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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).

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.

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].

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.

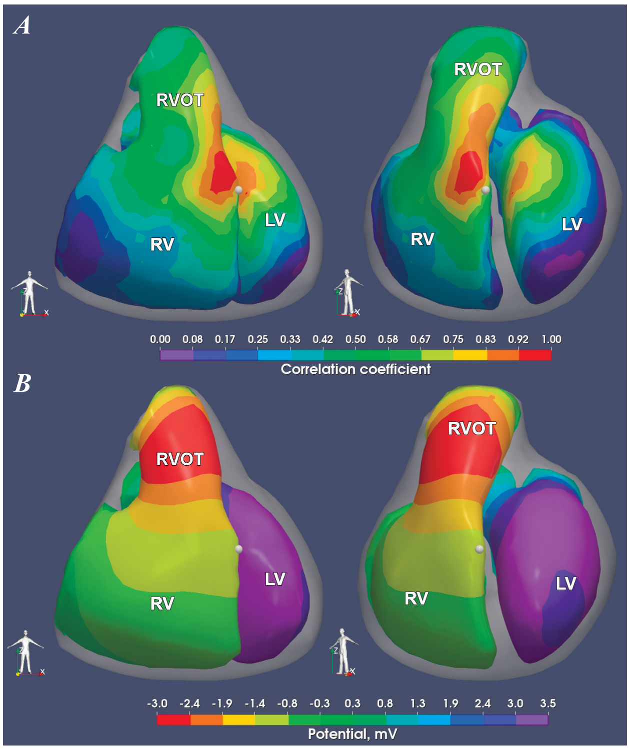

Figure 1. Semi-transparent three-dimensional epi-endocardial models of cardiac ventricles. The localization of the pacing electrode in the anterior-middle part of IVS is shown with a white marker. A (top). Correlation similarity maps based on new algorithm FRA-V. B (bottom). Isopotential map based on 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.

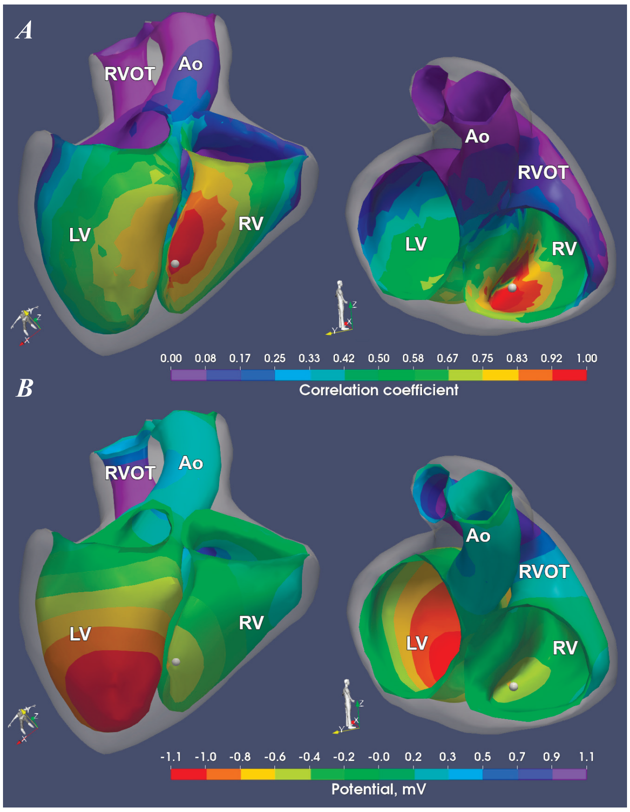

Figure 2. Semi-transparent three-dimensional epi-endocardial models of cardiac ventricles. The localization of the pacing electrode in the inferior-middle part of IVS is shown with a white marker. A (top). Correlation similarity maps based on new algorithm FRA-V. B (bottom). Isopotential map based on 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	-

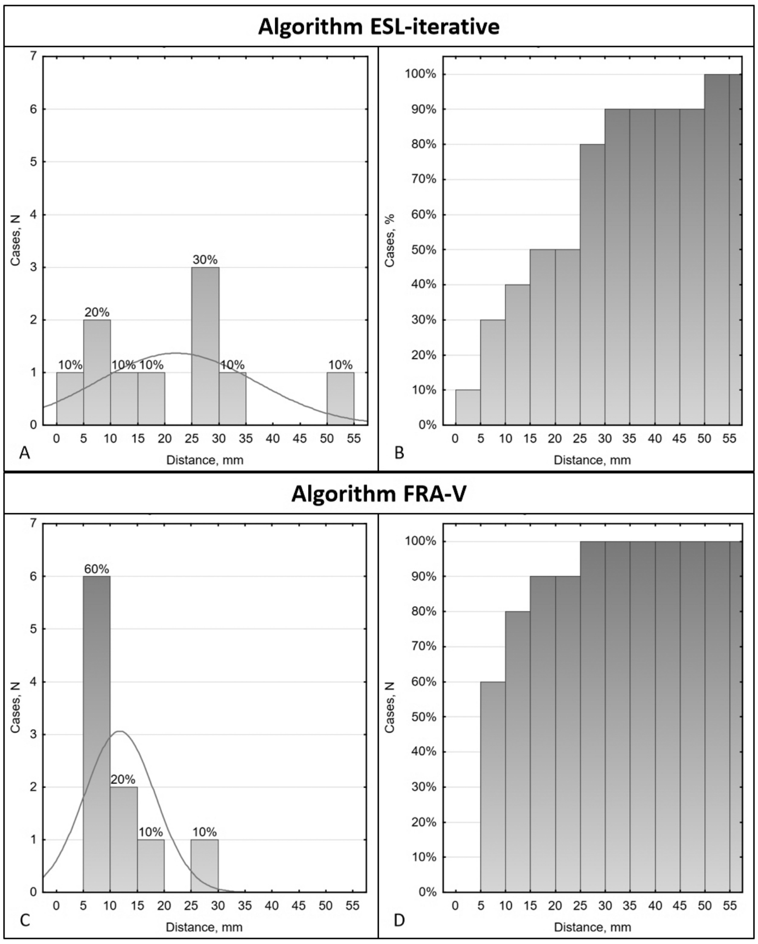

Figure 3: ECGI accuracy distribution histograms based on different algorithms for solving inverse ECG problem. X axis - distance between the pacing site and the early activation zone (Distance), Y axis - number (N) of observations (cases). On the left (A,C) - ECGI accuracy histograms, on the right (B,D) - 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

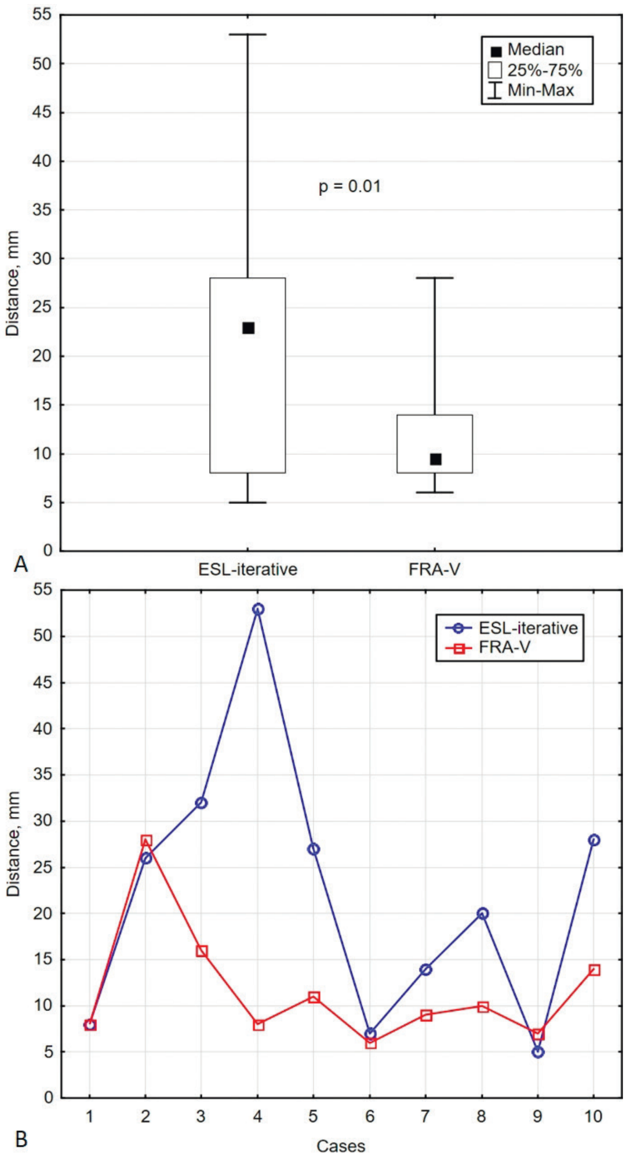

Figure 4. Comparative evaluation of ECGI accuracy using different algorithms for solving inverse ECG problem. A - Tukey box&whiskers plots Tukey of ECGI accuracy. X-axis - algorithm, Y-axis - the distance between the pacing site and the early activation zone (Distance); B - ECGI accuracy linear plot.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

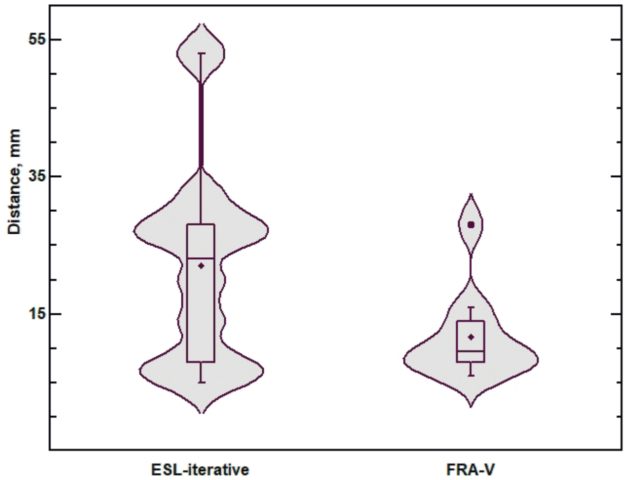

Figure 5. Violin plot of ECGI accuracy showing the distribution of values based on the bootstrap analysis method for different algorithms of solving the inverse ECG problem. Primary Tukey box&whiskers plot of ECGI accuracy used for generation of 1000 random repeated samples are located in the center 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.

of using ESL-iterative algorithm may indicate its less stability and robustness.

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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