


# Predictors of left atrial fibrosis in patients with atrial fibrillation referred for catheter ablation

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## Abstract

**Background:** Left atrial (LA) fibrosis in patients with atrial fibrillation (AF) is associated with an increased risk of AF recurrence after catheter ablation. Therefore, we searched for clinical risk factors that confer an increased risk of LA fibrosis, which can influence the treatment strategy.

**Methods:** We included 94 patients undergoing 3-dimensional electroanatomical voltage mapping-guided catheter ablation of AF. LA low-voltage areas during sinus rhythm as a surrogate parameter of fibrosis were measured with the CARTO3 mapping system and adjusted for LA volumes obtained by computed tomography. Blood tests including N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) and echocardiographic parameters of left ventricular function were also analyzed.

**Results:** Patients were  $62.5 \pm 11.4$  years old, and 29% were female. LA fibrosis was present in 65%, with 50% having a fibrotic area  $> 5\%$  ( $\geq$  Utah-Stage 1). Mean left ventricular ejection fraction (LVEF) was  $53.9 \pm 10.5\%$ . Patients with LA fibrosis had higher NT-proBNP levels ( $869 \pm 1056$  vs.  $552 \pm 859$  ng/L,  $p = 0.001$ ) and larger LA volumes (body surface area-corrected  $63.3 \pm 19.3$  vs.  $80 \pm 27.1$  mL/m<sup>2</sup>,  $p = 0.003$ ). In univariable analyses, LA fibrosis was significantly associated with female gender, older age, increased LA volumes, hypertension, statin therapy, higher NT-proBNP values, and echocardiographic E/e'. In bivariable analyses, higher NT-proBNP echocardiographic parameters of diastolic dysfunction, female gender, older age, and higher DR-FLASH scores remained as independent predictors of LA fibrosis.

**Conclusions:** In this single-center longitudinal study, surrogate parameters of elevated left-sided cardiac filling pressures such as higher NT-proBNP levels and higher echocardiographic E/e' values as well as female gender independently predicted the prevalence of LA fibrosis in patients referred for catheter ablation of AF. (Cardiol J 2022; 29, 3: 413–422)

**Key words:** atrial fibrillation, heart failure with preserved ejection fraction, diastolic dysfunction, gender medicine, atrial fibrosis

## Introduction

Atrial fibrillation (AF) is a common rhythm disorder affecting about 3% of adults [1]. Because left atrial (LA) fibrosis has been associated with an

increased incidence of stroke and AF recurrence after catheter ablation, it is important to identify potentially modifiable risk factors for LA fibrosis, and to identify patients who may benefit less from catheter ablation of AF [2]. Recent studies have

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suggested an approximately 2-fold higher amount of LA fibrosis in women as compared to men, but it is unclear whether this finding is an independent gender-dependent effect or linked to other risk factors. Recently, the APPLE-score, which does not include female gender, has been suggested as a potential tool to predict LA fibrosis prior to catheter ablation of AF [3].

In previous studies, LA fibrosis was mainly assessed by cardiac magnetic resonance imaging (CMR) with late gadolinium enhancement. CMR uses a different non-invasive method to assess LA fibrosis as compared to invasive 3-dimensional (3D) electroanatomical voltage mapping (EAM) with assessment of bipolar low-voltage areas (LVA), which can be used as a surrogate parameter for myocardial fibrosis [4–7]. Furthermore, there is previous evidence of the usefulness of targeting LVA to successfully treat AF [8]. Therefore, we sought to identify clinical risk factors of LA fibrosis by using EAM in a cohort of patients referred for catheter ablation of AF.

## Methods

### Study population

In this longitudinal single-center study, out of a total of 634 patients receiving AF ablation at our center, 94 patients were included in this analysis. The remaining patients were excluded for the following reasons: 1) Only LA maps obtained during sinus rhythm were included; 2) Some AF ablations were performed using cryoballoon technology; 3) Some LA maps were created using the “point by point” method with insufficient LA mapping points; 4) For methodological reasons we included only patients in whom radiofrequency (RF) ablation was performed by three operators, because those three had the same mapping/ablation approach; 5) Patients with incomplete electroanatomical LA maps were excluded; 6) At the beginning of 2019, we had a system crash of our EAM Software and the backup of several months (including maps) was lost. Therefore, 94 consecutive patients undergoing a catheter ablation procedure for AF during sinus rhythm (SR) were enrolled between 2016 and 2021. All patients underwent pulmonary vein (PV) isolation (PVI) using endocardial RF ablation guided by 3D EAM of the LA. Different types of AF were defined according to current European guidelines [1]. The APPLE and DR-FLASH score were calculated as previously described [7, 9]. The CHA<sub>2</sub>DS<sub>2</sub>-VASc score was adjusted for gender (–1 point in females). Subjects with a reduced

left ventricular ejection fraction (LVEF) < 40% or a known myocardial disease were assumed to have a diastolic dysfunction at least grade I in the absence of further documentation according to current guidelines [10]. This retrospective study was approved by the Ethics Committee of the Canton of Zurich (KEK-ZH-Nr.2016-00116).

### Cardiac computed tomography

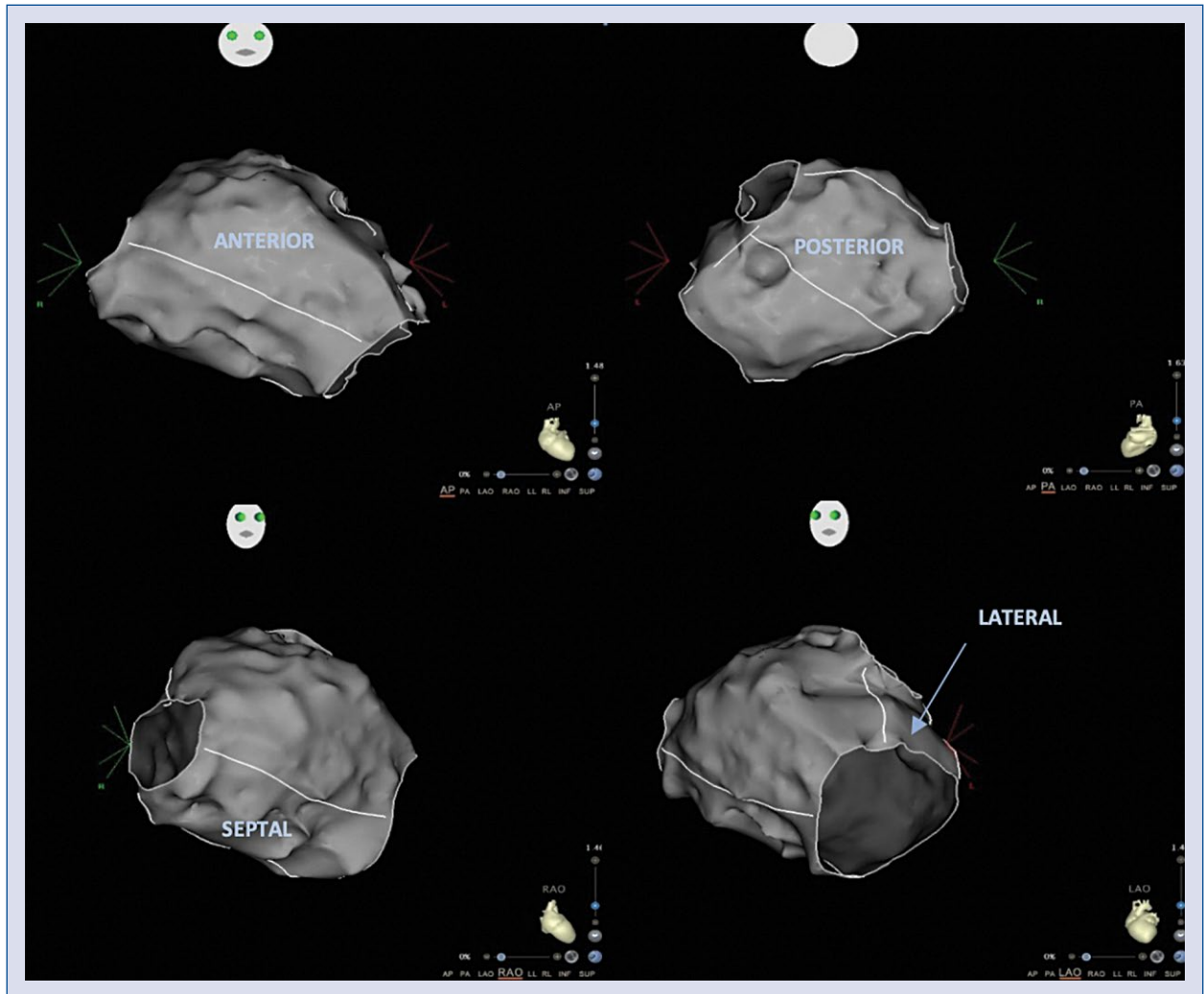
Cardiac computed tomography (cCT) was performed within < 48 h prior to the procedure to exclude LA thrombi and measure the LA volume. PV, left atrial appendage (LAA), and mitral valve were excluded from the volume analysis. Aortic dimensions (sinus portion and diameter of the ascending aorta) were assessed. Measurements were performed using Advanced Workstation GE software (v11.3, GE Healthcare, USA).

### Catheter ablation

All ablation procedures were conducted under general anesthesia. Diagnostic multipolar catheters were positioned in the coronary sinus and at the His-bundle. Access to the LA was performed by single or double trans-septal puncture [11]. 3D-LA anatomy was reconstructed during SR (Fig. 1) in the 3D-EAM CARTO3 system (Biosense Webster, Diamond Bar, California, USA). Only patients in whom conversion to SR was possible and in whom voltage maps were created during SR were included. After 3D reconstruction of the LA with the 20-polar Lasso Nav catheter or multipolar PentaRay catheter (Biosense Webster), the ostium of each PV was tagged to guide wide-area circumferential ablation. The goal was to achieve electrical isolation of the PV (entrance block) after a waiting period of 20 minutes, as previously described [12].

### Measurement of left atrial fibrosis

Prior to catheter ablation, an invasive endocardial 3D-EAM of the LA including the PV, mitral annulus (delineated with the ablation catheter by visualizing a large ventricular and much smaller atrial signal, and after matching with the 3D-CT-derived LA map), and LAA (separate map) was created during SR after gating for respiration. Bipolar low-voltage areas (< 0.5 mV) as a surrogate parameter of LA fibrosis were determined by using the area measurement tool (in cm<sup>2</sup>), and fibrosis was suspected if at least three adjacent points in an area covering 1 cm<sup>2</sup> had a bipolar voltage < 0.5 mV, as previously described [13]. The interpolation and color threshold of the voltage maps was set to 15 mm [2]. At least 100 points were acquired in



**Figure 1.** Left atrium divided into four segments in the CARTO3 software. Left upper (anterior-posterior view): anterior segment; right upper (posterior-anterior view): posterior segment; left bottom (right anterior oblique view): septal segment; right bottom (left anterior oblique): lateral segment. The pulmonary veins are not shown in this illustration

the LA. To assess the localization of LVA, the LA was subdivided into four areas (anterior, posterior, lateral, and septal; Fig. 1). The LAA was excluded because it almost never shows LVA and is often a very small structure. The ratio between LVA and total LA surface area (in %) and LVA to LA volume ratio assessed by cCT were calculated [4].

### Blood samples

Venous blood samples were collected prior to ablation (Vacutainer TM, USA) and were immediately processed. The electro-chemiluminescence immunoassays and the Cobas 8000 (Roche Diagnostics, Switzerland) were used for detection of the N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) [14].

### Statistical analysis

Continuous variables are presented as mean ( $\pm$  standard deviation) for normal distribution and median (interquartile range) for skewed distribution. Categorical variables are expressed as percentages, unless otherwise stated. Differences in baseline characteristics between the groups were assessed by independent Student's t-test or ANOVA for parameters with parametric distribution, while the Mann-Whitney U-test or Kruskal-Wallis test were used for parameters with a non-normal distribution. The  $\chi^2$  test was calculated for dichotomic variables. Univariable analysis for relevant clinical covariates was performed by Pearson or Spearman's test, as appropriate. To adjust for confounders, bivariable regression was performed

with a stepwise approach, and the strength of relationships was tested with F-test ANOVA. To avoid overfitting, multiple models restricted to a maximum of two clinical variables each were run. A two-sided p-value of < 0.05 was considered statistically significant. Receiver operating characteristic (ROC) curves were calculated to assess the area under the curve (AUC), and sensitivity and specificity of different NT-proBNP serum levels. According to the Utah stages, a cut-off of 5% for LA fibrosis and a cut-off of 20% for relevant LA fibrosis burden were considered for calculation of ROC curves [6, 15]. All statistical analyses were performed with SPSS software (v25, SPSS Inc., USA).

## Results

### Baseline characteristics and 3D electroanatomical mapping

Baseline characteristics of the study population are shown in Table 1. The mean patient age was  $62.5 \pm 11.4$  years. Twenty-nine percent of patients were female, and 33% had persistent AF. The average number of points collected during the ablation procedure was  $1362 \pm 1067$ . Endocardial bipolar LVA as a surrogate parameter of LA fibrosis was present in 65% of patients, with 50% having a fibrotic area > 5% (at least Utah Stage 1) [15]. Fibrosis was most prevalent in the anterior (91.5% of patients with > 5% fibrosis) and posterior area (83% of patients with > 5% fibrosis). Fibrosis was less commonly observed in the septal and lateral LA area (63.3% and 48.9%, respectively). AF patients with any amount of LA fibrosis had higher NT-proBNP values ( $869 \pm 1056$  vs.  $552 \pm 859$  ng/L,  $p = 0.001$ ) and larger LA volumes after correction for body surface area (BSA;  $63.3 \pm 19.3$  vs.  $80 \pm 27.1$  mL/m<sup>2</sup>,  $p = 0.003$ ) as compared to those without. A positive correlation between the ascending aorta diameters (corrected for BSA) and the amount of fibrosis in the anterior LA was found (Pearson correlation 0.301,  $p = 0.005$ ).

Atrial fibrillation patients with a higher burden of LA fibrosis presented with higher APPLE scores ( $2.2 \pm 1.3$  vs.  $1.5 \pm 1$ ,  $p = 0.007$ ) and higher DR-FLASH scores ( $3.6 \pm 1.4$  vs.  $2.4 \pm 1.5$ ,  $p < 0.001$ ).

### Gender differences

Most of the study population was male (71% vs. 29%). Although females did not present with significantly higher NT-proBNP values as compared to males ( $960 \pm 1327$  vs.  $622 \pm 786$  ng/L,  $p = 0.195$ ), and they were more likely to have fibrosis in the anterior, septal, and lateral LA (Fig. 2).

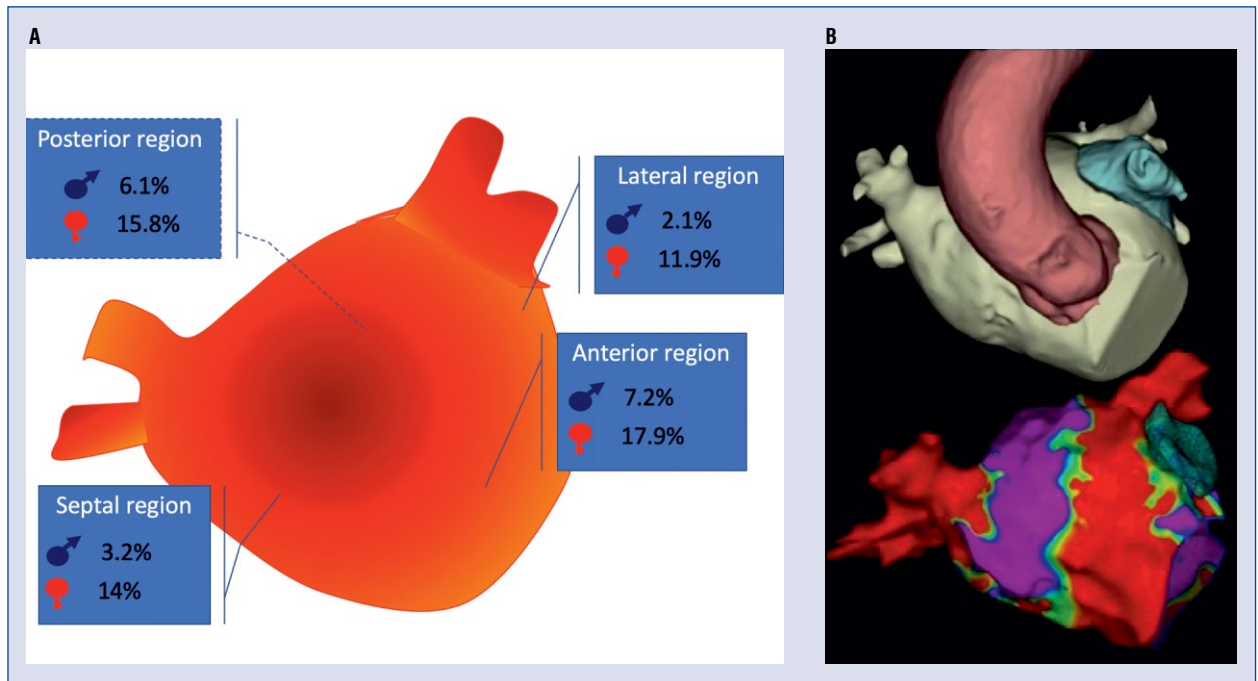
**Table 1.** Baseline clinical characteristics.

Patient characteristic	All patients (n = 94)
Age	62.5 (11.4)
Female	28.7%
BMI [kg/m <sup>2</sup> ]	26.9 (4.6)
Adjusted (for gender) CHA <sub>2</sub> DS <sub>2</sub> -VASc score	1.5 (1–3)
APPLE score	1.8 (1.2)
DR-FLASH score	3 (1.6)
EHRA score (n = 73)	2.2 (0.73)
Days since AF diagnosis	1044 (224–2116)
Total LA fibrosis [cm <sup>2</sup> ]	5.2 (0–26.6)
LVA in % based on 3D mapping	3.7 (0–17.1)
LA fibrosis corrected for LA volume from CT scan [%]	4.8 (0–18.3)
Smoking	20.2
Hypertension	54.3
Diabetes	10.6
Stroke	7.4
Vascular disease	4.3
Sleep apnea	10.6
NOACs	86.2
Beta-blockers	67
Amiodarone	19.1
Diuretics	28.7
Aldosterone-antagonists	8.5
ACE-I/ATII-ag	48.9
Statins	34
Leucocytes [G/L]	6.8 (2)
NT-proBNP [ng/L]	280 (151–927)
CRP [mg/L]	3.8 (8.9)
eGFR [mL/min/m <sup>2</sup> ]	73 (18.4)
TSH [mU/L]	1.9 (1.1)
Aorta sinus portion/BSA [mm]	17.1 (2.2)
Ascending aorta/BSA [mm]	17.1 (2.7)
LA volume/BSA	69.2 (52.7–84)
LVEF [%]	56 (51–61)
E/e'	9 (7–13.3)

Values are means (standard deviation), median (interquartile range) or numbers (percentages). BMI — body mass index; AF — atrial fibrillation; LA — left atrial; LVA — low voltage area; 3D — three dimensional; CT — computed tomography; NOACs — non-vitamin K oral anticoagulants; ACE-I/ATII — angiotensin-converting enzyme inhibitor/angiotensin-receptor blockers; NT-proBNP — N-terminal pro B-type natriuretic peptide; CRP — C-reactive protein; eGFR — estimated glomerular filtration rate according to CKD-EPI; TSH — thyroid stimulating hormone; BSA — body surface area; LVEF — left ventricular ejection fraction

Compared to males, females had larger diameters of the ascending aorta (corrected for BSA) ( $18.6 \pm 3.1$  vs.  $16.5 \pm 2.3$  mm/m<sup>2</sup>,  $p = 0.001$ ) and higher





**Figure 2. A.** Mean distribution of left atrial fibrosis in subjects with > 5% fibrosis divided for male (blue) and female (red). **B.** Three-dimensional reconstruction of the left atrium and aortic position by voltage mapping and corresponding computed tomography-scan.

E/e' values ( $13.5 \pm 6.7$  vs.  $9.4 \pm 4.2$ ,  $p = 0.002$ ) as a measure of diastolic dysfunction.

### Predictors of fibrosis

In univariable analysis, LA fibrosis was associated with female gender, older age, increased LA volumes (corrected for BSA), hypertension, higher NT-proBNP values, higher E/e' values, higher APPLE, DR-FLASH, and adjusted CHA<sub>2</sub>DS<sub>2</sub>-VASc scores. In bivariable analyses, incorporating relevant clinical variables from univariable analysis, the APPLE score did not independently predict LA fibrosis, while female gender independently predicted LA fibrosis. Furthermore, in other bivariable models, higher NT-proBNP levels, higher E/e' values, older age, and higher DR-FLASH scores also independently predicted LA fibrosis (Table 2).

The optimal NT-proBNP value for predicting LA fibrosis was found for a NT-proBNP of > 190 ng/L (for LA fibrosis > 5%: sensitivity 82% and specificity of 55%, Youden-index 0.37; for LA fibrosis > 20%: sensitivity 95% and specificity of 47%, Youden-index 0.42). To reduce the number of false positives, we individuated a NT-proBNP cut-off of > 400 ng/L, which yielded a sensitivity of 55% and specificity of 73% for predicting a LA fibrosis burden of  $\geq 5\%$ , and a sensitivity of 59%

with a specificity of 65% for predicting a LA fibrosis burden of  $\geq 20\%$  (Fig. 3; **Suppl. Fig. 1**).

### Ablation procedure

Acute procedural success was obtained in all patients. The mean procedural duration was  $82.4 \pm 72.5$  min, and mean fluoroscopy times and area dose products were  $7 \pm 7$  min and  $813 \pm 977 \mu\text{Gym}^2$ , respectively. There were no gender-related differences with regard to procedural duration ( $84.3 \pm 76$  vs.  $77.9 \pm 64.3$  min,  $p = 0.708$ ), fluoroscopy times ( $7 \pm 7.3$  vs.  $6.8 \pm 6$  min,  $p = 0.902$ ), and dose area products ( $919 \pm 1110$  vs.  $552 \pm 437 \mu\text{Gym}^2$ ,  $p = 0.107$ ). No periprocedural complications occurred.

### Discussion

In this single-center longitudinal study, higher NT-proBNP and higher E/e' — both markers of increased left-sided cardiac filling pressures — as well as older age, higher DR-FLASH scores, and female gender were independently associated with LA fibrosis in patients referred for catheter ablation of AF. LA fibrosis was most prevalent in the anterior followed by the posterior LA wall. A positive correlation between the ascending aorta

**Table 2.** Variables associated with bipolar endocardial low-voltage areas as a surrogate parameter of left atrial fibrosis.

Variable	Univariable analysis		Bivariable analysis		
	Pearson correlation	P	Standardized B	B (95% CI)	P
Gender	0.285	0.005	0.234 to 0.397	9.7 (2–17.4) to 14.9 (6.6–23.1)	0.001
Age	0.245	0.018	0.252	0.421 (0.08–0.76)	0.016
BMI [kg/m <sup>2</sup> ]	–0.087	0.404			
LA volume/BSA [mL/m <sup>2</sup> ]	0.204	0.048	0.086	0.065 (–0.105–0.236)	0.449
Hypertension	0.232	0.025			
Statin use	0.258	0.012	0.164	6.7 (–1.9–15.3)	0.126
eGFR [mL/min/m <sup>2</sup> ]	–0.095	0.364			
Serum NT-proBNP [ng/L]	0.299	0.006	0.232 to 0.298	0.005 (0.0–0.009) to 0.006 (0.002–0.01)	0.005 to 0.049
E/e'	0.482	< 0.001	0.339 to 0.394	1.1 (0.39–1.8) to 1.3 (0.5–2)	0.002
Adjusted CHA <sub>2</sub> DS <sub>2</sub> -VASc score	0.379	< 0.001			
APPLE score	0.282	0.006	0.155	2.57 (–1.28–6.42)	0.188
DR-FLASH score	0.401	< 0.001	0.316 to 0.286	3.92 (1.27–6.57) to 4.42 (2.2–6.6)	< 0.001
LVEF	–0.169	0.104	–0.018	–0.033 (–0.45–0.39)	0.877

Left atrial fibrosis was calculated as a continuous variable as a ratio between low-voltage area and total LA surface area (in %). BMI — body mass index; LA — left atrial; BSA — body surface area; GFR — glomerular fraction rate according to CKD-EPI; NT-proBNP — N-terminal pro B-type natriuretic peptide. P-values were calculated by Pearson correlation (univariable analyses) and regression analyses (bivariable analyses). Following models were calculated (\*p < 0.05): 1) NT-proBNP\*, gender\*; 2) NT-proBNP\*, age\*; 3) NT-proBNP\*, LA volume/BSA, mL/m<sup>2</sup> (p = 0.449); 4) NT-proBNP\*, APPLE score (p = 0.188); 5) DR-FLASH\*, gender\*; 6) NT-proBNP\*, LVEF (p = 0.877); 7) NT-proBNP\*, E/e'\*; 8) E/e', gender\*; 9) E/e'\*\*, age\*; 10) NT-proBNP\*, statins, age

diameters and the amount of fibrosis in the anterior LA was found. Females were more likely to have fibrosis in the anterior, septal, and lateral LA as compared to males.

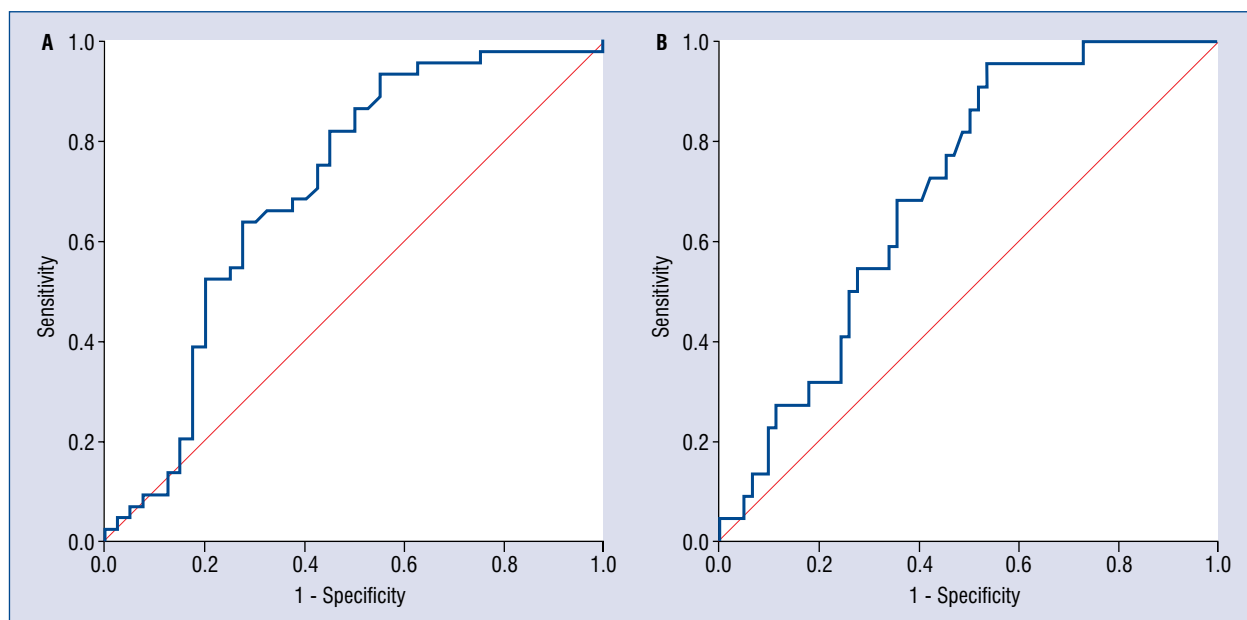
### Predictors of left atrial fibrosis

Left atrial fibrosis may represent the anatomical substrate altering electromechanical cellular coupling, favoring reentry, and thus predisposing to the onset and maintenance of AF. As such, myocardial fibrosis has been widely reported in AF patients both in histological and in autoptical studies [16, 17]. Based upon previous studies and clinical experience that fibrotic tissue yields a low voltage signal, besides histological studies, invasive 3D-EAM voltage mapping is a standard method to assess and stage the extent of atrial fibrosis [18, 19].

In bivariable analyses, we found that elevated NT-proBNP, higher E/e' values — both surrogate parameters of increased left-sided cardiac filling pressures — independently predicted LA fibrosis after correction for confounding factors. Moreover, a NT-proBNP cut-off of > 400 ng/L showed

a good specificity to predict significant LA fibrosis in our population. Both NT-proBNP levels and LA volumes are frequently elevated in the setting of heart failure with reduced, but also preserved, ejection fraction (HFpEF), which is related to high LA filling pressures [20]. In AF patients, an expanded myocardial extracellular volume has been associated with adverse LA remodeling, and LA enlargement is a typical finding in diastolic dysfunction and in patients with increased left-sided filling pressures [20, 21]. An independent association between LVA, higher LA volumes, and persistent AF has previously been described [5, 6]. Our findings are in line with previous studies and extend previous knowledge revealing that parameters of diastolic dysfunction and higher cardiac filling pressures (NT-proBNP and echocardiographic E/e') constitute important predictors of LA fibrosis. LA fibrosis itself may promote AF and synergistically increase left-sided filling pressures leading to a vicious cycle.

NT-proBNP levels reflect not only an increased myocardial wall stress, but it may also be related to



**Figure 3. A.** Receiver operating characteristic curves for serum N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) levels as a predictor of left atrial (LA) fibrosis (cut-off:  $\geq 5\%$ ); area under the curve (AUC) 70%,  $p = 0.001$ , NT-proBNP cut-off 400 ng/L: sensitivity 55%, specificity 73%; **B.** Receiver operating characteristic curves for serum NT-proBNP levels as a predictor of relevant LA fibrosis (cut-off:  $\geq 20\%$ ); AUC 70%,  $p = 0.005$ , NT-proBNP cut-off 400 ng/L: sensitivity 59%, specificity 65%.

intrinsic myocardial disease [22]. Similarly to our study, the SwedeHF register found an association between NT-proBNP and AF in HFpEF patients, suggesting a direct pathological linkage between higher filling pressures and development of AF. In this study, patients with AF and HFpEF were older, more likely to be male, and associated with a worse 1-year survival, even when compared to patients with a reduced ejection fraction [23]. The association between increased NT-proBNP values and LA fibrosis has been described by Kornej et al. [24], although this parameter did not independently predict LA fibrosis in their study.

Other biomarkers such as galectin-3, pro-collagen type III N-terminal pro-peptide (PIIINP), type I collagen C-telopeptide (ICTP), and fibroblast growth-factor 23 (FGF-23) have recently been suggested as biomarkers of fibrosis and might be helpful in identifying patients who are more likely to benefit from AF catheter ablation [25–28]. Although promising, these biomarkers are not yet clinically available, and NT-proBNP remains the most established and clinically available parameter.

Hypertension is an established risk factor for AF development and its perpetuation [1].

Interestingly, we found that approximately half of our population were hypertensive. This is possibly due to the fact that our patients were relatively young and the majority of them were referred for AF ablation of paroxysmal AF.

The APPLE score has recently been suggested as a powerful predictor of both LA fibrosis and AF recurrence after catheter ablation, and it has been externally validated [7, 24, 29]. Similarly, the DR-FLASH score proved to be effective in predicting the presence of LVA in more than 900 patients with AF [9]. Our study confirms these findings, as we found higher scores in subjects with a higher burden of LA fibrosis as well as a positive correlation between the two variables. The DR-FLASH score independently predicted LVA after adjustment for gender, while the APPLE score was not an independent predictor for LVA in bivariable analyses. Interestingly, persistent AF was not predictive of relevant fibrosis. Thus, AF duration may not represent per se a criterion to more intense ablation approaches.

These findings are clinically relevant when choosing the appropriate treatment strategy in these patients (e.g., more aggressive risk factor management) because increased LA fibrosis is as-

sociated with lower AF-free survival after catheter ablation and adverse events [30].

### Gender differences

In line with previous studies, female gender was an independent predictor of LA fibrosis [5, 6]. This finding seems to be related to a direct gender-dependent effect based on differences in the effect of sex hormones on adverse LA remodeling and fibrosis [14]. Although the presence of higher left-sided filling pressures likely plays a crucial role as a predictor of LA fibrosis, in our cohort diuretic treatment was not significantly more frequent in females and NT-proBNP values were not significantly different between males and females. On the other hand, both E/e' as an indicator of diastolic dysfunction and higher left-sided filling pressures were higher in females as compared to males, indicating that females with AF tend to present with higher left-sided filling pressures, thereby promoting LA fibrosis. However, in bivariable analyses, female gender per se remained an independent predictor of LA fibrosis, indicating that female gender is associated with LA fibrosis independently of higher left-sided filling pressures. We were able to confirm previous findings by invasively assessing LA fibrosis via EAM, which is considered to be an alternative method for detection of fibrosis as compared to late-gadolinium enhancement CMR [31]. CMR-based assessment of LA fibrosis is a well-established method in some experienced centers, but it requires great expertise in interpretation, and for some centers assessment of LA fibrosis during AF ablation by 3D-EAM may be more feasible. Most previous studies showing an association between female gender and LA fibrosis have performed their analyses based on absolute values without indexing LA volumes for BSA. We confirmed these findings in patients with paroxysmal and persistent AF and, in line with another study, after correcting LA volumes for BSA [32]. Regarding this, females had bigger LA volumes indexed for BSA compared to males. Furthermore, no differences in age were found between females and males, although females had lower body mass index.

Epidemiologically, the incidence and prevalence of AF is age-related [20]. However, it is still debated whether age is a risk factor per se or if it is mainly related to other co-morbidities [16]. In our study, we found older age to be related to higher amounts of LA fibrosis and to be an independent predictor of LA fibrosis [6, 33]. Similarly to previous studies, women receiving catheter ablation

for AF were older than the men in our study, suggesting that women develop AF at an older age as compared to men [6, 33]. However, as shown in the recent EAM study from Ammar-Busch et al. [31], fibrosis may be rather related to increased filling pressures than older age per se.

Compared to most previous studies, we found a relatively high incidence of LA fibrosis in a predominantly male population with paroxysmal AF. This is possibly due to the different method of detecting fibrosis by invasive EAM mapping as compared to MRI-LGE [5].

### Localization of left atrial fibrosis

Left atrial fibrosis was most prevalent in the anterior followed by the posterior LA wall. The septal and lateral LA wall showed less fibrosis, which may be related to the thickness of atrial tissue. With regard to this, a positive correlation between the ascending aorta diameters and the amount of fibrosis in the anterior LA was found. It has been previously reported that dilatation of the ascending aorta, e.g., by hypertension, can lead to chronic pressure on the anterior LA wall due to its anatomic proximity, thereby promoting fibrotic remodeling of this area [34, 35]. Females were more likely to have fibrosis in the anterior, septal, and lateral LA, which is in line with the observation that they presented with higher ascending aorta dimensions when adjusted for BSA. Moreover, an independent gender-specific effect may also play a role for LA fibrotic remodeling, which certainly needs further investigation.

### Limitations of the study

This was a small single-center study performed in patients with AF referred for catheter ablation, and only 29% of the population were female. Moreover, assessment of LA fibrosis by CMR is currently not performed in our center. The 20-polar Pentaray mapping catheter creating high-density maps with > 1000 of points has a much higher resolution to detect LVA, but is not routinely used for PVI in our center. Antiarrhythmic drugs and/or beta-blockers were recommended to be discontinued 3–5 half-lives prior to the ablation procedure (2 weeks for amiodarone), but due to symptoms this was not possible in all patients. These limitations may have influenced the data accuracy for EAM. Therefore, our data may not be generalizable to the overall AF population, and larger prospective studies including more women and MR data should be carried out in the future. Moreover, we cannot rule out that the accuracy of EAM might have



been influenced by functional voltage reduction related to electrical stunning rather than fibrosis in patients with longer episodes of persistent AF and electrical cardioversion.

## Conclusions

In this single-center longitudinal study, surrogate parameters of elevated left-sided cardiac filling pressures such as higher serum NT-proBNP levels and higher echocardiographic E/e' values as well as female gender independently predicted the prevalence of LA fibrosis in patients referred for catheter ablation of AF.

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