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Predictors of Left Atrial Severe Fibrosis in Patients with Nonvalvular Atrial Fibrillation

Objective	The search for predictors of severe (>35%) left atrial (LA) fibrosis in patients (pts) with nonvalvular atrial fibrillation (AF) directed for catheter ablation (CA).
Materials and Methods	69 pts with nonvalvular AF (57 paroxismal and 12 persistent) aged from 32 to 69 years (mean age 57.1±8.4, 28 females) were included in the study, among them 59 pts (86%) with arterial hypertension (AH), 24 (34.8%) – with AH and CAD. Complete physical study, laboratory tests (including NT-proBNP level), comprehensive echocardiography were performed. As a surrogate substrate of LA fibrosis, the area of low-voltage (<0.5 mV) zones in LA was estimated in the process of voltage electroanatomic mapping, as the first stage of CA. The total square of LA fibrosis in absolute values (Sf, cm^2) and in percent of total LA square (Sf%), as well as the degree of fibrosis: degree I – <5%, II – 5–19%, III – 20–35%, IV – >35% were calculated. Degree IV of fibrosis was considered as severe fibrosis.
Results	Extent of fibrosis didn't depend on sex, age, body weight, presence of diabetes, CHA_2DS_2VASc scores, duration of AF history. There was a tendency to smaller Sf in pts with spontaneous termination of AF compared to those who required cardioversion: 7.2 cm^2 (4.4; 17.1) and 12.6 cm^2 (4.2; 30.5), respectively (p=0.069). Although NT-proBNP level was normal in 62% of pts (<125 pg/ml), it was higher in Sf% ≥20% than in Sf% <5%: 146.0 (48.0; 276.0) and 42.8 (24.2; 91.0) pg/ml, respectively (p=0.0216). The distribution of pts by left ventricular (LV) geometry types was as follows: normal geometry (t.1) – 34, concentric remodeling (t.2) – 16, concentric LV hypertrophy (t.3) – 8, eccentric LV hypertrophy (t.4) – 11. Compared to pts with t. 1 (reference level), pts with t.3 and t.4 had higher LA volume and LV myocardial mass index, and pts with t.4 had larger end-diastolic LV volume and lower LV ejection fraction. Pts with t.4 tended to have higher Sf% than t.1: 31.1 (10.2; 46.2) and 11.2 (5.1; 28.0), respectively (p=0.053). Using logistic regression 3 independent predictors of LA severe fibrosis were detected: type 4 geometry of LV – OR=8.893 (95% CI 1.150; 68.78), NT-proBNP >128 pg/ml – OR=6.184 (1.01; 37.99), LA volume index >34 ml/m^2 – OR=5.92 (1.05; 33.38). According to ROC analysis, the area of the curve AUC = 0.839 (p<0.001), model specificity – 85.1%, sensitivity – 70.0%, predictive accuracy – 82.5%.
Conclusion	In pts with nonvalvular AF predictors of severe (>35%) LA fibrosis were LV geometry type in the form of eccentric LV hypertrophy, LA volume index >34 ml/m^2 and NT-proBNP >128 pg/ml.

Keywords	Atrial fibrillation; catheter ablation; left atrial fibrosis; electroanatomic mapping; low-voltage zones; eccentric hypertrophy
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Extensive information obtained in clinical and interventional studies confirmed that fibrosis of left atrium (LA) is a critical factor for atrial fibrillation (AF) drivers [1]. The synergetic activity of pathological factors such as fibrosis, changes in wall thickness and orientation of the muscle fibers, anisotropy, and electrical remodeling results in the unique characteristics of atrial tissue that contribute to the formation of AF driver [2]. It was proved that more stable forms of AF are associated with more severe fibrosis [3].

Late gadolinium enhancement cardiac magnetic resonance imaging (MRI) is the most commonly used technique to assess fibrosis [4, 5]. The DECAAF study showed that the degree of fibrosis, as determined by delayed contrast-enhanced MRI, is the most significant predictor of ablation efficacy [6]. It was also established that LA fibrosis could be visualized using electroanatomical voltage mapping (EAM). This technique allows assessing atrial fibrous tissue through the detection of a low voltage

(< 0.5 mV) signal [7, 8]. Although neither technique is a gold standard, a close correlation between the MRI and EAM results was shown [9, 10].

There is evidence that the efficacy of catheter ablation (CA) in AF depends on the severity of LA fibrosis [11, 12], which is why trying to predict LA fibrosis size through the non-invasive techniques before CA is extremely important, as it allows choosing a patient with an estimated high efficacy of CA or, on the contrary, deciding in favor of conservative if the expected efficacy of CA is low [13].

The objective of the study was to identify predictors of severe LA fibrosis in patients with nonvalvular AF referred for CA.

Materials and Methods

The pilot study included 69 patients (28 females, 41 males) with nonvalvular AF, at the age of 32 to 69 years old (mean 57,1 ± 8,4 years old) hospitalized for primary CA due to AF in Tyumen Cardiology Research Center.

Inclusion criteria: individuals of both gender at the age of 21 to 70 years old inclusive with paroxysmal or persistent AF of nonvalvular etiology and indications for primary CA due to AF as to the Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation [14].

Exclusion criteria: individuals younger than 21 and older than 70 years old with rheumatic valvular heart disease or mechanical heart valve prostheses, without indications for CA due to AF or contraindications to this procedure (a thrombus in the LA cavity identified by transesophageal echocardiography, acute or exacerbation of chronic inflammatory diseases, no remission in the case of cancer) [14].

The study was performed under the Declaration of Helsinki, the study protocol approved by the facility's local ethics committee. Informed consent was obtained from all subjects. Source of financing: Tyumen Cardiology Research Center, Tomsk National Research Medical Center of RAS, Tomsk, Russia

Clinical characteristics of patients are provided in Table 1. 82.6% of patients had the paroxysmal form of AF, 8 (11.6%) patients had an isolated form. Forty-five patients (65.2%) with the preserved systolic function of LV presented with signs of chronic heart failure (CHF), predominantly of functional classes (FC) I and II.

Drug therapy included oral anticoagulants (OACs), antiarrhythmic drugs (AADs), and background therapy of the underlying disease. OACs were administered in all patients at the outpatient stage before being admitted to the hospital and within the hospitalization period and continued even during the catheter ablation. The OACs were distributed as follows: dabigatran – 22 patients, rivaroxaban – 20, apixaban – 15, warfarin (the target level of international normalized ratio (INR) to be maintained at 2.0 to 3.0) – 12 patients. The antiarrhythmic therapy included amiodarone in 10 patients, propanorm – 15, sotalol – 17, allapinin – 4, beta-blockers in 21 patients. Two patients did not receive the AADs. As the background therapy, ACE inhibitors were administered in 20 patients, sartans – 34, diuretics – 22, statins – 50, calcium antagonists – 8 patients.

All patients underwent before surgery the following examinations: standard 12-lead electrocardiography (ECG), transthoracic echocardiography with a detailed assessment of the structural and functional state of the heart, and laboratory blood tests. Endocardial bipolar voltage mapping of LA was performed as an initial stage of the catheter isolation of the pulmonary vein (PV) mouths.

Transthoracic echocardiography included the assessment of sizes and volumes of the cardiac chambers [15] and systolic and diastolic LV functions under the current recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [16]. The examinations were performed by one investigator who used the Vivid E9 scanner, the data were saved, and indicators averaged for three consecutive cardiac cycles were calculated. The type

Table 1. Clinical characteristics of the examined patients

Parameter	Value
Age, years	57.1±8.4
Female, n (%)	28 (40.6)
AH, n (%) • stage 1, n • stage 2, n • stage 3, n	59 (86) 6 29 24
CAD, n (%) including CAD combined with AH, n History of MI, n	26 (37.7) 24 2
CHF, n (%) • FC I, n • FC II, n • FC III, n	45 (65.2) 25 18 2
AF pattern • Paroxysmal, n (%) • Persistent, n (%)	 57 (82.6) 12 (17.4)
Isolated AF, n (%)	8 (11.6)
Duration of AF history • less than 1 year, n • 1 to 3 years, n • more than 3 years, n	 7 22 40
Mean CHA_2DS_2-VASc score, points • > 0 point, n • > 1 point, n • ≥ 2 points, n	1.9 7 22 40

CAD, coronary artery disease; MI, myocardial infarction; CHF, chronic heart failure; FC, functional class; AF, atrial fibrillation.

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of LV geometry was determined by the calculations LV mass index (LVMI) and relative wall thickness (RWT) LV [15]. LV RWT is calculated by the following formula: 2 x LV posterior wall thickness (mm)/LV end-diastolic diameter (mm). The following types of LV geometry were distinguished: type 1 (normal cardiac geometry): normal LVMI (≤95 g/m^2 in females and <115 g/m^2 in males) and RWT ≤0,42; type 2 (concentric remodeling): normal LVMI and RWT >0.42; type 3 (concentric hypertrophy): increased LVMI (>95g/m^2 in females and >115 g/m^2 in males) and RWT >0.42; type 4 (eccentric hypertrophy): increased LVMI and RWT ≤ 0,42.

LA EAM was carried out as a first stage of the primary radiofrequency isolation of PV orifices. The 3D-navigation system Carto 3, the mapping ablation electrode Thermocool Smart Touch, and/or the multi-pole circular mapping electrode Lasso NAV were used. Bipolar mapping was mainly automatic using the mapping module Confidence module or manual by the point-by-point method. The voltage map of changes LA was analyzed after surgery by an experienced electrophysiologist. Regions of low voltage were identified at the bipolar signal amplitude <0.5 mV [13].

Fibrosis sizes were calculated using the Area Measurement module followed by automatic calculation of the area of LA fibrosis; areas of the mitral valve and the PV orifices were excluded from the calculation. The following parameters were calculated: total area of LA fibrosis (Sf, cm^2, by summing up the individual zones), Sf (%) – the percentage of fibrosis in the total area of LA, the degree of fibrosis as by the UTAH score: degree I – <5%, II – 5–19%, III – 20–35%, IV – >35% [4]. Fibrosis degree IV was used as a criterion of significant fibrosis.

The laboratory tests included complete blood count, blood chemistry, including serum creatinine, followed by the calculation of glomerular filtration rate, N-terminal pro-brain natriuretic peptide levels – NT-proBNP (pg/mL), insulin (μIU/L).

When the signs of CFH were identified, a 6-minute walk test was performed to clarify the functional class.

Statistical analysis was carried the using Statistica 12.0 and SPSS 21.0 software packages. The distribution of continuous variables was evaluated with the Kolmogorov-Smirnov test. In the normal distribution, data were presented as the mean and standard deviation (M ± SD). If the variables were not normally distributed, the data were presented as the median and interquartile range, Me [25%; 75%]. Depending on the distribution, the values in two independent groups were compared using the Student's t-test or Mann-Whitney U-test, when three or more independent groups were compared using ANOVA or the Kruskal-Wallis test and the multiple-comparison approach. The quality indicators were compared using the chi-squared test and the Fisher's exact test. The correlations between pairs of quantitative parameters were estimated using the nonparametric Spearman's rank correlation coefficient. The method of logistic regression was used to search for predictors of fibrosis and build the model. The quality and efficacy of the model were assessed using the ROC-analysis. The results were estimated as significant at $p < 0,05$.

Results

In the assessment of fibrosis severity, total area Sf varied from 0 cm^2 to 89.8 cm^2, median – 9.15 [4.2; 24.9] cm^2. The relative area of fibrosis Sf ranged from 0% to 95.6%, median – 13.8 [5.3; 34.3] %. Patients were distributed by the degrees of fibrosis as follows: degree I (< 5%) – 14 patients, II (5–19%) – 24 patients, III (2035%) – 16 patients, IV (> 35%) – 15 patients.

The comparative analysis between the groups of patients with fibrosis of varying degrees revealed no significant differences in such parameters as gender, age, body mass index, diabetes status, chronic kidney disease, and anemia. There was a trend towards less severe fibrosis in patients with spontaneous reversal of fibrillation as compared with those who required electric or drug cardioversion to stop arrhythmia: Sf 7.2 [4.4; 17.1] cm^2 and 12.6 [4.2; 30.5] cm^2, respectively ($p = 0,069$), and Sf% 11.9 [5.2; 27.9] % and 27.2 [6.8; 38.1] %, respectively ($p = 0,086$).

The Spearman analysis showed no significant correlation between the size of fibrosis and CHA2DS2-VASc score, CHF FC and duration of AF history. NT-proBNP levels were within the normal range (< 125 pg/mL) in 62% of patients. Nevertheless, and despite the lack of a significant correlation between the size fibrosis and CHF FC, patients with Sf% > 20% had higher levels of NT-proBNP than patients with Sf% < 5%: 146.0 [48.0; 276.0] pg/mL and 42.8 [24.2; 91.0] pg/mL, respectively ($p = 0,0216$).

The relationship between the size of fibrosis and echocardiographic parameters was studied: fibrosis area Sf was significantly directly correlated with LA diameter index ($R = 0.47$; $p < 0.05$), end-diastolic volume of LA ($R = 0.44$; $p < 0.05$), LVMI ($R = 0.35$; $p < 0.05$), end-systolic size of LV ($R = 0.26$; $p < 0,05$), and negatively correlated with ejection fraction (EF) of LV ($R = –0.27$; $p < 0.05$). Systolic pulmonary artery pressure (sPAP) increased with higher degree of LA fibrosis: sPAP in patients with fibrosis degree IV (28.07 ± 6.96 mm Hg) was higher than in patient with fibrosis degree I and II: 23.14 ± 3.74 mm Hg ($p = 0.0114$) and 22.04 ± 5.54 mm Hg ($p = 0,0057$), respectively.

As there are no significant differences in most of the determined parameters of LV diastolic function in

patients with LA fibrosis of varying degrees, their detailed presentation is unreasonable. As for LA volume index as one of the main criteria of diastolic dysfunction in normal LVEF, significant differences were found between the groups of patients with LA fibrosis degrees IV and I: 34.75 ± 10.04 mL/m² and 26,49 ± 7,39 mL/m², respectively (p = 0,0462). LA volume index > 34 mL/m² is known to be one of four main criteria of the diagnosis of LV diastolic dysfunction with preserved EF [16].

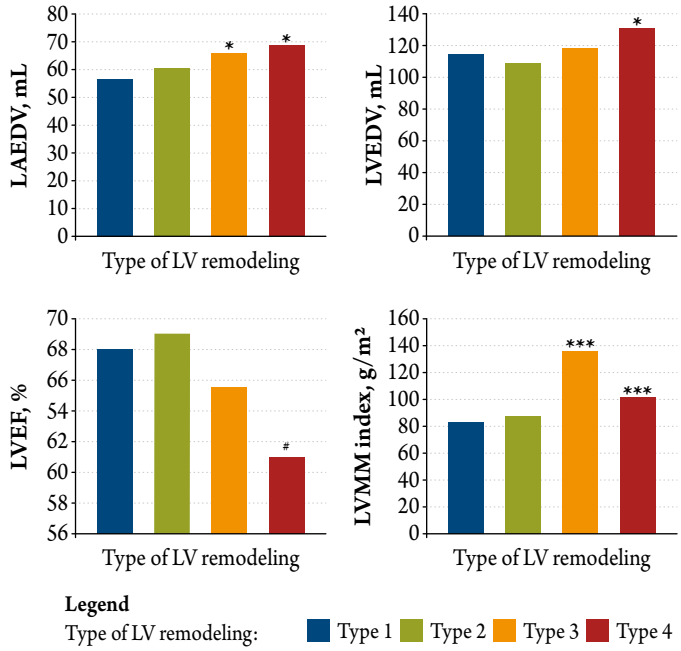
Patients are distributed by the types of LV geometry as follows: 34 patients had regular cardiac geometry, 16 – concentric remodeling, 8 – concentric LV hypertrophy, and 11 – eccentric hypertrophy of LV. The results of the comparison of the echocardiography parameters of patients with different types of remodeling and regular LV geometry are shown in Figure 1 (values of patients with regular geometry were used as reference). Patients with concentric (type 3) and eccentric (type 4) hypertrophy differed by higher volumes of LA and LVMI. Patients with eccentric hypertrophy had additional differences, such as the larger end-diastolic volume of LV and lower LVEF. Thus, a trend toward the decrease in LV systolic was observed in patients with eccentric LV hypertrophy, unlike in patients with regular LV geometry.

When the sizes of fibrosis were compared in patients with different types of cardiac geometry, a significant trend toward a larger area of fibrosis Sf% was observed in patients with eccentric LV hypertrophy as compared with the regular LV geometry: 31.2 [10.2; 46.2] cm² and 11.2 [5.1; 28.0] cm², respectively (p = 0,053; Figure 2.); Sf% didn't differ significantly between patients with concentric remodeling and concentric hypertrophy and patients with regular geometry: 12.7 [0.8; 33.4] cm² and 24.0 [11.7; 45.5] cm², respectively.

The next stage was the search for predictors of severe LA fibrosis, as an arbitrary criterion of which fibrosis degree IV was chosen (i.e., >35% of the total area of LA). Potential predictors considered were the parameters showing significant difference (p <0,05) or trend toward significant differences (p <0,1) between the patient groups with and without LA fibrosis >35% (Table 2).

The logistic regression was used to search for the independent predictors of severe fibrosis. LA fibrosis of > 35% was used as the dependent variable. The listed parameters (see Table 2) were used as potential predictors. The cut-off values of the individual parameters were found using the ROC-analysis, which allowed a variable to be presented in binary form. Eventually, it increased the significance and quality of the model and made it more convenient to use. These cut-off points were NT-proBNP > 128 pg/mL and LA volume index > 34 mL/m². The results of the logistic regression analysis are provided in Table 3.

Figure 1. Comparison of echocardiographic parameters with different types of LV remodeling



Type 1 – normal geometry of LV; type 2 – concentric remodeling of LV; type 3 – concentric hypertrophy of LV; type 4 – eccentric hypertrophy of LV. EF, ejection fraction; LV, left ventricle; LVMM, left ventricular myocardial mass; LVEDV, left ventricular end-diastolic volume.
Significance of differences versus type 1:
* p <0,05; ** p <0,01; *** p <0,001; # p <0,1.

The regression equation for the calculation of the probability of fibrosis > 35% can be as follows:

$$F = -5{,}54 + 2{,}158 \times \text{eccentric hypertrophy} + 1{,}822 \times \text{NT-proBNP} > 128\ \text{pg/mL} + 1{,}778 \times \text{LA volume index} > 34{,}0\ \text{mL/m}^2$$

The probability of LA fibrosis > 35% can be calculated after applying the logit transformation of the resulting linear regression equation:

$$P = 1/(1+e^{(-F)}),$$

where P is the probability of the event; e is the mathematical constant equal to 2.718; F is the value of the regression equation.

The cut-off value for the LA fibrosis > 35%, is 0.15.

The ROC-analysis was used to estimate the quality of the resulting model (Figure 3): AUC = 0,839 (p < 0.0001), specificity of the model is 85.1%, sensitivity – 70.0%, prognostic accuracy – 82.5%: prognostic accuracy of the positive test result is 50%, prognostic accuracy of the negative test result – 93.0%.

Thus, this study made it possible to build a mathematical model allowing to predict, with a high probability

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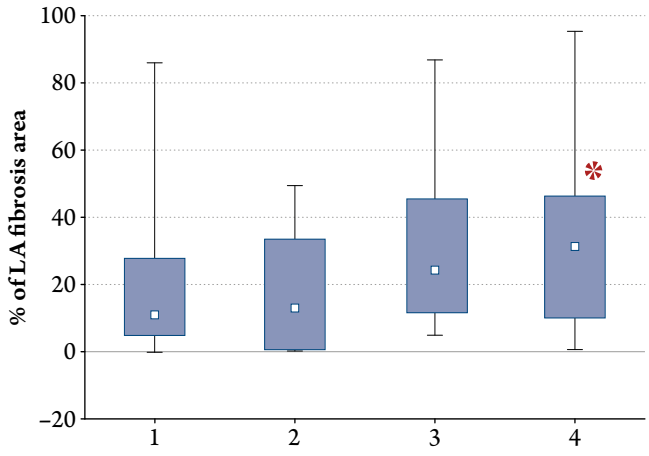
Figure 2. Comparison of the area of LA fibrosis (Sf%) in patients with different types of LV geometry



Types of remodeling:
1 – regular geometry, 2 – concentric remodeling,
3 – concentric hypertrophy,
4 – eccentric hypertrophy of LV.
LA – left atrium; LV – left ventricle.

* p = 0,053 between geometry types 1 and 4.

(82.5%) and using available noninvasive parameters, whether patients with nonvalvular AF have severe (>35%) LA fibrosis, which is essential to choose the optimal management.

Discussion

It has been established that radiofrequency CA is a successful treatment technique in many patients with AF. However, approximately ⅓ of patients suffer post-surgery AF recurrences even after several procedures [14, 17]. With stable AF, the recurrence rate reaches 50% [18]. Therefore one of the ways to increase the efficacy of this treatment method may be to improve the selection of candidates for CA surgery.

Since fibrosis is associated with stable AF and recurrences of AF after ablation [19], assessment of LA fibrosis before surgery may help to select patients for successful primary or repeat procedure.

A recent prospective cohort study [13] has revealed that the size of low-voltage regions exceeding 30% of the LA area is a powerful predictor of recurrence within the first year after primary CA. In this connection, fibrosis degree IV was (i.e., > 35%) was chosen as a criterion of significant fibrosis, which was clearly associated with the expected low efficacy of planned surgery.

The development of AF is known to be associated with remodeling and dilation of LA and remodeling of LV [20]. However, the association between a particular type of LV geometry, dilatation of LA, and the development of AF is still understudied. A recent retrospective analysis of 4,444 patients showed that the incidence of AF depends

Table 2. Results of comparative analysis of the parameters depending on the presence or absence of severe LA fibrosis

Parameter	Degree of LA fibrosis <35% (n = 53)	Degree of LA fibrosis >35% (n = 16)	p
sPAP, mm Hg	23.0±5.0	28.0±7.0	0.005
RA volume index, mL/m²	23.2±7.4	28.0±8.4	0.035
Eccentric hypertrophy of LV, n (%)	6 (11.3)	5 (31.3)	0.056
Normal geometry, n (%)	30 (56.7)	4 (25.0)	0.044
LVEF, %	67±5	61±7	0.002
NT-proBNP, pg/mL	70.8 [28.8; 148.5]	154.0 [113.5; 390.5]	0.012
LA volume index, mL/m²	29.5±7.8	35.4±10.1	0.019
LVMI, kg/m²	91.3±21.4	103.8±17.3	0.007
Serum insulin, μIU/L	13.5±10.3	7.8±4.4	0.038

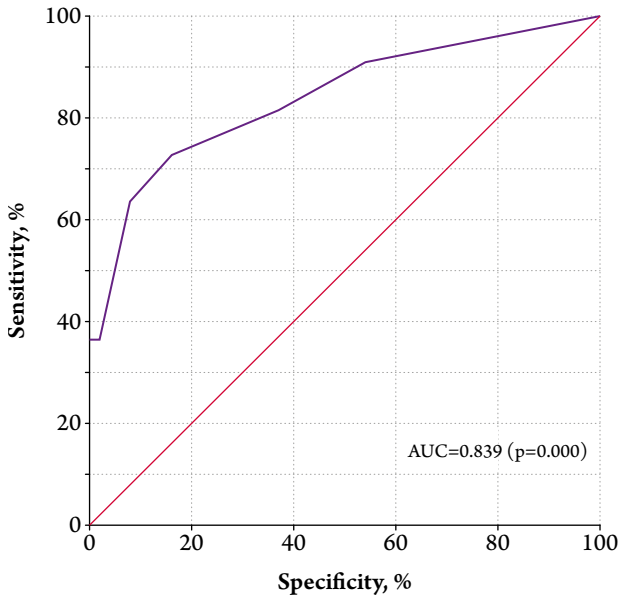
sPAP, pulmonary artery systolic pressure; RA, right atrium; LV, left ventricle; EF, ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; LA, left atrium; LVMI, left ventricular mass index.

Table 3. Results of the logistic regression analysis to predict severe LA fibrosis

Predictors	B	Wald test	p	OR	95 % CI
Eccentric hypertrophy of LV (0 – no, 1 – yes)	2.185	4.384	0.036	8.893	1.150–68.775
NT-proBNP > 128 pg/mL (0 – no, 1 – yes)	1.822	3.868	0.049	6.184	1.006–37.999
LA volume index > 34 mL/m² (0 – no, 1 – yes)	1.778	4.061	0.044	5.920	1.050–33.383
Constant	–5.540	11.416	0.001	0.004	–

LA, left atrium; OR, odds ratio; CI, confidence interval; LV, left ventricle; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Figure 3. ROC-curve analysis to predict LA fibrosis > 35%



on the type of geometric LV remodeling, which in turn is associated with the size of LA and LVEF [21]. According to this study, such type of LV geometry as eccentric LV hypertrophy is most closely associated of all types of remodeling with an increase in LA volume, reduced LVEF and the incidence of AF, which was higher in patients with eccentric hypertrophy (16.8%) than in patients with regular LV geometry (10,4%), concentric remodeling (10.5%) and concentric hypertrophy (14.8%) ($p < 0.0001$). This is entirely consistent with our findings showing that the LA fibrosis was most commonly observed in such type of LV geometry as eccentric hypertrophy. According to our findings, it is the presence of the eccentric LV hypertrophy that was the most significant predictor of severe LA fibrosis: it increased the risk of LA fibrosis > 35% 8.89-fold (95% CI 1.150–68,775; p = 0,036). As shown above, this type of cardiac geometry was associated with the most severe dilation of LA, increased LV myocardial mass, incipient LV dilatation, and a tendency towards reduced LV function.

NT-proBNP > 128 pg/mL was the second independent predictor of severe fibrosis. NT-proBNP > 125 pg/mL is one of the criteria for the diagnosis of CHF with preserved LVEF [22]. Although we have not found a significant association between fibrosis sizes and clinical signs of CHF, it is still can be concluded that severe LA fibrosis is associated with the initial preclinical manifestations of CHF. The effect of many AF risk factors is known to be often implemented through LV diastolic dysfunction [23]. We have not found any significant associations between the degree of fibrosis and most parameters of LV diastolic function. However, the 3rd independent predictor, i.e., LA volume index > 34 mL/m^2, is one of the main criteria of LV diastolic dysfunction [15].

The mathematical model incorporating data obtained using the available non-invasive techniques can be used in real-world clinical practice to identify patients with severe LA fibrosis, which will allow selecting in advance either a conservative treatment strategy or consider comprehensive intervention in the arrhythmogenic substrate of AF in LA during the primary CA.

Limitations

The study included a small number of patients. The point-by-point EAM did not establish the optimal parameters of mapping density. EAM was performed in individual patients with AF, which could cause an error in calculating the LA areas of low voltage.

Conclusion

Thus, when choosing patients for catheter ablation due to atrial fibrillation, it is useful to predetermine the probability of severe left atrial fibrosis by assessing the left ventricular geometry, left atrial volume index and determining blood levels of NT-proBNP.

Eccentric left ventricular hypertrophy, left atrial volume index > 34 mL/m^2, and NT-proBNP > 128 pg/mL are the predictors of severe left atrial fibrosis (more than 35% area of the left atrium).

No conflict of interest is reported.

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