Russian Journal of Cardiology 2021;26(7):4526
doi:10.15829/1560-4071-2021-4526
https://russjcardiol.elpub.ru

ORIGINAL ARTICLES
ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

Electroanatomic substrate of atrial fibrillation in patients after COVID-19

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Aim. To determine the features of left atrial electroanatomic structure and the arrhythmia substrate in patients with atrial fibrillation (AF) after coronavirus disease 2019 (COVID-19).
Material and methods. The pilot study included 20 patients with AF who underwent catheter radiofrequency ablation. Ten patients had COVID-19 and 10 patients were included as a control group. AF substrate was identified using anatomic and bipolar mapping. Zones with following amplitudes were analyzed: <0,25 mV, <0,5 mV, from 0,5 to 0,75 mV inclusive, and >0,75 mV. Left atrial volume was determined based on anatomic map.
Results. The groups were homogeneous in AF type, number of patients after prior pulmonary vein isolation, and heart rate during mapping. In the COVID-19 group, there was a higher area of fibrous zones with an amplitude of <0,25 mV (51,5±16,6% vs 29,1±16,1% in the control group, p=0,007), <0,5 mV (76,7±11,5% vs 45,6±22,7% in the control group, p=0,001) and a lower area of intact myocardium with an amplitude >0,75 mV (11,6±8,0% vs 45,0±25,0% in the control group, p=0,001). In 7 COVID-19 patients, the posterior wall was isolated due to low-amplitude zones. Of these, three patients underwent surgery for the first time. According to ROC analysis, in patients after COVID-19, fibrous tissue (<0,5 mV) occupies more than half of the area, while normal tissue (>0,75 mV) — ~30% or less.
Conclusion. This study shows that SARS-CoV-2 infection may cause left atrial remodeling in the form of diffuse fibrosis. The arrhythmia substrate in patients after COVID-19 can be localized not only in pulmonary vein mouths, but also in other left atrial areas. This must be taken into account before ablation, even if the procedure is being performed for the first time. It is recommended to perform amplitude mapping for all patients who have had SARS-CoV-2 infection in order to identify fibrous zones and plan the operation extent.

Keywords: atrial fibrillation, radiofrequency ablation, coronavirus infection, fibrosis, amplitude mapping.

Relationships and Activities: none.

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Received: 27.05.2021
Revision Received: 15.06.2021
Accepted: 03.07.2021

For citation: Osadchy An. M., Semenyuta V. V., Kamenev A. V., Shcherbak S. G., Lebedev D. S. Electroanatomic substrate of atrial fibrillation in patients after COVID-19. *Russian Journal of Cardiology*. 2021;26(7):4526. (In Russ.) doi:10.15829/1560-4071-2021-4526

Coronavirus disease 2019 (COVID-19) has been studied by researchers around the world since its inception. To date, the proportion of patients who have suffered a disease caused by the severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) is consistently increasing. A large number of observations show that a more severe course and high mortality are associated with cardiovascular comorbidities. However, the pathogenesis of infection and the effect of virus on cardiac structure are not fully understood.

The central mechanism of SARS-CoV-2 penetration into cells is its binding with angiotensin-converting enzyme 2. This enzyme is also actively expressed in cardiac tissue and, to a greater extent, in cardiomyocytes themselves [1]. It is assumed that it is through this receptor that the virus can have a direct pathogenic effect on myocardium.

To a certain extent, cardiac tissue affinity is not unique to SARS-CoV-2. Other, more studied viruses, including other human coronaviruses — SARS-CoV and MERS-CoV, as well as the influenza A virus subtype H1N1, has similar properties [2]. A number of clinical observations of patients with COVID-19 have been published, which show that myocardial damage is observed in 12-23% of patients [3]. Morphologically, such damage has no specifics and manifests as moderate mononuclear cell infiltration [4].

The manifestations of myocardial involvement in COVID-19 are diverse and non-specific. There are abnormalities according to electrocardiography and transthoracic echocardiography, including ischemic. In some patients, there is an increased level of troponins I and T, creatine phosphokinase MB, as well as a heart failure marker N-terminal pro-brain natriuretic peptide [5]. Moreover, a high level of troponin I is also associated with a more severe course of infection [6]. However, an increase in this particular marker as a criterion of myocardial involvement in COVID-19 remains not entirely convincing. There is evidence that troponin I is elevated in all COVID-19 patients. An increase >99 percentile is observed in 8-12% of cases [7]. Also, an increase in troponin I concentration is observed in patients with renal failure due to slow metabolism and elimination of the enzyme from blood [3].

Elevated troponin levels may reflect both myocardial ischemic damage and myocardial inflammation. Previously, using magnetic resonance imaging (MRI), it has already been proven that some types of coronaviruses can cause acute myocarditis [8].

In patients with COVID-19-related fulminant myocarditis, blood interleukin-6 level is significantly increased, which, in turn, is associated with a more severe disease course [5]. Also, in the serum of patients, there is an increase in other pro-inflammatory cytokines, for example, CXCL10, interleukin-8, tumor necrosis factor-alpha, etc. [9]. Inflammatory mediators, in particular transforming growth factor beta, contribute to atrial fibrosis and electrophysiological abnormalities in myocardium, increasing the risk of cardiac arrhythmias, including atrial fibrillation (AF) [10]. This is confirmed by recent clinical studies where arrhythmias in patients with COVID-19 were detected in 12,9% of cases, of which AF was observed in 61,5% of patients [11].

Left atrial (LA) myocardial fibrosis plays a significant role in the initiation and maintenance of AF, as well as recurrence after lapse after pulmonary vein isolation [12]. One of the methods for determining electroanatomic substrate of AF is contact mapping using 3D endocardial navigation systems. The combined use of amplitude mapping and contrast-enhanced MRI made it possible to establish that LA areas with an amplitude of <0,5 mV are associated with fibrosis zones [13, 14].

Large low-amplitude areas associated with LA myocardial fibrosis are an unfavorable predictor of AF recurrence after pulmonary vein isolation. Given this, it is especially important to perform amplitude mapping before radiofrequency ablation (RFA) in patients after COVID-19, since this can change surgery strategy.

The aim was to determine the features of left atrial electroanatomic structure and arrhythmia substrate in patients with AF after COVID-19.

Material and methods

The pilot study included 20 patients with AF who underwent RFA between May 2020 and May 2021. Of these, 10 patients had COVID-19 and 10 patients were included as a control group. The inclusion criterion in the COVID-19 group was a prior mild or moderate viral respiratory infection verified by real-time polymerase chain reaction (PCR) test. Three participants with moderate COVID-19 received in-hospital treatment, while the rest of patients were treated on an outpatient basis. Patients underwent a full course of treatment followed by determination of anti-SARS-CoV-2 immunoglobulin G level by quantitative enzyme-linked immunosorbent assay (ELISA) at least 1 month later. Hospitalization for RFA was performed at least 1,5 months after an infection. The average time from virus verification to surgery was 124±98 days (minimum — 45; maximum — 313). The inclusion criterion for control group was the absence of documented COVID-19 and recorded contacts with COVID-19 patients, as well as the absence of anti-SARS-CoV-2 IgG antibodies by ELISA for

Table 1

Clinical characteristics of patients

Parameter	Control group (n=10)	COVID-19 (n=10)	p	ES
Age, years	61±7 [56; 67]	66±6 [61; 70]	0,180	0,62
Sex Male/female	8 (80%)/2 (20%)	4 (40%)/6 (60%)	0,085	0,41
AF/AFL	4 (40%)	7 (70%)	0,301	0,35
Type Paroxysmal/persistent	4 (40%)/6 (60%)	3 (30%)/7 (70%)	0,639	0,10
Prior surgery Primary/repeated	5 (50%)/5 (50%)	6 (60%)/4 (40%)	0,653	0,10
Baseline rhythm Sinus/AF-AFL	5 (50%)/5 (50%)	1 (10%)/9 (90%)	0,070	0,44

Abbreviations: ES — effect size, AF — atrial fibrillation, AFL — atrial flutter.

at least 1 month before procedure. After negative ELISA results for IgG antibodies, two patients in the control group underwent a course of vaccination within 1,5 months before surgery. There were following exclusion criteria: two or more prior RFA procedures; a negative ELISA for IgG antibodies with a positive PCR for SARS-CoV-2; a negative PCR test with a positive ELISA for IgG antibodies.

All patients underwent real-time PCR test of oropharyngeal swabs for SARS-CoV-2 RNA before hospitalization. Prior to study inclusion, all patients signed written informed consent. The operation was performed under local anesthesia using right common femoral vein access. Interatrial septum puncture with a BRK-1 needle was performed using fluoroscopy guidance. Determination of AF electroanatomic substrate was performed by automatic anatomical and bipolar mapping using the CARTO 3 system (Biosense Webster) and the Confidence module with a SmartTouch ThermoCool ablation catheter or a LassoNav catheter. Points was included evenly along the LA anterior and posterior walls, roof, as well as in the area of venous pools. Points at pulmonary vein orifices and mitral annulus were excluded from the analysis. The area of substrate was determined using a standard Area Measurement tool. Amplitude areas were analyzed in the range <0,25 mV, <0,5 mV, from 0,5 to 0,75 mV inclusive, as well as >0,75 mV. The LA volume was determined based on anatomical map.

Statistical analysis was performed using SPSS v.26 and STATISTICA 12 software. Distribution normality was assessed by the Shapiro-Wilk method. Quantitative variables are presented as mean and standard deviation (SD) with 95% confidence interval (CI) (Mean±SD [CI -95%; CI +95%]), as well as median and quartiles (Me [Q25; Q75]). The significance of differences in quantitative variables was assessed using the Student's t-test and Welch's t-test, as well as the Mann-Whitney U-test. The effect size is represented by Cohen's d coefficient, while d value >0,8 was regarded as a high level of effect. To exclude the influence of independent factors, multivariate analysis of variance with Tukey's test was performed. The optimal threshold values of quantitative variables were determined by receiver operating characteristic (ROC) analysis. The cut-off point was chosen by the Youden method. Testing the hypothesis on differences in the contingency tables was assessed using Fisher's exact and χ^2-Pearson tests, and the effect size (ES) — using phi coefficient and Cramer's V. Correlation analysis was carried out using the Pearson correlation coefficient, while assessment of statistical significance — using the t-test. Differences were considered significant at $p<0,05$ and test power $1-\beta >0,8$.

Results

The clinical characteristics of patients are presented in Table 1. The groups are homogeneous in AF type, number of patients after prior pulmonary vein isolation, and heart rate during mapping. These factors, both individually and in combination, did not significantly affected on the area of analyzed amplitude zones ($p>0,05$).

Mapping was performed immediately before ablation and, in the presence of sinus rhythm, was performed on atrial pacing at a cycle length of 600 ms. The number of points in the groups did not differ significantly (625 [491; 864] in the control group versus 938 [680; 1035] in the COVID-19 group, $p=0,1$). The analysis of anatomical and amplitude maps is presented in Table 2. Patients with prior COVID-19, significant and with a high effect level, had a higher fibrosis area with an amplitude of <0,25 mV, <0,5 mV and a lower area of normal atrial tissue with an amplitude >0,75 mV (Figure 1, 2). In the COVID-19 group, there is a tendency to an increase

Table 2

Analysis of anatomic and amplitude maps

Parameter	Control group (n=10)	COVID-19 (n=10)	p	Cohen's d
Left atrial volume, ml	101,2±40,5 [72,2; 130,1]	128,6±50,3 [92,5; 164,6]	0,197	0,599
Zone <0,25 mV, %	29,1±16,1 [17,5; 40,6]	51,5±16,6 [39,6; 63,4]	0,007	1,370
Zone <0,5 mV, %	45,6±22,7 [29,4; 61,8]	76,7±11,5 [68,4; 84,9]	0,001	1,728
Zone of 0,5-0,75 mV, %	9,4±3,7 [6,7; 12,0]	11,7±6,2 [7,3; 16,2]	0,312	0,465
Zone >0,75 mV, %	45,0±25,0 [27,1; 62,9]	11,6±8,0 [5,9; 17,3]	0,001	1,799

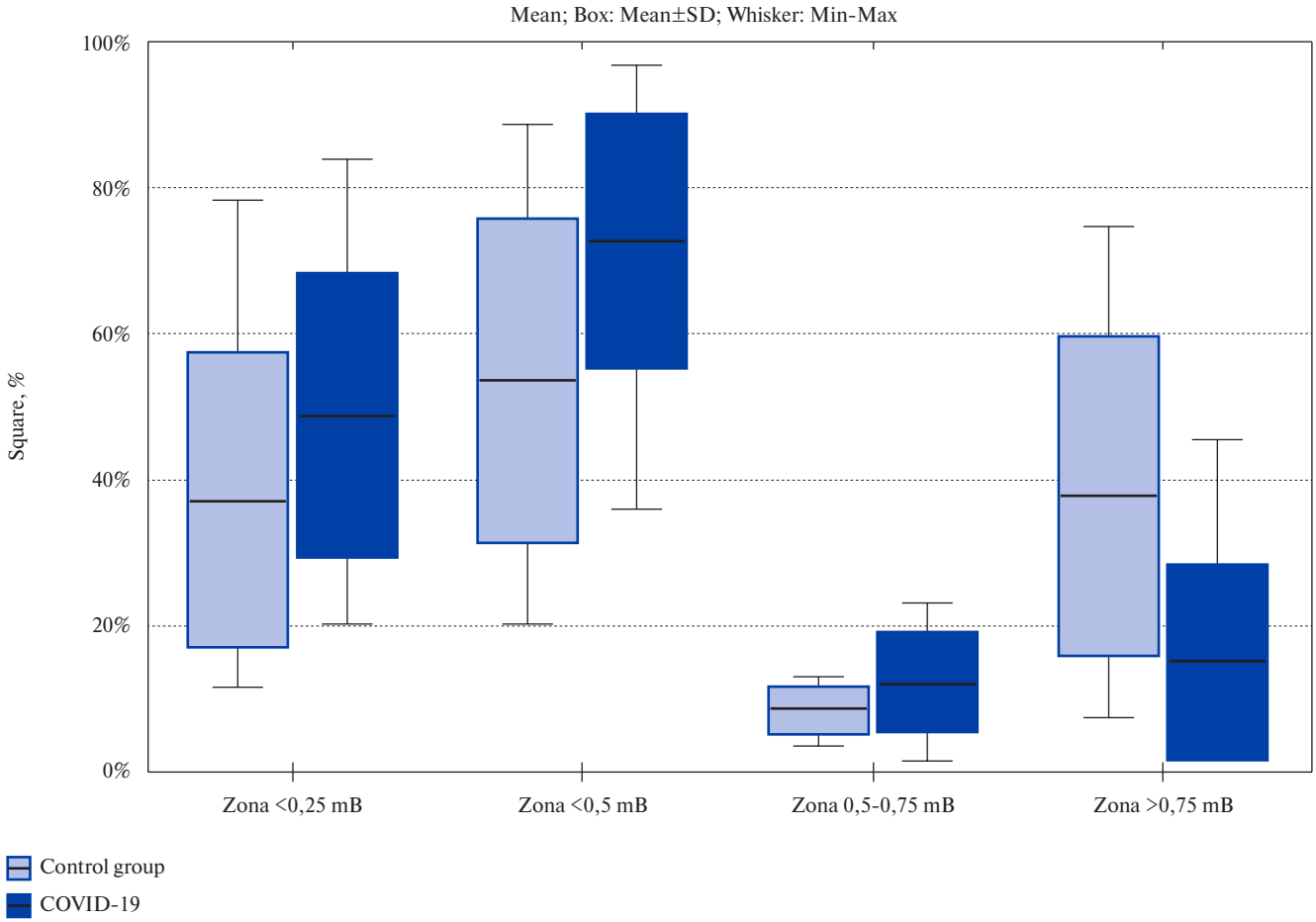

Figure 1. Area of amplitude zone.
Abbreviation: SD — standard deviation.

in LA volume and area with delayed conduction with an amplitude of 0,5-0,75 mV; the effect level was moderate, but differences were insignificant. These changes did not show any correlation taking into account the time from virus verification to operation (Table 3).

The volume of operations performed is presented in Table 4. Isolation of LA posterior wall was performed in 1 patient in the control group due to absence of electrical activity in pulmonary vein orifices after previous ablation. In the COVID-19 group, posterior wall isolation was required in 7 cases, and in 3 patients the operation was performed for the first time (Figure 3). In one case, there was also no electrical activity in pulmonary vein orifices after previous isolation. In other cases, the reason was the presence of diffuse low-amplitude zones in LA.

The ROC analysis (Figure 4) showed that in patients after COVID-19, fibrous tissue (<0,5 mV) occupies more than half of the area (Table 5), while normal tissue (>0,75 mV) ~30% or less. LA volume after infection tends to increase and reaches >120 ml (maximum, 206,9 ml).

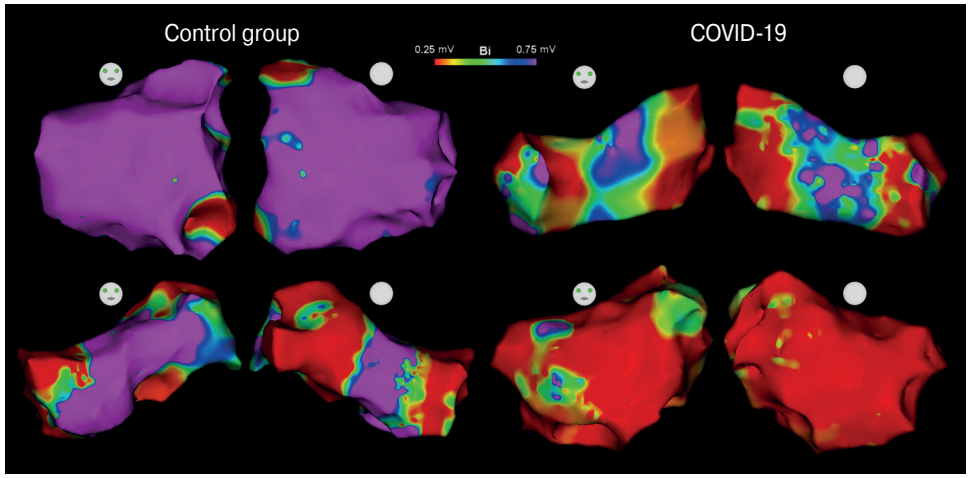

Figure 2. Amplitude maps of patients.
Abbreviation: the figure shows LA bipolar amplitude maps. Fibrous areas with an amplitude <0,25 mV are shown in red, and normal tissue with an amplitude >0,75 mV — purple. Both patients in the control group completed the full course of vaccination 1,5 months before surgery. Above shows the amplitude maps of patients who underwent surgery for the first time, below — patients with prior pulmonary vein isolation.
Abbreviation: LA — left atrial.

Table 3

Correlation analysis taking into account the time from SARS-CoV-2 verification to the operation

Parameter	Pearson coefficient (R)	Determination coefficient (R^2)	p
Left atrial volume, ml	0,44	0,189	0,209
Zone <0,25 mV, %	-0,05	0,003	0,883
Zone <0,5 mV, %	-0,39	0,150	0,269
Zone of 0,5-0,75 mV, %	-0,09	0,008	0,803
Zone >0,75 mV, %	0,63	0,394	0,051

Table 4

RFA volume

Parameter	Control group (n=10)	COVID-19 (n=10)	p	ES
Pulmonary vein isolation	9 (90%)	9 (90%)	0,763	0
Posterior wall isolation	1 (10%)	7 (70%)	0,010	0,61
CTI ablation	2 (20%)	3 (30%)	0,500	0,12

Abbreviation: ES — effect size, CTI — cavotricuspid isthmus.

Conclusion

Amplitude map points in presented work was included either at sinus rhythm or at AF. In both groups, there are patients with paroxysmal and persistent AF. Some studies have described the effect of heart rate and AF type on the signal amplitude during endocardial mapping, but this effect was not found in our study.

One study compared amplitude maps for AF and sinus rhythm after electrical cardioversion in the same patients [15]. According to study results, the baseline rhythm significantly correlates with the average amplitude of bipolar signal and also depends on arrhythmia type. In paroxysmal AF, the average amplitude is higher than in persistent AF, both in sinus rhythm and in AF. So, it follows that the total amplitude <0,5 mV obtained during AF corresponds to an amplitude <1,5 mV at sinus rhythm, and this error must be taken into account when comparing these groups of patients. At the same time, other researchers have not confirmed these results [16].

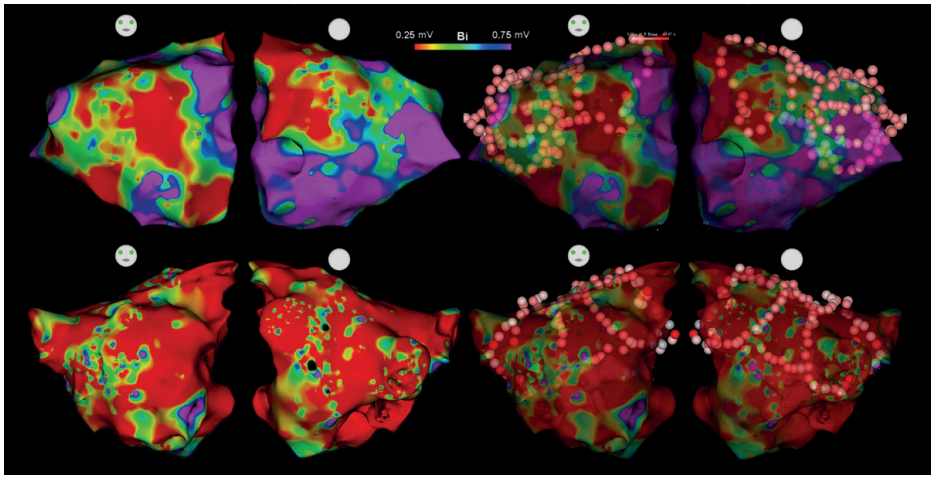

Figure 3. Amplitude maps of COVID-19 patients.
Note: the figure shows LA bipolar amplitude maps in two patients after COVID-19, who underwent RFA for the first time in combination with LA posterior wall isolation. Fibrous areas with an amplitude <0,25 mV are shown in red, and normal tissue with an amplitude >0,75 mV — purple. Ablation points are projected on the right maps.
Abbreviations: LA — left atrial, RFA — radiofrequency ablation.

Table 5

ROC-analysis

Parameter	Cut-off point	Sensitivity	Specificity	AUC±SD [CI +95%; CI -95%]	p
Left atrial volume, ml	121,9	80%	80%	0,710±0,128 [0,460; 0,960]	>0,05
Zone <0,25 mV, %	40,5%	80%	80%	0,850±0,085 [0,682; 1,018]	<0,001
Zone <0,5 mV, %	58,6%	100%	70%	0,920±0,060 [0,803; 1,037]	<0,001
Zone of 0,5-0,75 mV, %	10,7%	70%	70%	0,650±0,129 [0,396; 0,904]	>0,05
Zone >0,75 mV, %	29,8%	100%	70%	0,930±0,055 [0,822; 1,038]	<0,001

Abbreviations: AUC — area under the ROC curve, CI — confidence interval, SD — standard deviation.

Also, this conclusion does not correlate with other studies that compared amplitude maps and fibrosis images on delayed contrast-enhanced MRI. These studies did not take into account the rhythm during mapping and AF type. The results of both studies show that the fibrous areas according to contrast-enhanced MRI have an amplitude <0,5 mV [13, 14].

In another study, also when comparing amplitude maps with fibrosis images on delayed contrast-enhanced MRI, but in patients after previous ablation, the cutoff point for scarring identification was chosen <0,2 mV for pulmonary veins and posterior wall and <0,45 mV for the rest areas of LA [17]. The authors suggest that inconsistency of cut-off points is due to the fact that all patients had previously undergone pulmonary vein ablation.

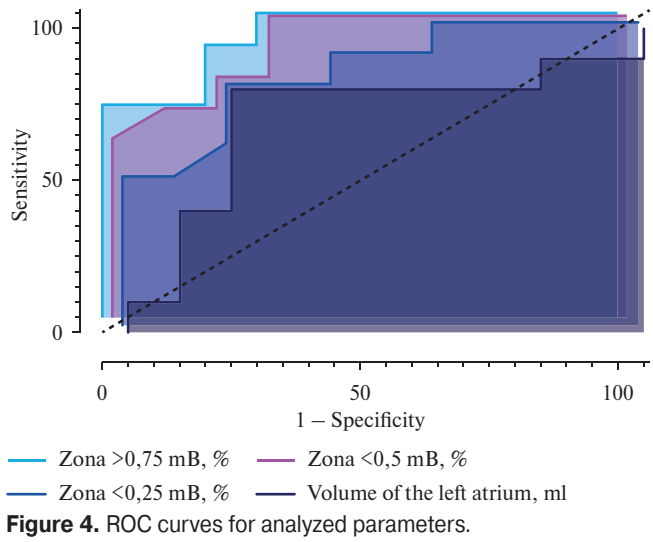

Figure 4. ROC curves for analyzed parameters.

The authors also assume that the cut-off point for fibrosis, not related with RFA, may differ. However, when compared with delayed contrast-enhanced MRI images, the authors chose a cut-off point of 0,27 mV to define the scar area.

It is also assumed that the region with an amplitude ⩽0,75 mV possesses the properties of arrhythmogenic substrate, since it is associated with a conduction slowing [18]. However, there is no conclusive evidence that an area with an amplitude of 0,5-0,75 mV is fibrous tissue.

Based on this, it follows that the fibrous tissue of LA has an amplitude of <0,45-<0,5 mV and does not depend on either the heart rate during mapping or arrhythmia type. Therefore, there is no need to take into account the error in mean signal amplitude from LA when assessing the fibrotic area.

Considering that the extensive fibrous LA areas are an unfavorable prognostic factor for AF recurrence after pulmonary vein isolation, some researchers have proposed a modified individual approach for AF substrate ablation [19]. It consists in performing isolation of LA posterior wall in the presence of fibrous areas, identified during amplitude mapping. A further large-scale study by these authors found an improved prognosis for recurrent arrhythmias in patients with a modified approach [20].

Study limitations. This is a pilot study and is currently ongoing. Due to the small number of patients meeting the inclusion and exclusion criteria, it was decided to combine patients referred for primary surgery with patients after prior pulmonary vein isolation, patients with different AF types and different heart rhythms during mapping. However, these indicators, both in univariate and multivariate analysis, did not have a significant effect on the area of analyzed amplitude zones.

Conclusion

This study shows that SARS-CoV-2 infection may cause left atrial remodeling in the form of diffuse fibrosis. These abnormalities can be detected using bipolar endocardial mapping. The arrhythmia substrate in patients after COVID-19 can be localized not only in pulmonary vein orifices, but also in other left atrial areas. Moreover, the arrhythmia substrate is mainly represented by fibrotic areas with an amplitude of <0,25 mV and <0,5 mV. This must be taken into account before ablation, even if the procedure is being performed for the first time. It is recommended to perform amplitude mapping for all patients who have had SARS-CoV-2 infection in order to identify fibrous zones and plan the operation extent.

Relationships and Activities: none.

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