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ALGORITHM FOR DETERMINING THE FIBROSIS STAGE USING HIGH-DENSITY MAPPING

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Aims. To develop an algorithm for assessing the stage of fibrosis based on high-density endocardial mapping. To study the effect of the stage of left atrial (LA) fibrosis on the results of atrial fibrillation (AF) catheter ablation.

Methods. The study included 64 patients with paroxysmal or persistent AF, who underwent high-density LA mapping and catheter ablation. After the intervention procedure, we analyzed the electroanatomical maps of the left atrium, assessed the prevalence of low-voltage areas according to the developed algorithm. Patients were divided into 4 groups depending on the prevalence of areas of low voltage based on the Utah score.

Results. The follow-up period was 14.5 ± 6.7 months. AF recurrence developed in 18 (28.1%) patients after the ablation procedure. AF recurrence after ablation was more frequent in patients with a low-voltage area of more than 20% than in patients with a low-voltage left atrial area of less than 20%, 6 (15.4%) versus 12 (48%), p=0.02. A logistic regression analysis was performed to identify AF recurrence predictors in the postoperative period. As a result, only widespread areas of low-amplitude activity were an independent predictor of AF recurrence after the pulmonary veins isolation, this predictive model was significant (p=0.026). Significant statistical differences between groups I, II and III,I V are the ejection fractions and the duration of the P-wave. Patients with low-voltage regions have lower left ventricular ejection fraction (62.8±6.9% versus 58.1±5.7%, p=0.01), and longer P-wave duration (84.7±8,2 ms versus 101.5±11.0 ms, p=0.01).

Conclusion. LA high-density mapping before AF ablation makes it possible to determine the prevalence of low-voltage areas. After regression analysis, it was proved that common low-voltage areas are an independent predictor of AF recurrence after pulmonary vein isolation. Patients with low-voltage areas of more than 20% of the LA surface have longer P-wave duration and lower left ventricular ejection fraction.

Key words: high-density mapping; atrial fibrillation; catheter ablation; left atrial fibrosis

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Catheter ablation is a surgical treatment for patients with atrial fibrillation (AF). The main target of catheter ablation in AF is the elimination of arrhythmia triggers localized in the pulmonary veins [1]. Electrical and structural atrial remodeling are the main determinants of the pathogenesis and progression of AF [2]. Histological analysis of the structure of the atrial myocardium in patients with AF revealed multiple accumulations of fibroblasts and diffuse dissemination of collagen fibers [3].

A multicenter prospective DECAAF study showed that areas of left atrial (LA) fibrosis identified by magnetic resonance imaging (MRI) were independent predictors of AF recurrent after catheter ablation [4]. Some studies have shown that areas of accumulation of gadolinium-containing contrast agent are characterized by areas of low-amplitude activity (0.38±0.28 mV) compared with the intact atrial myocardium, where the amplitude of the bipolar signal is higher (1.38±1.23 mV) [5, 6]. However, these and other previous studies analyzed electroanatomical maps constructed using 20-pole circular or ablation catheters [5, 6].

The purpose of the study was to develop an algorithm for assessing the stage of fibrosis according to high-density endocardial mapping, to study the effect of the stage of LA fibrosis on the results of AF catheter ablation.

MATERIAL AND METHODS

The study included 64 patients with paroxysmal or persistent AF, who underwent high-density LA mapping and AF catheter ablation. We analyzed the clinical characteristics of the patients included in the study (Table 1). All patients underwent preoperative echocardiography, computed tomography of the LA, transesophageal echocardiography, clinical blood count, and gastroscopy. In the presence of risk factors for coronary heart disease and/or a clinical presentation of it, patients underwent coronary angiography at the preoperative stage. If hemodynamically significant narrowing of the coronary arteries was detected, patients underwent myocardial revascularization, and these patients were excluded from the study.

Inclusion Criteria:

• Age over 18;
• AF recorded on the electrocardiogram (ECG);
• Indications for catheter ablation;
• Signed informed consent form.

Exclusion Criteria:

• Pregnancy or planned pregnancy within the terms of the clinical study;
• Contraindications to the catheter procedure (patients with acute and subacute myocardial infarction, as well as those with decompensated heart failure, patients with decompensated concomitant diseases, etc.).
• Previous interventional treatment of cardiac arrhythmias or any cardiac surgery;
• With implantable devices.
• Valvular heart disease, requiring surgical correction;
• Presence of signs of a fragmented or floating thrombus in the LA.

This study was approved by the local ethics committee. All patients signed an informed consent prior to enrollment in the study.

High Density Mapping

Patients included in the study underwent LA mapping using a basket catheter, which contains 8 splines with 8 electrodes on each (the distance between the electrodes is 2 mm).

Mapping was performed with a uniform distribution of annotated points using a filling threshold of 1 to 3 mm, voltage maps contained at least 10,000 points. Low-voltage areas were defined as areas with a bipolar signal of less than 0.2 mV, and transitional areas - from 0.2 to 0.5 mV; an endocardium with a bipolar signal of more than 0.5 mV was considered intact.

In low voltage areas, the maximum number of points was annotated for a more accurate assessment of structural changes. The stability of the catheter was limited to fluctuations of 3 mm. To avoid annotating incorrect mapping points due to poor contact of the mapping electrode with the tissue, we set the filtering of the distance between the projection of the electrode and the geometric surface of the model to 2 mm. The signals were filtered with a frequency from 30 to 400 Hz. The automatic mapping function made it possible to avoid manual verification of all endograms on the obtained voltage maps.

Algorithm for determining the stage of LA fibrosis

The evaluation of the propagation stage of low-voltage regions was carried out as follows. After constructing a high-density voltage map containing more than 10,000 mapping points, the atria were divided by one plane into 2 parts using the Reset Clipping Plane tool (Fig. 1). Next, the total surface area was measured. The area of each half of the atrium was measured sequentially. After that, the obtained results were summarized. Using the “Area measurement” tool, the area of each area was alternately measured, where the signal amplitude was less than 0.2 mV, the results were summarized (Fig. 2).

According to the formula S of low-voltage sections / S of the total area * 100% (where S is the area), the area of low-voltage sections was measured. Subsequently, the patients were divided into 4 groups.

Table 1.

Clinical characteristics of patients

	I group (n=20)	II group (n=19)	III group (n=8)	IV group (n=17)
Age, years	63 [50.5-68.5]	60 [51-64]	56 [42-62.5]	66 [56-70]
Persistent AF, n (%)	6 (30.0)	7 (36.8)	3 (37.5)	9 (52.9)
Paroxysmal AF, n (%)	14 (70.0)	12 (63.2)	5 (62.5)	8 (47.1)
Duration of arrhythmia history, years	3 [2-5]	5 [3-12]	6.5 [4.5-10.5]	6 [2-7]
Volume of the left atrium, ml	133.9±25.7	139.8±29.7	144.2±37.3	161.1±56.1
Left ventricular ejection fraction, %	64.3±6.5	61.2±7.2	60.4±4.9	56.9±5.8
AF recurrence, n (%)	2 (10)	4 (21)	2 (25)	10 (59)
Low-voltage areas, %	6,6±2.4	13.6±2.7	24.0±2.2	54.5±16.9
P-wave duration, ms	84.2±8.1	85.4±8.4	91.4±6.7	106.2±9.3
Diabetes mellitus, n (%)	3 (15)	5 (26)	1 (13)	4 (24)
Arterial hypertension, n (%)	13 (65)	10 (53)	5 (63)	11 (65)
Postponed coronavirus infection, n (%)	6 (30)	6 (32)	4 (50)	8 (47)
Radiofrequency ablation, n (%)	15 (75)	14 (74)	8 (100)	16 (94)
Cryoablation, n (%)	5 (25)	5 (26)	0	1 (6)
Sotalol + lappaconitine hydrobromide, n (%)	4 (20.0)	3 (15.8)	2 (25.0)	3 (17.6)
Amiodarone, n (%)	7 (35.0	6 (31.6)	3 (37.5)	4 (23.6)
Propafenone, n (%)	3 (15.0	3 (15.8)	0	1 (5.9)
Beta blockers, n (%)	6 (30.0)	7(36.8)	3 (37.5)	9 (52.9)

Note thereafter: AF - atrial fibrillation.

By the Utah gadolinium MRI fibrosis staging scale used in the DECAAF study, in our work we divided fibrosis grades in a similar way:

Stage 1 - with total low-voltage areas of less than 10%;
Stage 2 - with total low-voltage areas of 10-20%;
Stage 3 - with total low-voltage areas of 20-30%;
Stage 4 - with total low-voltage areas of more than 30%.

Catheter treatment

Catheter ablation was performed under intravenous sedation. The ablation procedure was preceded by transesophageal echocardiography performed to exclude thrombosis of the LA appendage.

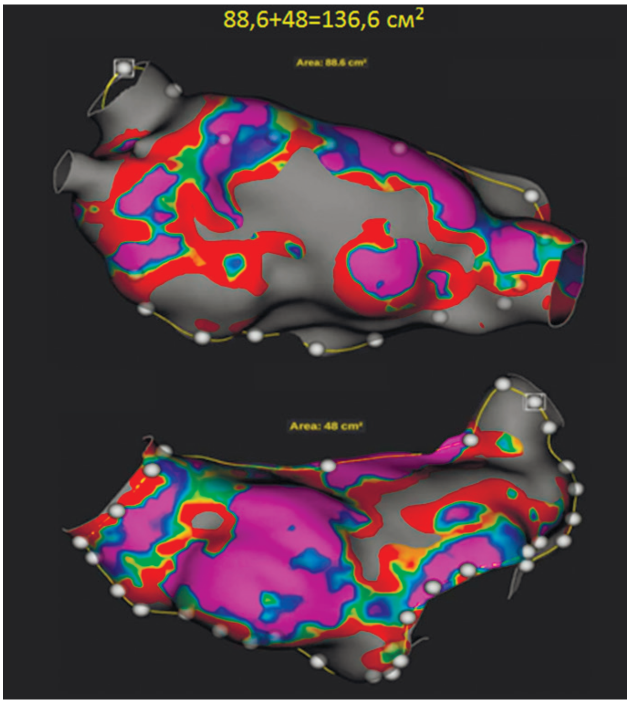

Fig. 1. Electroanatomical voltage map of the left atrium. Using the «Reset Clipping Plane» tool. The surface area of the two halves of the atrium was calculated and the total area was determined to be 136.6 cm^3. Areas where the signal amplitude is higher than 0.5 mV are colored in purple; red - signal amplitude from 0.5 to 0.2 mV; gray - signal amplitude less than 0.2 mV.

In the operating room, punctures of the femoral and subclavian veins were performed according to the Seldinger technique. A 10-pole diagnostic electrode was positioned in the coronary sinus. All patients underwent transseptal puncture under fluoroscopic control. Patients underwent catheter isolation of the pulmonary veins using cryoballoon ablation or radiofrequency ablation.

Radiofrequency exposures were carried out point by point. Radiofrequency energy during ablation was limited to 34 W and 44°C, irrigation of the catheter tip during exposure was 30 ml/min. During ablation on the posterior wall of the LA, the power did not exceed 32 W, the duration of exposure did not exceed 10 seconds at each point.

During the cryo-procedure, the cryoballoon was positioned in each pulmonary vein sequentially until complete occlusion, then a cryo-exposure was performed for 180 seconds at a temperature not lower than -60°C, but not higher than -40 °C.

The impact was carried out until the complete electrical disconnection of the antrum of the pulmonary veins from the LA, when it was not possible to register the potentials of the pulmonary veins along the antrum or inside the veins using a mapping catheter.

Intraoperatively, heparin was administered intravenously to patients at a calculated dosage of 100 units per kg. During mapping and interventional treatment, activated clotting time was monitored, the target values of which ranged from 250 to 300 seconds.

The revision of the veins was performed using a multipolar circular catheter to verify the residual potentials of the pulmonary veins, if necessary, further ablation was performed to eliminate them. Additional extrapulmonary ablation lines were not performed.

In order to detect recurrence of AF, patients were invited for follow-up examinations 3, 6, and 12 months after surgical treatment. At the control examination, ECG registration and daily ECG monitoring were performed. Also, when symptoms appeared outside the follow-up examinations, an ECG or 24-hour ECG monitoring was recommended. Registration of AF paroxysm lasting more than 30 seconds was taken into account as a recurrence of AF in the postoperative period.

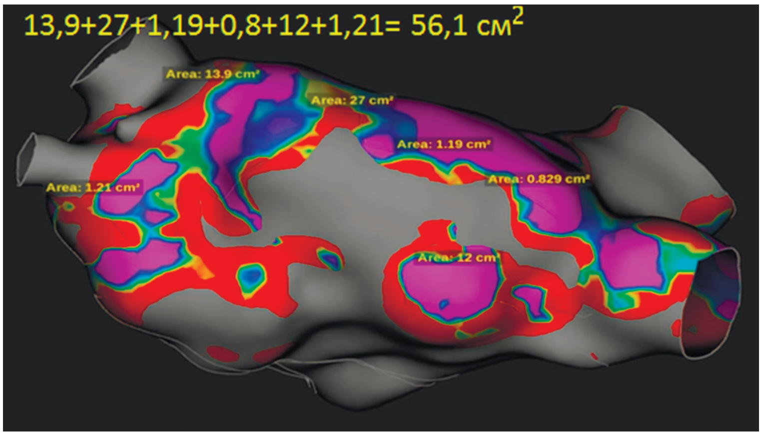

Fig. 2. Electroanatomical voltage map of the LA. Using the «Area measurement» tool. The total low-voltage area was determined to be 56.1 cm^3. Areas where the signal amplitude is higher than 0.5 mV are colored in purple; red - signal amplitude from 0.5 to 0.2 mV; gray - signal amplitude less than 0.2 mV.

Statistical analysis

Statistical analysis was performed using STATISTICA 10 software. All continuous variables were tested for normal distribution using the Shapiro-Wilk test. Normally distributed continuous variables are presented as mean ± standard deviation. Non-normally distributed continuous variables are presented as the median [interquartile range]. For qualitative variables, absolute frequencies and percentages of the total are shown. Comparisons between groups were made using the Mann-Whitney test. Box plots are provided to illustrate the significance of differences between groups. In order to identify predictors and the significance of the binary classification model, a logistic regression analysis was carried out, where R2 McF is the McFadden determination coefficient, illustrating the quality of the binary model. For all statistical tests, a two-sided significance level p=0.05 was used.

RESULTS

Low-voltage areas in the LA of high-density mapping were observed in all patients in the range from 4 to 88%. Comparison of baseline clinical characteristics is shown in Table 1.

All continuous variables except for the variables “age” and “duration of arrhythmia history” have a normal distribution (p>0.05). The continuous variables “age” and “ duration of arrhythmia history” have a non-normal distribution (p<0.05) and are presented as the median [interquartile range].

When analyzing the results obtained, the patients were divided into 4 groups according to the low-voltage area. The distribution was carried out by the Utah scale. The first group included 20 patients with a low-voltage area - 6.6±2.4%, in the second group - 19 patients, with a low-voltage area - 13.6±2.7%, in the third group - 8 patients, with a low-voltage area - 24±2.2%, the fourth group included 17 patients, low-voltage area - 54.5±16.9%.

All groups included patients with persistent and paroxysmal AF. In the group I - 6 patients with persistent AF and 14 with paroxysmal, in group II - 7 patients were diagnosed with persistent AF and 12 patients were diagnosed with paroxysmal AF, in group III there were 3 patients with persistent AF and 5 patients with paroxysmal AF, in group IV, most of the patients had persistent AF - 9 people, and 8 patients had paroxysmal AF.

In the preoperative and postoperative periods, patients took antiarrhythmic therapy (Table 1). All patients with paroxysmal AF continued to receive similar antiarrhythmic therapy after surgical treatment. Patients with persistent AF in the preoperative period received drugs of the beta-blocker group, after surgical treatment, patients were prescribed amiodarone as antiarrhythmic therapy.

In groups I and II, there is a smaller volume of LA and a higher left ventricular ejection fraction than in patients of groups III and IV.

In patients with low-voltage areas less than 10%, the volume of LA, determined according to the data of computed tomography, was 133.9±25.7 ml, in patients of group II - 139.8±29.7 ml, in patients of group III - 144 .2±37.3 ml, in patients of group IV - 161.1±56.1 ml.

In patients with a low-voltage area of less than 10%, the left ventricular ejection fraction, determined according to transthoracic echocardiography, was 64.3±6.5%, in patients of group II - 61.2±7.2%, in patients of group III - 60 .4±4.9%, in patients of group IV - 56.9±5.8%.

The comorbidities of the patients included in the study were also analyzed. Three (15%) patients from group I, 5 (26%) patients from group II, 1 (13%) patient from group III and 4 (24%) patients from group IV had diabetes mellitus.

Arterial hypertension was present in more than half of the patients in each group. In group I, 13 (65%) patients suffered from high blood pressure, in group II - 10 (53%) patients, in group III - 5 (63%) patients, in group IV - 11 (65%) patients.

In 2020, the world was hit by a pandemic of a new coronavirus infection. A total of 24 (37.5%) patients from our study had a new coronavirus infection, the distribution by group is presented in Table 1.

The choice of ablation technique was made after evaluation of computed tomography data of the LA and pulmonary veins. Pulmonary vein isolation was achieved in all patients. No complications associated with ablation procedures have been reported. Before and after catheter ablation, an LA voltage map was constructed in all patients. The number of mapping points averaged 14190±6179, mapping time averaged 19.7±7.8 minutes.

During the follow-up period of 14.5±6.7 months, AF recurrence was registered in 18 (28.1%) patients after the ablation procedure. The frequency of AF recurrence after ablation was lower in patients of groups I and II than in patients of groups III and IV. In 6 (15.4%) patients from

Table 2.

Comparison table of patients depending on the total low voltage areas

	I, II group	III, IV group	p
Age, years	61 [51-67]	63 [51-68]	0.57
Women/men	16 / 23	10 / 15	0.94
Body mass index, kg/m2	28.8±5.1	28.2±3.5	0.93
Duration of arrhythmia history, years	4 [2-6]	6 [3-8]	0.16
Left ventricular ejection fraction, %	62.8±6.9	58.1±5.7	0.01
Volume of the left atrium, ml	138.9±31.9	154.3±49.5	0.35
P-wave duration, ms	84.7±8.2	101.5±11.0	0.01
Diabetes mellitus, n (%)	8 (21%)	5 (20%)	0.97
Arterial hypertension, n (%)	23 (59%)	16 (64%)	0.69
Postponed coronavirus infection, n (%)	12 (31 %)	12 (48 %)	0.17

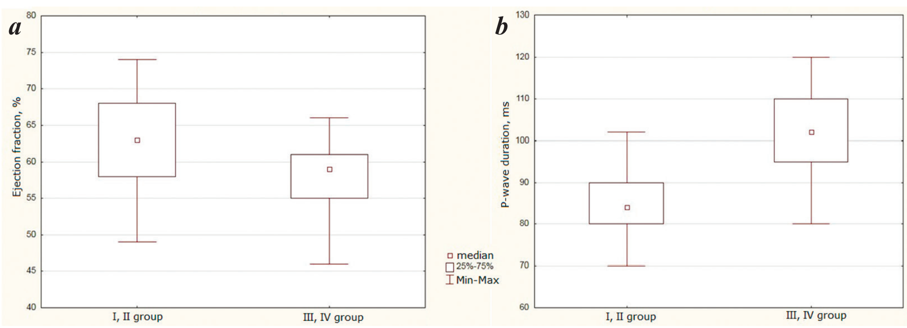

Fig. 3. Box plot illustrating the LV ejection fraction, % (a) and P-wave duration, ms (b) in groups with a low-voltage area of less than 20% (groups I and II) and more than 20% (groups III and IV).

groups I, II and in 12 (48%) patients from groups III, IV, recurrence of atrial fibrillation was recorded after catheter treatment (p=0.02).

To obtain statistical significance, patients were grouped, stages I, II of fibrosis and III, IV stages of fibrosis were analyzed. The results of the comparative evaluation are presented in Table 2.

Significant statistical differences were obtained in terms of ejection fraction and P-wave duration. Patients with a low-voltage areas have a lower left ventricular ejection fraction (62.8±6.9% vs. 58.1±5.7%, p=0.01 (Fig. 3a) and longer P-wave duration 84.7±8.2 ms vs 101.5±11.0 ms, p=0.01) (Fig. 3b).

Logistic regression analysis was performed to identify predictors of AF recurrence in the postoperative period. As a result, only low-voltage areas were an independent predictor of AF recurrence after isolation of pulmonary vein ostia, and this predictive model was significant (p=0.026). Determination coefficient R2 McF= 0.162.

DISCUSSION

This is the first domestic study that used high-density mapping (> 10,000 points) to assess the stage of fibrosis in patients with paroxysmal and persistent AF. Past studies have characterized the LA substrate according to electroanatomical mapping data, but only with 54-158 mapping points [5, 6].

In 2005, a study by Verma A. described the effect of the presence of areas of fibrosis in the left atrium on the results of primary pulmonary vein isolation [7]. The results of amplitude mapping of 700 patients were analyzed. Low voltage areas were defined where the bipolar signal was less than 0.5 mV, as described in previous studies [8,9]. The low voltage areas in this study were calculated manually by summing the area of the rectangular areas with low voltage activity. Mapping was performed with a 20-pole circular catheter, most of the mapping points were annotated manually. As a result of this study, low-voltage areas were an independent predictor of failure of radiofrequency pulmonary vein isolation. In our study, we used automatic mapping to automatically annotate points that meet the selection criteria, and we also used a multi-pole basket catheter to reduce mapping time and annotate more points (more than 10,000). The high-density mapping study also found a direct relationship between low-voltage areas and recurrence of AF in the postoperative period.

Masuda M. et al. demonstrated a direct relationship between the induction of atrial fibrillation after isolation of pulmonary veins in patients with low voltage areas. A total of 147 patients were analyzed. The majority of patients with low-voltage areas have been induced atrial tachyarrhythmias after antral isolation of the pulmonary veins. AF was induced in 70% of patients with low-voltage areas versus 16% of patients without low-voltage areas (p=0.0001); perimitral macroreentry atrial tachycardia - in 18% versus 0% (p=0.0001) [10]. This study proves the importance of voltage mapping prior to AF catheter treatment. We evaluated the occurrence of AF in the late postoperative periods in our study. It was also found that in patients with low-voltage areas (groups III and IV), AF occurs more often in the long-term period.

Today there is no consensus on the threshold values of the bipolar amplitude of fibrosis areas. Kapa et al. proposed voltage limits of 0.2-0.45 mV for "abnormal" tissues [11]. Harrison et al. based on histological data, MRI with gadolinium-containing contrast agent, and LA amplitude mapping data, pigs reported mean bipolar signal values of 0.3-0.6 mV [12]. Jadidi et al. demonstrated that electrograms in areas of accumulation of gadolinium-containing contrast agent have an average bipolar value of 0.63-0.8 mV [13]. Given the inconsistency of the results of modern studies, we decided to use the most common thresholds in the literature from 0.2 to 0.5 mV.

In 2019, a study was conducted in Spain evaluating the effectiveness of high-density mapping in predicting AF recurrence after catheter ablation. Ninety eight patients were analyzed, 40.8% of whom had persistent AF. Arrhythmia recurrence after a year of observation developed in 29 (29.6%) patients. When conducting regression analysis in this study, the only most significant predictor of arrhythmia recurrence after AF catheter treatment was also obtained - this is structural remodeling of the LA myocardium. In this study, it was evaluated using the MATLAB software [14]. However, this study included patients who had previously undergone AF catheter treatment, which could also influence the recurrence of AF or its absence in the long-term period. In our study, catheter ablation of the pulmonary veins was performed for the first time in all patients. Also, in the presented study, LA fibrosis was not quantified, the analysis was carried out on the basis of data obtained in the MATLAB software, the mean value of the bipolar signal (Vm) and the slope of the scatterplot (Vslope) were estimated. In our study, low-voltage areas were quantified using the algorithm we developed.

Study limitations

The study is relatively small and conducted at a single center, but is powerful enough to show a primary outcome. The area of the left atrial appendage was not always fully mapped due to the size of the mapping catheter and the risk of perforation.

CONCLUSION

High-density mapping of the left atrium before interventional treatment of atrial fibrillation allows to determine the stage of fibrosis. Regression analysis proved that low-voltage regions are an independent predictor of atrial fibrillation recurrence after pulmonary vein isolation. Patients with low-voltage areas greater than 20% have a longer P-wave duration and a lower left ventricular ejection fraction.

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