In 21.1% of patients with hIOH, other types of arrhythmias were noted (p <0.05).

On the 1st day after CB (perioperative period), arrhythmias were noted in 14 patients, 11.4%, p <0.00. Most often (26.31%) of perioperative period arrhythmias were noted in the third group with hIOH, p <0.001). Life-threatening and hemodynamically significant arrhythmias in this period in the group with a high degree of IOH accounted for about half of all arrhythmias, which is significantly more than in the 1st and 2nd groups, p <0.001.

In the early period, arrhythmias developed in 10.6% of examined patients with CB. In the group with hIOH, arrhythmias were observed in 10 (26.3%) patients, in the group with lIOH - in 3 people (7.14%, p<0.001), in the group without IOH - arrhythmias were not observed (p<0.001).

Correlation analysis using the non-parametric Kendall criterion (Rs) revealed the presence of associations between the indicator characterizing the degree of IOH - [Hb] in blood plasma and the frequency of arrhythmias in the postoperative period (Rs = 0.70, p <0.001), including in perioperative period (Rs = 0.46; p <0.001) and in the early period (Rs = 0.33; p <0.001) after CB.

Table 4.
Frequency and structure of arrhythmias in patients with coronary artery disease after CBS

	Частота аритмий			p
	All	PP	EP	
Total, n (%)	27 (22.0)	14 (11.4)	13 (10.6)	>0.05
VF, n (%)	3 (2.43)	2 (1.63)	1 (0.81)	>0.05
VT, n (%)	3 (3.25)	3 (2.43)	-	>0.05
AFib, n (%)	7 (5.70)	3 (2.43)	4 (3.25)	>0.05
Afl, n (%)	2 (1.62)	1 (0.81)	1 (0.81)	>0.05
SVT, n (%)	1 (0.81)	-	1 (0.81)	>0.05
AVB_{1-2}, n (%)	2 (1.6)	-	2 (1.6)	>0.05
VPB, n (%)	5 (4.1)	4 (3.25)	3 (2.43)	>0.05
SVPB, n (%)	4 (3.3)	1 (0.81)	3 (2.43)	>0.05

Description: PP - postoperative period, EP - early period, VF - ventricular fibrillation, VT - ventricular tachycardia, AFib - atrial fibrillation, Afl - atrial flutter, AVB - atrioventricular block, VPB - ventricular premature beats, SVPB - supraventricular premature beats

A correlation analysis revealed a moderate associative relationship between postoperative arrhythmias and a history of arrhythmias (Rs=0.4167, p=0.000003). There were also weak associations of the frequency of arrhythmias with the duration of the operation (Rs = 0.21, p = 0.018) and the time of clamping of the aorta (cardioplegia, Rs = 0.19, p = 0.026).

Based on logistic regression and ROC analysis, data were obtained that testify to the significance of the [Hb] indicator in assessing the likelihood of arrhythmias (Fig. 2).

A high risk of developing arrhythmias in patients with coronary heart disease after CB was determined with a value of [Hb]>0.85 g/l (sensitivity - 86.4%, specificity - 92.7%, PPV (predictive value of a positive result) = 96.9 %, NPV (predictive value of a negative result) = 70.4%, area under the ROC-curve (AUC) = 0.892 (0.803-0.981), 95% confidence interval.

DISCUSSION

As noted earlier, before the operation, cardiac arrhythmias occurred in 22 people (17.89%). Among arrhythmias, AF paroxysms, supraventricular and ventricular extrasystoles, as well as blockade of the right and left legs of the bundle of His were found. AF paroxysms were observed in 2 people (in 1 - in groups with lIOH and in 1 - in group with hIOH. The groups were comparable in history and frequency of arrhythmias in history (p>0.05). However, the incidence of arrhythmias in postoperative the period was highest in the third group with hIOH, and in the second group with lIOH it was greater than in the group without IOH According to the literature, the occurrence of arrhythmias associated with CB is caused by the restoration of blood flow in the ischemic zone, as a result of which the resumption of oxygenation initiates the development of oxidative stress [21]. Action a reactive forms of oxygen and nitrogen leads to structural and metabolic disturbances, manifested by damage to cell membranes, electrolyte imbalance, forming a state of electrical myocardial heterogeneity, impaired excitability, pulse generation and conduction in the heart. Post-traumatic remodeling of heart chambers can contribute to the development of arrhythmias [6, 7, 9].

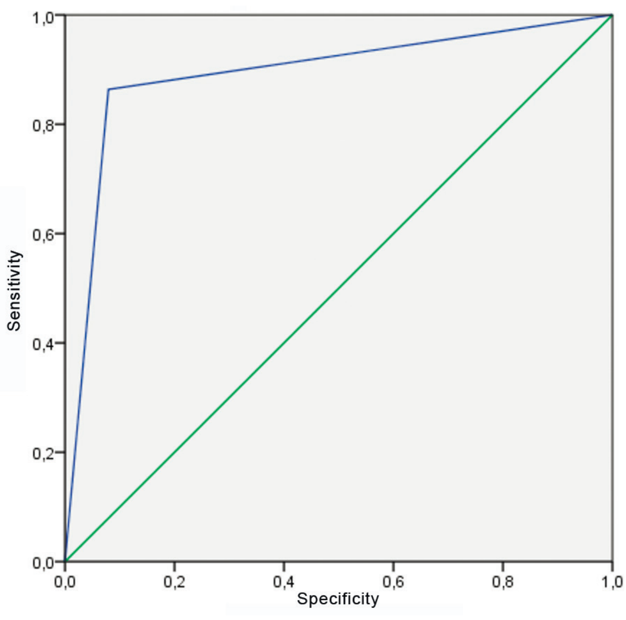

Fig. 2. ROC curve characterizing the sensitivity and specificity of the method for assessing the likelihood of developing postoperative arrhythmias by the concentration of free hemoglobin in blood plasma.

It was shown that not only the frequency of arrhythmias in groups after CB has changed, but also the structure. Transformation of less life-threatening arrhythmias (extrasystole, blockade of the bundle of His) into arrhythmias was noted, which had more serious consequences for hemodynamics and posed a greater threat to the lives of patients (atrioventricular block of the 1st degree, atrial fibrillation and flutter, paroxysmal ventricular and supraventricular ventricles).

Some authors have identified the relationship between arrhythmias and the features of surgical treatment (inadequate myocardial protection during surgery, due to the composition of the cardioplegic solution used, the direction of its administration, temperature, and the duration of cardioplegia). A positive correlation was revealed between the occurrence of arrhythmias and the duration of IR, the intensity of inotropic support, blood transfusion, and the level of leukocytosis after surgery [13]. Other authors have not found such a dependence on the duration of artificial circulation [22, 23].

CB has been shown to be most conducive to the development of arrhythmias in patients who had morphological changes in the heart (post-infarction cardiosclerosis) and a history of arrhythmias [12, 23].

Studies on the study of arrhythmias after CB using correlation, as well as logistic and ROC analysis revealed the dependence of the frequency of arrhythmias on the level of free hemoglobin as an indicator of the degree of intraoperative hemolysis. The destruction of red blood cells due to their mechanical damage in the artificial circuits of the exerts a pathogenic effect on the state of the rhythmogenic function of the cardiac conduction system and myocardial excitability, predisposing to the development of arrhythmias. The largest number of arrhythmias in the group with a high level of free hemoglobin, as well as the presence of correlation between the frequency of arrhythmias and [Hb] In the blood plasma at the end of the operation, as well as the results of the logistic and ROC analysis, indicate the important role of intraoperative hemolysis in their occurrence in perioperative and early periods. The pathogenetic role of free hemoglobin in the development of rhythm disturbances in CB, it is advisable to develop a set of perioperative preventive measures aimed at chelation of free iron, which reduce the activity of oxidative processes. Elimination of patient-dependent risk factors for increased hemolysis (smoking, alcohol consumption, normalization of blood pressure, body weight and cholesterol) is also important for the prevention of cardiac arrhythmias, as one of the most common complications of coronary artery bypass surgery.

CONCLUSIONS

Coronary artery bypass surgery in cardiopulmonary bypass leads to the development of arrhythmias in the postoperative period in 22% of patients with coronary heart disease. A significant proportion is arrhythmias, which pose a threat to the patient's life and arrhythmias that cause hemodynamic disturbances and hypoperfusion of vital organs.

The largest number of patients with cardiac arrhythmias after coronary artery bypass grafting was noted in the group with a plasma hemoglobin level of 0.5 g/l or more ($p<0.001$), which indicates a relationship between the occurrence of arrhythmias and the degree of intraoperative hemolysis. A high risk of arrhythmias in patients with coronary heart disease after coronary artery bypass surgery is determined when the content of free hemoglobin is more than 0.85 g/l.

One of the directions for assessing the risk of developing heart rhythm disturbances should be to determine the level of free hemoglobin in the blood plasma of patients in the intraoperative period of coronary artery bypass grafting, which is necessary for the timely prevention and correction of possible hemodynamic disturbances.

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LEFT MAIN CORONARY TRUNK SPASM DUE TO ACCIDENTAL CATHETER ABLATION IN THE ARTERY OSTIUM

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The results of the examination and treatment of a patient with frequent ventricular ectopy are presented in the article. During ablation of an ectopic focus in the left coronary sinus of the aorta, as a result of dislocation of the ablation catheter, a spasm of the left coronary artery has been diagnosed and successfully managed.

Keywords: ventricular ectopy; radiofrequency catheter ablation; coronary sinus of aorta; ablation catheter; main left coronary trunk; intracardiac echocardiography

Conflict of Interests: nothing to declare
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Coronary artery (CA) damage during radiofrequency ablation (RFA) for cardiac arrhythmias is a dangerous complication, requiring urgent diagnosis and restoration of coronary blood flow. Nonetheless occurrence of such complication is extremely low. For example, presented data on the results of RFA in 4655 and 3357 patients, demonstrated incidence of this complication 0.09% and 0.029%, respectively [1, 2]. Literature data presented mainly by clinical examples which are difficult to systematize due to their individuality. There are no previous reports of the left CA (LCA) spasm during RFA for ventricular ectopy (VE). In this work, we demonstrate the case of complication and subsequent decisions in patient management.

Patient O., 32 years of age, was admitted to clinic with frequent VE in order to perform RFA, because of the main complaint of palpitations. Anamnesis data: arterial hypertension is not diagnosed, palpitations for two years, according to Holter ECG monitoring frequent single monomorphic VE were recorded in amount of 39 thousand with type of bi-, tri- and quadrigeminy, which served as a reason for planned intervention. The patient had not a significant concomitant pathology and had not received any antiarrhythmic therapy. An objective examination revealed arrhythmic heartbeat due to frequent ectopic beats; there were no abnormal findings in other organs and systems. The patient's ECG is shown in fig. 1. According to echocardiography, the sizes of heart chambers were within normal limits, the first degree of mitral valve prolapse without hemodynamic disturbance, left ventricular false tendon. Laboratory data without pathology.

Radiofrequency ablation procedure

the patient underwent an electrophysiological study (EPS) procedure. As a first stage an electroanatomical mapping (CARTO 3, Biosense Webster, Israel) of right ventricle was performed. Based on local activation time and pace mapping the early zone was defined in the septal region of the right ventricular outflow tract (RVOT), with local electrogamm advancing of -28 ms relative to QRS onset. However, pace mapping failed to achieve fully identity of stimulated complexes and an area of 'suboptimal' pacing criteria in RVOT was wide. This area was ablated with the following parameters: temperature -43°C, power 43W in irrigated mode at rate of 17 ml/min. During the RF applications, we repeatedly observed the effect of ectopic focus 'warming up' in the form of ventricular tachycardia with QRS-complexes similar to native VE morphology. We also observed short episodes of eliminated ectopic activity by the end of RF application. The total RFA time was 6 minutes. Due to inefficiency of RFA in RV, we decided to perform left ventricle mapping. Through the right femoral artery approach left ventricle and aortic sinuses were examined using ablation electrode. An earliest activation zone was located in the left coronary sinus, where the local electrogram activation time of -42 ms, and noted positive criteria during pace mapping (Fig. 2).

Further the distal pole of the mapping electrode was advanced at the LCA ostium, which was confirmed by contrast angiogram through an external irrigation circuit. The LCA ostium was marked on the activation map. The measured distance to the ectopic focus amounted to 12 mm, which is considered as acceptable safety [3]. During application ectopic activity disappeared at 6th second, according to temperature rising. RF application was supposed to continue till the target time of 60 seconds. At 40 second of exposure, electrode displaced toward the ostium of LCA, that initially was considered as an allowable change in position of the electrode due to a respiratory excursion, which led to the continuation of the application for 5 seconds more with a further cessation. Thus, the total RF exposure time was 45 seconds. After 10 seconds of RF discontinuation, an episode of ST segment depression in leads II, III and aVF up to 2 mm was observed, which lasted at *about 30 seconds. This episode was not accompanied by subjective manifestations and hemodynamic disturbances. Due to the presence of transient ischemic changes in the ECG and the proximity of the RFA zone to the ostium of LCA, coronary angiography (CAG) was performed, 60% stenosis of the left main trunk was detected, with negative nitroglycerin test, which was considered as LCA stenosis, but not a spasm. The right CA was without pathology. The LCA was reviewed with intravascular ultrasound (IVUS): the lumen area of LCA trunk was 5.04 mm^2, i.e. stenosis is interpreted as significant (Fig. 3).*

The IVUS results indicated to the presence of edema or persistent spasm. Based on the above data, decision was made in favor to conservative strategy of management. Overseeing in an intensive care unit and double antiplatelet therapy with aspirin and clopidogrel were assigned. The noticeable increase of troponin T up to 1.4 ng/l, creatinkinase and its MB fraction up to 135 and 26 U/l, respectively, was regarded as a manifestation of radiofrequency myocardial damage. Later, laboratory parameters returned to normal within 2 days. The patient's condition remained stable; there were no ischemic changes in the ECG. On the 5th day after RFA, control coronarography was performed. No data were found for stenosis of the LCA trunk (Fig. 4).

On the 7th day after RFA, with conditions of stable hemodynamics, no complaints and ischemic ECG changes, patient was discharged from the department. The VE were absent for the entire postoperative period.

With further observation, no complaints regard to cardiovascular system were noted. Three months later, bicycle ergometer exercise testing was performed: at a load of 100W, the test was terminated according to the criterion for achieving a submaximal heart rate of 160 beats/min with no ischemic changes. According to the results of Holter ECG monitoring, ventricular ectopic activity was absent. Control coronary angiography was performed 4 months after RFA; no pathology was detected. One year after, the patient's condition remained stable, which allowed us not to carry out follow-up examinations.

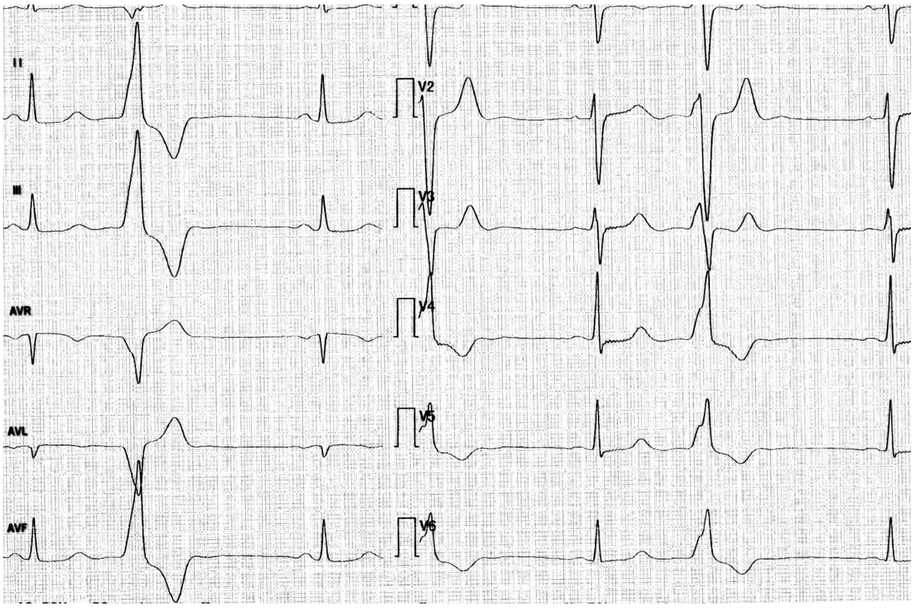

Fig. 1. Patient's electrocardiogram: sinus rhythm, frequent ventricular extrasystoles.

DISCUSSION

One of the first description of CA injury during RFA was made by P. Chatelain et al. in 1995 in the case of the left-sided accessory pathway ablation. [4]. Further publications, as mentioned above, indicated an extremely rare frequency of such complications. The damages of CA were represented as an acute occlusion of branches of the right CA and trunk of the LCA, which required immediate stenting of the corresponding arteries, or conservative strategy was adopted due to insignificant stenosis of the narrow ar-

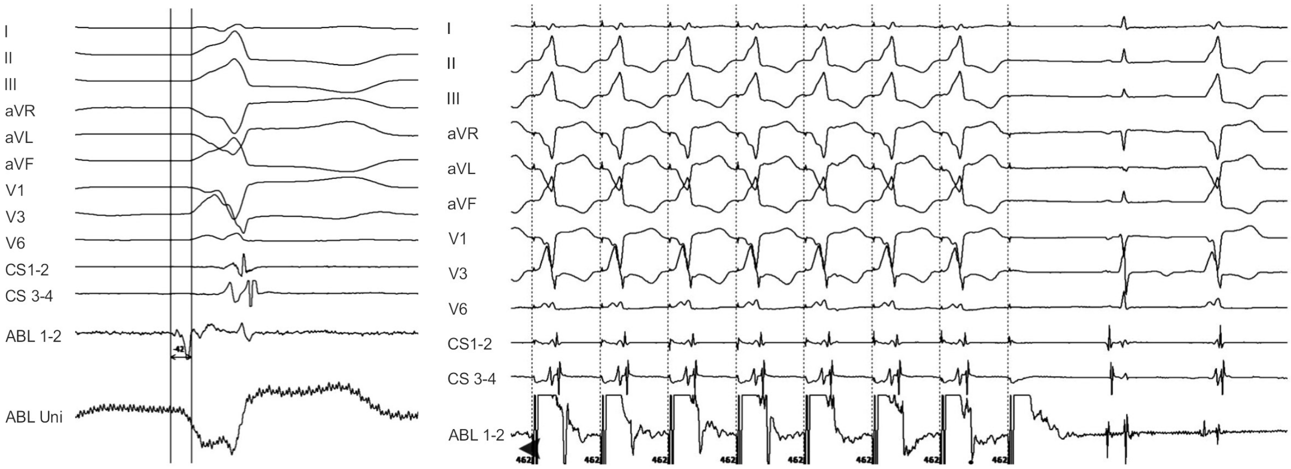

Fig. 2. Results of EPS. On the left panel the local electrogram activation time is -42 ms before the onset of QRS complex; on the right panel the identity of stimulated and spontaneous QRS complexes. I, II, III, aVR, aVL, aVF, V1, V3, V6 - surface ECG leads (leads V2, V4, V5 were not evaluated as less informative); CS 1-2 and CS 3-4 - bipolar electrograms from the coronary sinus; Abl 1-2 and abl Uni - bipolar and monopolar electrograms from the distal pole of ablation electrode.

tery [1, 5]. As well described cases of delayed development of CA stenosis in the 'normal' state of the artery immediately after RFA, which required stenting later [6]. With all this, anatomical data demonstrates the proximity of the coronary arteries and, in particular, the LCA trunk to the site of RF-application [3]. According to C. Hasdemir et al., the distance between endocardium of the area of cavotricuspid isthmus and the posterolateral branch of the right CA may be about 5 mm, and the minimum distance between the coronary sinus and circumflex artery - 2 mm, which theoretically should suggest a higher coronary vessels complication rate [7]. Therefore, according to some authors, the low number of such complications due to RFA can be explained by the presence of undiagnosed cases [8]. For the most part, the absence of CA lesions in the ablation zone is associated with the protective effect of intracoronary blood flow on the vessel wall, which provides convective cooling of the area adjacent to the site of RF application [9, 10].

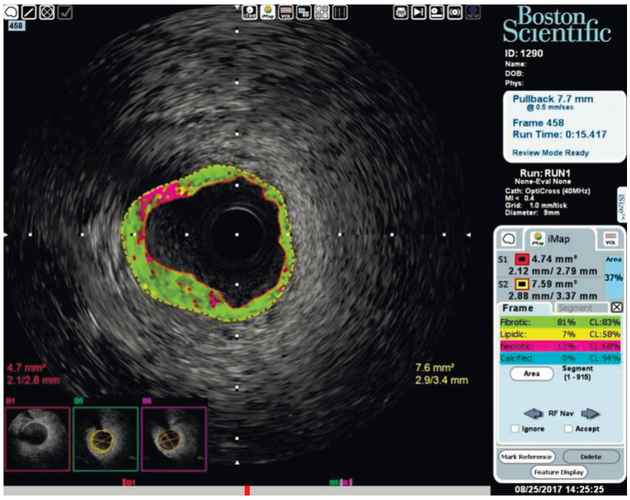

Fig. 3. IVUS data of the left CA system: the absence of pronounced signs of morphological damage of the artery wall, narrowing has an eccentric pattern.

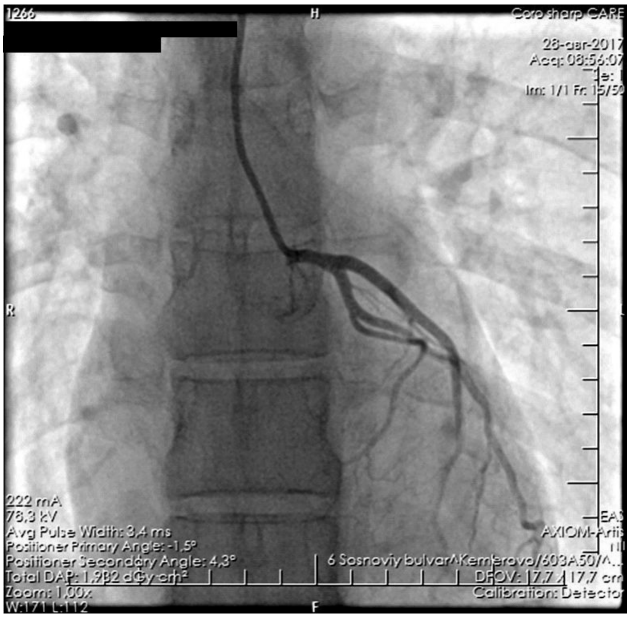

Fig. 4. Results of coronary angiography after 5 days of RFA.

In our description, the LCA trunk damage could occur during RFA in the right ventricular outflow tract or, most likely, during ablation in the left sinus of Valsalva and directly at the ostium of the LCA. The damage of LCA at the RVOT ablation theoretically is possible to suppose, as the last were applied close to location of the ectopic focus, as indicated by the subsequent mapping of the aortic sinuses, the presence of a response of ectopic focus and the temporary elimination of activity. Nevertheless, this assumption is unlikely due to the absence of ischemic changes in the ECG at the time of RF applications, and anatomical data suggest, as a rule, a quite remote relative position of the RVOT and the LCA trunk [3]. It is more likely that the damage occurrence is a result of an inadvertent dislocation of the ablation electrode at the ostium of LCA and the continued application for 5 seconds with direct contact of the tip of electrode with the endothelium of CA. Upon termination of exposure, the electrode was immediately withdrawn to the ascending aorta, therefore, the assumption of its dislocation to the ostium of LCA is based on navigation data. At the same time, the exposure was short, so it did not lead to a rupture of endothelium or a concentric narrowing of the LCA, which was documented during IVUS. The follow-up of the patient was predetermined by the duration of the scar formation after RFA, which is about 8 weeks [11]. At the end of this period, the examination, including coronarography revealed no abnormalities.

CONCLUSION

The main goal that we set when describing this complication is to demonstrate that the stenosis of CA, which developed immediately after radiofrequency damage, does not always require immediate stenting. In some cases, it is only necessary to monitor the patient. The use of IVUS may assist in deciding on the undesirability of early stenting. In deciding on the possibility of discharge the patient from the hospital, stress testing can help. Also, since there are literature cases descripting late development of stenosis in the CA despite of 'normal' state immediately after the RFA, observation is required for at least three months with repeated coronary angiography in the delayed period. All the above allows one to safely avoid unnecessary stenting of the CA in some cases. In this example, a comparison of clinical data with the results of CA and IVUS made it possible to confine ourselves for conservative treatment of 60% stenosis of the left coronary artery trunk in conditions of targeted dynamic monitoring of the patient.

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CATHETER ABLATION OF ATRIAL TACHYCARDIA FROM THE NON-CORONARY VALSALVA SINUS

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A case report of atrial tachycardia ablation form the non-coronary Valsalva sinus is presented.

Key words: atrial tachycardia; interatrial septum; atrioventricular connection; non-coronary sinus of Valsalva; mapping; radiofrequency ablation

Conflict of Interests: nothing to declare
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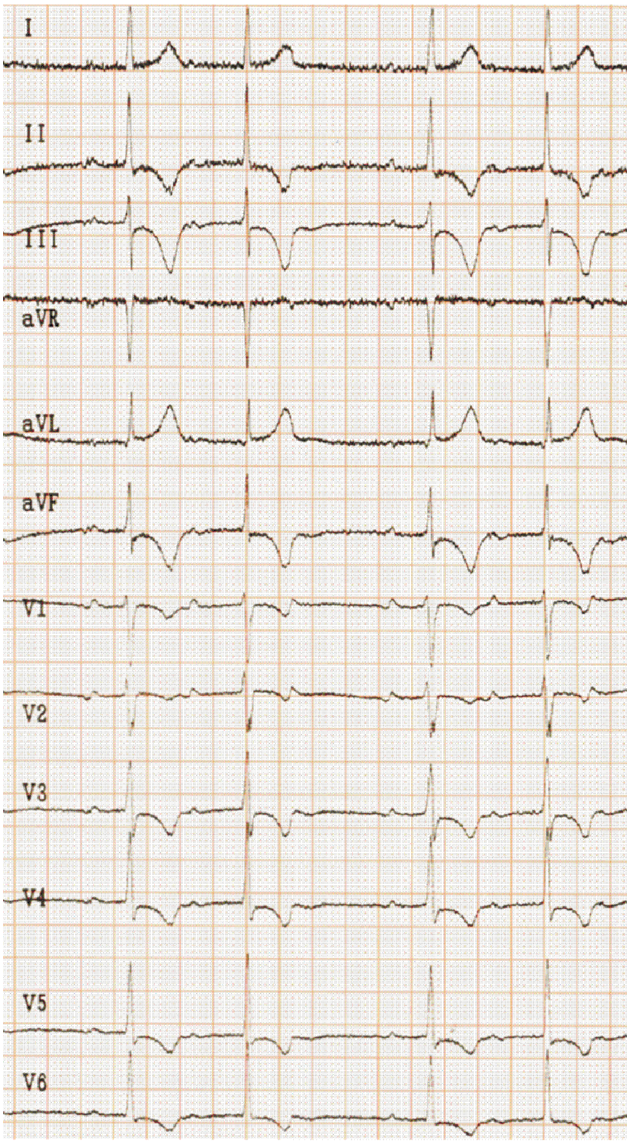

Fig .1. ECG of patient K. Sinus rhythm, frequent atrial premature beats in a bigeminal pattern.

Currently endocardial catheter ablation is the method of choice in the treatment of the most forms of cardiac arrhythmias, including the entire spectrum of supraventricular tachycardia. However, in the treatment of atrial tachycardia, its efficiency can vary widely [1], which is due to both the localization of the arrhythmogenic substrate and the difficulties of its mapping, as well as problems associated with the stability of the positioning of the ablation catheter, as well as the safety of exposure.

The localization of the substrate of atrial tachycardia is primarily associated with the following areas: crista terminalis, interatrial septum, annulus of mitral and tricuspid valves, right and left atrial appendage, ostium of pulmonary veins and coronary sinus (CS) ostium [2-8]. As a rule, in the most of these cases standard transvenous endocardial access is able to ensure success in determining the localization and ablation of the arrhythmia substrate with minimal risk of possible complications. However, for some patients, the standard approach does not guarantee the success and safety of treatment for arrhythmia. In particular, when it comes to the localization of the tachycardia substrate in the anterior region of the interatrial septum, where the anatomical proximity to the compact part of the atrioventricular (AV) joint makes it difficult to place optimally the ablation catheter, since radiofrequency (RF) exposure in this area has a high risk of disruption of AV conduction.

Peculiarities of atrial tachycardia arising from the anterior part of the atrial septum were widely discussed earlier [9-18, 22]. The main electrophysiological characteristics of this tachycardia were noted: easy induction and stopping of tachycardia after programmed stimulation of the heart, its start without previous ectopic activity in the atria, mapping of the earliest activation of tachycardia in the projection of the His bundle in the right atrium. It is possible to stop this type of tachycardia by intravenous administration of adenosine.

From January 2013 to July 2018, we operated 83 patients (mean age 47.3±16.5 years, 44 women) with atrial tachycardia. All procedures were performed using the navigation system CARTO-3, and in addition, cryoablation was done in 2 patients. The distribution of patients in accordance with the localization of the arrhythmogenic substrate was the following: in 32 patients (39%) the arrhythmia substrate was localized in the region of crista terminalis, in 19 (23%) in the left atrium, in 11 (13%) in the ostium of CS, in 6 (7%) in the area of cavotricuspid isthmus and in 16 patients (19%) in the area of interatrial septum. At the same time, in 8 patients ablation of the arrhythmia substrate was performed in more than one of these areas, for example, combined procedures were done in the region of crista terminalis and atrial septum, as well as in crista terminalis and cavotricuspid isthmus.

From 16 patients with the arrhythmia substrate originating from interatrial septum, 14 patients underwent successful RF ablation using the navigation system CARTO-3 and 2 patients underwent cryoablation of the arrhythmia substrate in the immediate vicinity of the His bundle. In all patients, the standard transvenous approach was used initially for mapping, additionally 3 patients required puncture of the interatrial septum for mapping from the left atrium.

In 3 patients from 16, the localization of the tachycardia substrate was verified in the anterior part of the interatrial septum (area of fast pathway of AV-conduction and His bundle) using activation mapping. Despite the accurate determination of the arrhythmia substrate location, RF ablation was nevertheless carried out in adjacent areas to reduce the risk of inadvertent AV-block. Due to the inefficiency or transient effect of RF ablation in these patients, we used transaortic access from the non-coronary sinus of Valsalva (SV). When mapping non-coronary SV, in all patients areas of even earlier activation of the arrhythmogenic substrate were verified (on average from 5 to 15 ms) compared to the data obtained by mapping from the right atrium. All 3 patients underwent successful ablation. Introducing the clinical observation of one of these patients.

A patient K., 47 years old, was admitted to the hospital with a diagnosis: Arterial hypertension stage II, degree 2, risk 3. Paroxysmal atrial tachycardia. Frequent atrial premature beats (APB) in a bigeminal pattern. Condition after two radiofrequency ablations of atrial tachycardia (2009 and 2010). Postoperative transient complete AV block. Implanted two-chamber pacemaker with endocardial electrodes. Congestive heart failure (CHF) stage I, NYHA functional class II. Twice reposition of the ventricular electrode due to dislocation. Class II obesity by WHO.

Prior to this hospitalization, the patient had been twice attempted to perform RF ablation of atrial tachycardia. Both procedures were ineffective, the second was complicated by a transient complete AV blockade, as a result of which a pacemaker was implanted. After repeated ablation, in the patient there were remained attacks of frequent rhythmic heartbeat (up to 5-6 times per day) with a ventricular contraction rate from 150 to 200 beats/min and with duration from 30 min to 4 hours.

Upon admission on ECG (Fig.1), there is sinus rhythm with heart rate (HR) 85 beats/min, frequent APB. During transesophageal electrophysiological examination, paroxysm of regular atrial tachycardia with HR 175 beats/min was induced. Echocardiographic examination showed that cavities size is not enlarged, left ventricular ejection fraction (EF) was 54%. According to daily ECG monitoring, frequent APB in a bigeminal pattern, short runs of atrial tachycardia with HR 125-180 beats/min was

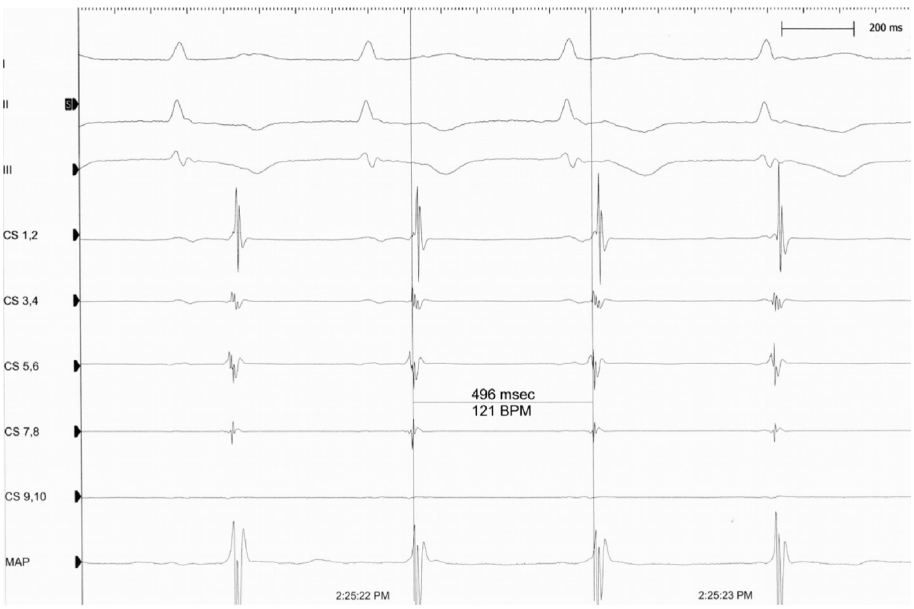

Fig. 2. Mapping of patient K. Paroxysmal atrial tachycardia with heart rate up to 120 beats/min.

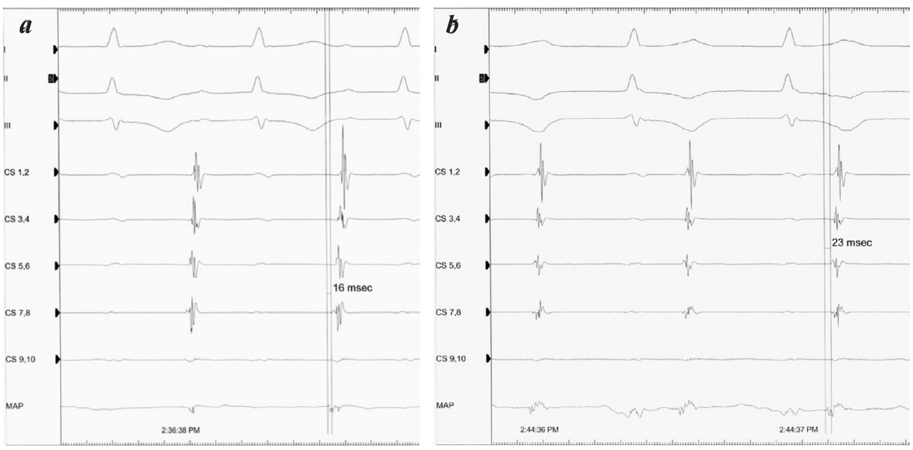

Fig. 3. Activation mapping of the arrhythmia substrate of patient K. in the atrial septum from the left atrium (a) and the right atrium (b).

recorded. When examining the implanted pacemaker, there was no dysfunction of the device, right ventricular stimulation was no more than 10%.

The surgery was conducted using the navigation system CARTO-3. Under local anesthesia, punctures of the subclavian and femoral veins, as well as further femoral artery, were performed. A diagnostic electrode is placed in CS. Short paroxysms of atrial tachycardia without a clear front of excitation propagation along the CS were recorded (Fig. 2). Atrial septum puncture was performed. During paroxysmal atrial tachycardia, an activation map of the left and right atria was constructed. At navigational mapping, the earliest possible activation of the arrhythmia substrate was determined in the anterior-septal region of the right atrium (-25 ms) (Fig. 3) in close proximity to the AV connection. The distance from the zone of the earliest atrial activation to the mapping of His bundle was not more than 5 mm. Due to the high risk of unintentional AV blockade, a series of radiofrequency interventions were performed (temperatures up to 43 °C, power 25W, irrigation feed rate 18 ml/min) in areas as close as possible to the area of early activation. All RF exposures were not effective for arrhythmia substrate elimination.

Then, by ablation catheter through transaortic access the mapping of SV was performed. In the area of non-coronary sinus, a zone of even earlier activation of the tachycardia substrate (-28 ms) was determined (Fig. 4). In this area, a series of RF exposures was performed. A convection electrode was used with the following ablation parameters: temperature up to 55° C, power 35 W. There was noted a relief of paroxysm of atrial tachycardia and atrial ectopic activity in the first seconds of the first RF exposure. When conducting a control intracardiac electrophysiological examination using various pacing protocols, atrial rhythm disturbances are no longer induced. The postoperative period was without complications.

DISCUSSION

According to the literature and our clinical experience, patients with a focal form of atrial tachycardia consist no more than 5% of the total number of patients with tachyarrhythmias [23]. Our experience has shown that the effectiveness of its treatment is quite high. However, some localizations of the ectopic atrial substrate can be difficult for successful mapping and ablation: in particular, anterior-septal localization. According to aggregate data, the proportion of such patients can be 4-12% of the total number of patients with focal atrial tachycardia [12, 13, 15]. An important aspect of the effective treatment of tachycardia of this localization is the determination of the area of the earliest substrate activation [20]. This may require mapping of the interatrial septum, both from the left and right atria, as well as from the non-coronary SV [24].

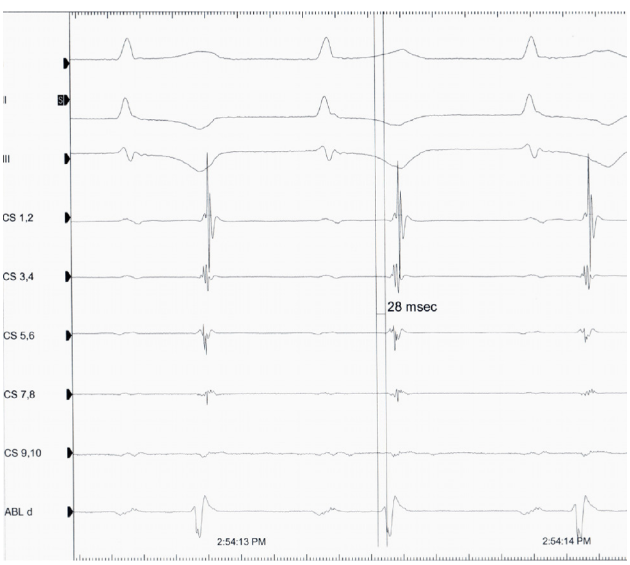

Fig. 4. Activation mapping of patient K. from the non-coronary sinus of Valsalva.

To date, there is no consensus on the mechanisms of the focal form of atrial tachycardia. Three priority versions are considered: increased automatism, trigger activity, and micro re-entry [21]. In favor of non-reentry dependent mechanism of this form of tachyarrhythmias, in particular, the fact that focal RF or cryo ablation in the area of the earliest atrial activation are always effective and stop tachycardia. This type of tachycardia can almost always be stably induced and stopped when performing program and asynchronous cardiac stimulation.

Analysis of the morphology of the P-wave on a surface ECG in 12 leads gives very limited information in determining the specific location of the tachycardia substrate at the preoperative stage. A marker of the anterior-septal localization of the tachycardia substrate can be a positive P-wave in I and aVL leads, negative or isoelectric in II, III and aVF leads and a two-phase P wave in precordial leads V1 and V2. At the same time, the analysis of the morphology of the P-wave may be difficult due to its possible imposition on the tooth T.

Previously published materials detected the prevalence of the female contingent among patients with atrial tachycardia of anterior-septal substrate localization [12, 13, 15], which is consistent with our observations, where all three patients were women. Our practice has shown that an accurate determination of the localization of the substrate of atrial tachycardia in the anterior-septal region, as a rule, requires extensive mapping of the atrial septum, both from the right and left atria. In case of localization of early atrial activation in the area of visualization of His bundle, we recommend mapping of non-coronary SV and, when verifying earlier ectopic atrial activation, perform RF exposure in this zone. In our observations, the effect of stopping tachycardia was revealed in all patients already in the first seconds of exposure. All RF ablations were performed with convection electrodes without irrigation. At the same time, in our practice there was a clinical case when RF ablation in non-coronary SV was not effective, and the zone of maximally early activation was located in the visualization region of the His bundle in the right atrium. In this case, we used focal cryoablation with a positive clinical result. Thus, access from non-coronary SV for RF ablation of atrial tachycardia with localization of the substrate from the anterior-septal region of the atrial septum is safe and increases the efficiency of the procedure.

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THORACOSCOPIC IMPLANTATION OF AN EPICARDIAL PACEMAKER IN A CHILD WITH COMPLETE ATRIOVENTRICULAR BLOCK

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A case report describing thoracoscopic approach for implantation of a cardiac pacemaker in a 3.8 years old girl with complete atrioventricular block is presented.

Key words: bradycardia; congenital complete atrioventricular block; epicardial cardiac stimulation; thoracoscopy; thoracotomy; children

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Complete atrioventricular block (CAVB) is a disturbance of the electrical impulse from the atria to the ventricles due to structural or functional disorders in the conduction system of the heart. CAVB is considered congenital in the case of diagnosis of the disease in perinatal age or early childhood without any connection with another pathology [1].

The first congenital CAVB was described by Morquio L. in 1901 [2]. The prevalence rate of CAVB is approximately 1 per 20 000 live-born infants [3, 4].

There are a number of factors concomitant with the development of CAVB, such as the presence of structural pathology of the heart, autoimmune damage to the conduction system of the heart, which in most cases is associated with the presence of systemic lupus erythematosus in a child or his immediate family [3, 5, 6]. The possibility of a genetic predisposition to the development of the disease has been confirmed in a number of studies [7, 8]. Idiopathic CAVB is diagnosed with the exclusion of known causes of CAVB [1].

The appearance of clinical symptoms of CAVB depends on the etiology of the disease, the presence of concomitant pathology, the age of the child, the severity of bradycardia, and the maximum duration of pause rhythms [6]. Most often, CAVB is manifested by syncopal or pre-syncopal conditions, less often - a decrease in tolerance to physical activity, a delay in physical and psy-

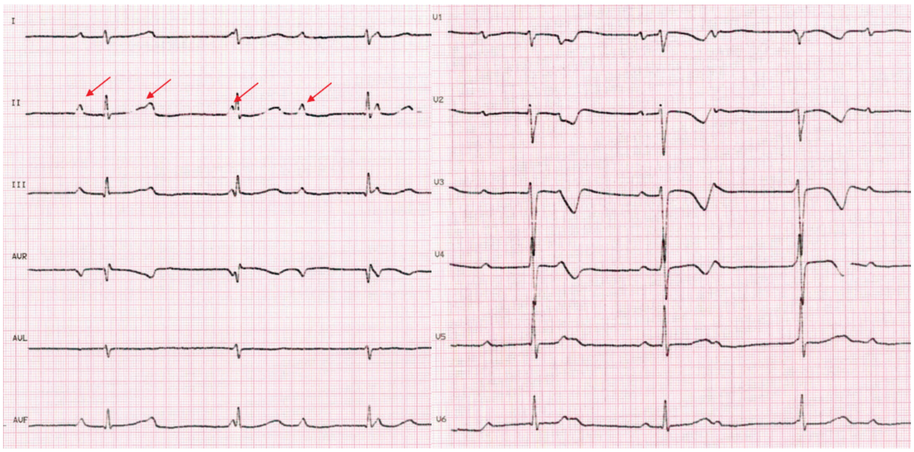

Fig. 1. ECG on admission. CAVB with a rate of atrials 88-109 bpm, and ventricles 57-59 bpm. Vertical position of the electrical axis of the heart. QRS=60 ms, QT=440 ms, QTc=436 ms. P-waves marked by arrows.

Fig. 2. The 24-hour ECG monitor on admission. Complete atrioventricular block was constantly registered. An average heart rate was 59 bmp. Average heart rate was 59 bpm (normal rate is 99-112 bpm), maximum - 98 bpm in the daytime. Average heart rate was 44 bpm (normal rate is 80-89 bpm), minimum - 39 bpm in the night time. An average daily heart rate was 59 bmp (normal rate is 93-105 bmp). The maximum rhythm pause was 2685 ms (normal up to 1300 ms).

chomotor development. Often, CAVB is asymptomatic and becomes an accidental finding on an electrocardiogram (ECG) [9, 10].

Carrying out constant pacemaking (PM) is a recognized method for the treatment of patients with CAVB regardless of the etiology of the disease. It was proved that implantation of PM increases the quality and life expectancy not only in patients with clinical manifestations, but also in asymptomatic patients [4, 9, 11]. According to modern concepts, in children weighing less than 15 kg, the epicardial arrangement of the electrodes is preferable, which allows preserving the possibility of venous access for further implantation of endocardial stimulation systems [9, 12-15]. According to various researchers, the percentage of complications during implantation of PM in children with an epicardial arrangement of electrodes reaches 14% [16, 17].

Our patient underwent thoracoscopic implantation of the epicardial pacing system. The advantages of thoracoscopic surgery have been repeatedly demonstrated in adult patients [18–20], however, there are no references of its use in children with bradyarrhythmias in the literature.

A 3 year-old female child was admitted to Veltishchev Research and Clinical Institute for Pediatrics of the Pirogov Russian National Research Medical University in May 2017. From the anamnesis of life, it is known that the girl was born via normal vaginal delivery, the second pregnancy was a threatened abortion in the third trimester. Birth weight was 3180 g, body length 54 cm, Apgar score 7/8. There are no reliable data about the period of early childhood. According to the parents' opinion, the girl has physical and psychosocial developmental delays compared to peers, as well as insufficient weight gain.

Anamnesis of the disease: for the first time, a rhythm disturbance in the form of CAVB was detected at the age of 2 years, when, after an acute respiratory illness, the first ECG was performed. The child was observed at the place of residence; non-steroidal anti-inflammatory therapy courses were conducted at age-related dosages without effect. There was no family history of heart or autoimmune diseases.

On examination, the patient has evidence of weakness, reduced emotion, the child avoided physical activity. Physical development of the patient was disharmonious due to lack of body weight: body weight was 13 kg, which corresponds to a range of values lying below 3 ‰ according to centile tables [21]. The height of the child fell in the range of 50 ‰, equaling 101 cm.

An objective examination showed severe bradycardia with the heart rate ranging between 58 bpm (resting) and 62 bpm (orthostasis). According to existing standards obtained during the all-Russian clinical and epidemiological study on ECG screening of children and adolescents, the patient's heart rate was less than 2th percentile for her age (the border is 76 bpm) [22]. During auscultation, heart tones sounded rhythmic, the blood pressure was 100/55 mmHg on both arms. There were no signs of stagnation in the pulmonary and systemic circulations.

A blood count, urine test, biochemical blood test including serum cardiospecific markers were normal. An increased titer of anti-nuclear factor, anti-SSA and anti-SSB antibodies were detected neither in girl nor in parents.

Electrocardiography (Fig. 1) and 24 hours Holter monitoring (Fig. 2) showed CAVB. Echocardiography showed no structural changes in the heart, but there was a mild dilatation of the left chambers of the heart, which was the sign of arrhythmogenic cardiomyopathy. The ejection fraction according to the Teicholz method was 73%,

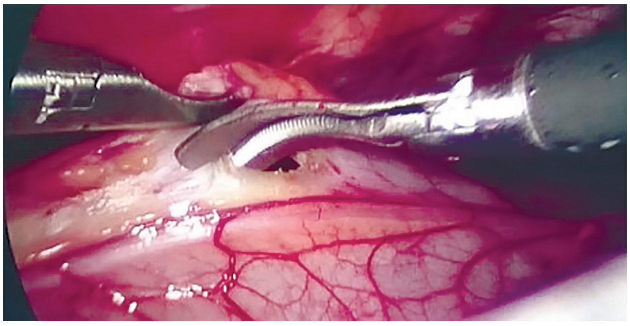

Fig 3. Intraoperative photo from the video camera screen. Dissection of the pericardium by a longitudinal section of 3-4 cm.

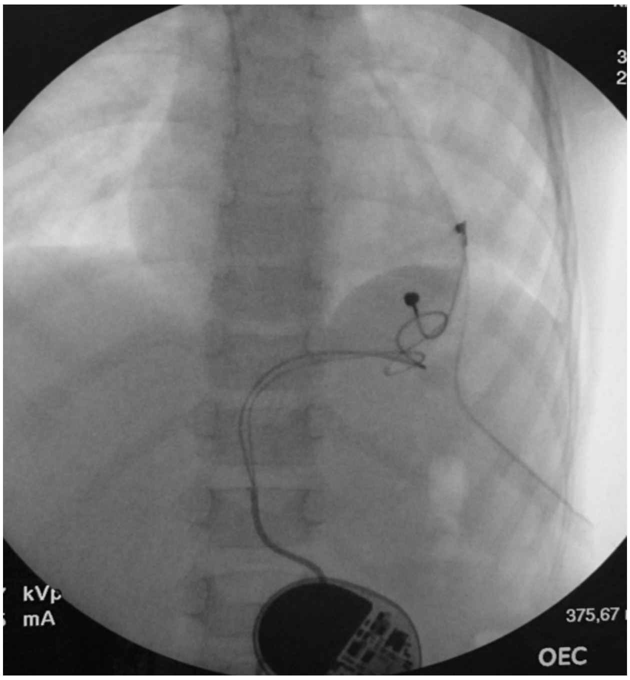

Fig. 4. Postoperative X-ray with the location of the pacemaker in the abdominal cavity and epicardial leads.

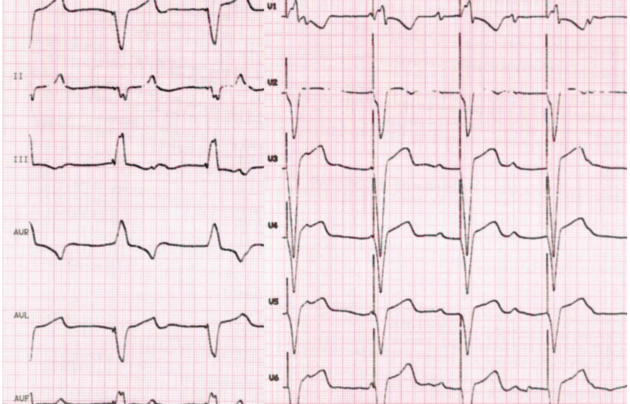

Fig.5. ECG after surgery. The rhythm from pacemaker VVIR with basic rate 70 imp/min.

according to the Simpson method - 64%. A final diagnosis was made based on life history, medical case history, and diagnostic findings: «Complete atrioventricular block. Arrhythmogenic cardiomyopathy». CAVB, identified at an early age in a child with a lag in physical and psychomotor development, was highly likely congenital. Due to the lack of structural abnormalities in the development of the heart and data for the autoimmune nature of arrhythmia, the idiopathic genesis of the development of CAVB was suggested.

According to existing recommendations for the management of patients with congenital CAVB, systolic left ventricular dysfunction and heart ventricular rate of 50 bpm or slower in this patient were standard criteria for pacing implantation [23]. Video-assisted thoracoscopic of epicardial pacing was chosen due to the low weight of the child and high trauma rate of open surgery.

Technique for surgical intervention

The procedure was performed using complex intratracheal anesthesia. Applying intravenous and inhalation anesthetics allows for achieving adequate anesthesia simultaneously and minimizing adverse effects of drugs. The patient was intubated with a single lumen endotracheal tube, which was sufficient to ensure adequate ventilation of the patient by capnography for a collapsed left lung. Three incisions were made: the first and the second at the anterior axillary line in the fourth and in the ninth intercostal space and in the 6th intercostal space at the medium axillary line, toracoports were installed through it, one of which serves for holding a video camera, and the rest for holding tools. The lung collapsed due to CO2 insufflation. For visualization and access to the heart, pressure in the left pleural cavity was supported at the level of 10 mmHg. The pericardium was dissected longitudinally for 4 cm toward the front of n. phrenicus (Fig. 3). An epicardial bipolar lead (CapSure Epi 4968-25cm) was promoted via thoracoport. Polar of the lead was fixed in the nonvascular area of the anterior and anterolateral walls of the left ventricle with rare loop sutures. Pacing threshold was 0.5V at 0.4 ms, R-wave was 15mV, impedance was 1478 Ohm. The incision in the epicardial area was made. Connector part of leads was positioned in the epicardial area in approximately 1 cm below the xiphoid appendix. The pericardium was sutured with rare loop sutures and thoracoscopic incisions - with single loop sutures. The tissue bed in the left rectus abdominis was formed for implantation of pacemaker Adapta ADSR01 with VVIR mode and basic rate 70 imp/min (Fig. 4). The postoperative period was without any complication. The patient discharged home on the 9th post-procedure day.

On ECG after surgery the rhythm from pacemaker VVIR with basic rate 70 imp/min was registered (Fig. 5). The 24-hour ambulatory ECG monitor reported an average heart rate of 84 bpm (minimum 70 bpm and maximum 142 bpm) in the daytime and an average heart rate of 71 bpm (minimum 70 bpm and maximum 91 bpm) in the night time, respectively. An average daily heart rate was 74 bmp.

During systematic pacemaker monitoring, the stable function of the device was noted: amplitude and resistance indicators were without negative dynamics, the battery charge was sufficient.

During the 1.8 year follow-up period of the child, indicators of the heart rate became normal, weight gain was sufficient, as of January 15, 2019 the weight and height of the girl was 108 cm and 18 kg, respectively. The child's physical activity increased, and there was an interest in outdoor games. Parents noted the improvement of the girl's psychoemotional status.

CONCLUSION

Minimally invasive thoracoscopic implantation of the epicardial pacemaker has several advantages compared with traditional method, such as shorter procedure time, reduced risk of blood loss, less postoperative pain, as well as better cosmetic effect. It can be assumed that the accumulation of experience of thoracoscopic implantation of the epicardial pacing in children, and collection of long-term follow-up data lead to a greater dissemination of this technique. In the future, the widespread use of the method will reduce the number of days spent in the hospital, which makes it economically feasible to prefer minimally invasive intervention to the traditional one with transthoracic access. This clinical case report demonstrates that thoracoscopic implantation of the pacemaker is the effective low-traumatic method of surgical correction of CAVB in children.

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