

Is the extent of left atrial fibrosis associated with body mass index in patients undergoing pulmonary vein isolation for atrial fibrillation?

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ABSTRACT

Background: Left atrial (LA) fibrosis is associated with a higher rate of recurrence of atrial fibrillation (AF) after pulmonary vein isolation (PVI). Body mass index (BMI) is strongly associated with the prevalence of AF, but there is insufficient data about the association between BMI and LA fibrosis.

Aims: The aim of the study was to examine the association between LA fibrosis and BMI in patients with AF undergoing PVI.

Methods: In 114 patients an electro-anatomical voltage map was created using the CARTO 3 three-dimensional system before PVI. The total fibrosis area (voltage criteria ≤ 0.5 mV), percentage, and the number of fibrotic areas were calculated. A general linear model was used to determine the differences in BMI with confounders between groups of patients with differing extents of fibrosis and numbers of focuses.

Results: Advanced fibrosis was found in 53 (47%) patients, in up to 9 areas with a median of 2 and an interquartile range (IQR) of 0–3. The median total fibrotic area was 27.3 cm² with an IQR of 0.1–30.3 cm². Patients were stratified by percentage of fibrotic area: <5%, 5%–20%, 20%–35%, and above 35%; no significant difference in mean BMI was found between the groups ($P = 0.57$). When stratified by the number of fibrotic areas (0, 1, 2, and ≥ 3 fibrotic areas), no difference in BMI was noted between the groups ($P = 0.67$).

Conclusions: Fibrosis of the LA, as the strongest predictor of AF recurrence after PVI, does not correlate with BMI in patients with AF where PVI is indicated.

Key words: atrial fibrillation, body mass index, fibrosis, pulmonary vein isolation, recurrence

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INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia with a prevalence in the general population of 2.3%–3.4% [1]. AF impairs quality of life and may increase the risk of stroke, heart failure, and cardiovascular mortality [1]. The pathogenesis of AF includes initiation triggers, such as rapid firing of ectopic foci located within the pulmonary veins and perpetuating substrate, and abnormal tissue of the left atrium (LA) [2]. Microfibrosis of the myocardium resulting in loss of side-to-side cell connections (coupling) and consequent anisotropic electrical conduction has been proposed

as a major mechanism for the initiation and perpetuation of AF [3, 4]. Increased fibrosis has been found in surgically obtained left atrial specimens of patients with AF [5, 6].

Fibrosis and scarring of the myocardial tissue result in a reduced voltage of the electrical signals from the affected area. Electro-anatomical voltage mapping (EAVM) shows a good correlation between pathological findings and the electrophysiological characteristics of fibrosis [7]. Several studies have shown a strong correlation between left atrial fibrosis and AF recurrence using EAVM. Verma et al. [8] used EAVM to measure the extent of LA fibrosis (<0.5 mV)

WHAT'S NEW?

Left atrial (LA) fibrosis is associated with a higher rate of recurrence of atrial fibrillation (AF) following pulmonary vein isolation (PVI), but does not correlate with age, hypertension, diabetes, or the clinical type or duration of AF. Excess body weight is strongly associated with the prevalence of AF, but its association with LA fibrosis has not yet been established. This study is the first to investigate the association between excess body weight and LA fibrosis in humans. The main result of this study was that no association was found between the prevalence or the extent of LA fibrosis and body mass index in patients with AF undergoing PVI. Further studies comparing the AF burden, presence and extent of LA fibrosis, AF recurrence after PVI, and different indices of obesity are needed to clarify if PVI could be routinely planned regardless of body mass index.

and its prognostic value for AF recurrence after pulmonary vein isolation (PVI) in 700 patients. LA scarring was the only predictor associated with higher AF recurrence [8]. Another study using EAVM prior to PVI provided strong evidence that LA fibrosis can be found in a significant proportion of patients with paroxysmal AF [9]. The presence and extent of atrial fibrosis did not correlate with any other potential risk factor (clinical type, LA diameter, age, duration of AF, etc.) in these studies. Kottkamp et al. suggested a new entity — fibrotic atrial cardiomyopathy (FACM) [10–12]. FACM is described as a specific preexisting chronic progressive disease of the LA predisposing patients to AF in the presence of modulators (inflammation, hypertension, obesity) and triggers (pulmonary vein foci). The authors suggested 5 stages of severity of fibrosis based on EAVM, defining normal voltage as above 1.5 mV: FACM 0 without any fibrosis; FACM I with moderate fibrosis (1.0–1.5 mV); FACM II with one area of severe fibrosis (<0.5 mV); FACM III with at least two areas of severe fibrosis, and FACM IV with severe diffuse fibrosis of the LA.

Advanced age, hypertension, diabetes, obesity, obstructive sleep apnoea, and excessive alcohol consumption are all well-established risk factors for the development of AF [13]. Together with hypertension and diabetes, cigarette smoking, and vigorous or low physical activity are also associated with the risk of AF and its recurrence after PVI or electrocardioversion [14]. Moreover, structured weight reduction, abstaining from alcohol, and treatment of obstructive sleep apnoea significantly reduce new-onset and recurrence of AF after PVI [15]. Age is the strongest risk factor for AF. However, the histopathological study of the specimens from different parts of the LA collected during autopsies of 30 patients with AF showed no correlation between age and extent of fibrosis [16]. No difference in the extent of atrial fibrosis using late enhancement magnetic resonance could be found between lone AF patients and those with AF and co-morbidities [17].

Excess weight is strongly associated with the prevalence of AF. Wong et al. [18] estimated a 3.5%–5.3% excess risk of AF for every unit of body mass index (BMI) increase, based on a meta-analysis of 51 studies. The association of BMI with AF was found to be independent of hypertension, diabetes, and myocardial infarction [19]. Body mass index is a predictor of progression from paroxysmal to permanent

AF [20]. Conversely, weight loss was found to be associated with greater freedom from AF, as well as with reversal of the type and progression of AF [21]. Several mechanisms of AF development in obese patients have been investigated so far. Could LA fibrosis also play a role? This cross-sectional study examined the extent of LA fibrosis in patients undergoing PVI and explored cross-sectional associations with BMI. The prevalence and extent of atrial fibrosis and its role in the AF burden in overweight and obese patients have not been investigated so far.

METHODS

Patients

All patients with a history of symptomatic paroxysmal or persistent AF who met the inclusion and exclusion criteria were consecutively included in this prospective observational study immediately before the planned PVI procedure. The exclusion criteria included: permanent AF, previous PVI, left ventricular ejection fraction <50% measured by echocardiography, history of myocardial infarction, acute or chronic inflammatory disease, history of malignant neoplasm, and hypo- or hyperthyroidism. In the period between March 2019 and June 2020, a total of 125 patients in whom PVI was performed were initially included. Subsequently, 11 patients who did not have an adequate electro-anatomical map of the LA according to the protocol described here were excluded from the study. The research was approved by the ethics committee at the University of Osijek Faculty of Medicine (KLASA: 602-04/19-08/04; URBROJ: 2158-61-07-19-09). All patients signed their informed consent.

Clinical parameters

The following clinical parameters were examined: age, sex, BMI, type of AF (paroxysmal, persistent), drugs and preparations taken (including antiarrhythmics and anticoagulants), as well as history of hypertension, coronary heart disease, diabetes, and cerebrovascular stroke. BMI was determined according to the definition of the World Health Organization: normal weight patients with BMI <25 kg/m², overweight patients with BMI between 25 and 30 kg/m², and obese patients with BMI ≥30 kg/m². Left atrial volume measures were assessed by standard echocardiography.

Assessment of left atrial fibrosis

A detailed anatomical map (fast anatomical mapping [FAM]) and a voltage map (EAVM) of the LA were created using a three-dimensional mapping system and an ablation catheter with a Biosense Webster SmartTouch contact force sensor (CARTO 3, Biosense Webster) [10, 11]. The map was created exclusively in sinus rhythm, taking a minimum of 400 individual points evenly distributed throughout the LA. Points with catheter contact force of less than 5 g and more than 20 g were excluded. The program displays surfaces of the same voltage in the same color. Surfaces with a voltage criterion of ≤ 0.5 mV (low voltage zones [LVZ]) are shown in red, which indicates advanced tissue fibrosis. Areas with moderate fibrosis of voltage criterion between 0.5 and 1.5 mV are shown in blue and green. Healthy tissue of voltage criteria above 1.5 mV is shown in purple. The density of the points, defined by the distance between two points, is set at a minimum of 5 mm. The system is programmed to take only points at the end of expiration that meet the criteria for a minimum contact force of 5 g and adequate catheter stability. As a result of the EAVM, the following parameters were calculated using Biosense Webster CARTO 3 software: the volume of the LA, the total surface area of the LA, the number and total surface area of LVZs (described by voltage points ≤ 0.5 mV) and the share of LVZs in the surface of the LA.

Data analysis

Data was analyzed and visualized using the Python programming language (version 3.8.3) and Jupyter Notebooks

[22]. Percentages of fibrosis were assigned first to two groups (NO group if fibrosis was less than 5%, and YES group if it was above 5%), then to four groups (NO for fibrosis $< 5\%$, I 5%–20%, II 20%–35%, and III above 35%). Areas of fibrosis were divided into four groups (NO if a patient was without fibrosis, I for 1 fibrotic area, II for 2 fibrotic areas, and III for 3 and more fibrotic areas). The dependent variable was tested for normality using the Shapiro–Wilk test of normality before performing ANCOVA to determine the differences in BMI between groups of patients with age, sex, hypertension, diabetes, and persistent AF as confounders. T-test and Mood's median test, as appropriate, were used to assess differences between groups stratified by the presence of fibrosis in quantitative variables, while Fisher's exact test was employed to examine respective differences in qualitative characteristics. All the tests were performed using SciPy, statsmodels, and pandas packages. Quantitative data are reported as mean (standard deviation [SD]) for normally distributed variables or median (interquartile range [IQR]) for not normally distributed data, while categorical variables are presented as the number of individuals (% of total).

RESULTS

The population of the study consisted of 114 patients (65% male and 35% female). The baseline characteristics of all patients, as well as the two groups of patients when stratified by the presence of significant LA fibrosis, are described in Table 1. No significant differences were observed, apart from more frequent use of antiarrhythmic medication in

Table 1. Patient characteristics stratified by the presence of significant left atrial fibrosis

Variable	All patients (n = 114)	No fibrosis group (n = 52)	Fibrosis group (n = 62)	P value
Age, years (SD)	61.5 (8.7)	62.5 (9)	62.6 (8.3)	0.135 ^a
Male	74 (65)	36 (69)	37 (60)	0.330 ^b
BMI, kg/m ² , mean (SD)	29.1 (4.4)	29.3 (4.5)	28.9 (4.3)	0.690 ^a
Normal BMI	21 (19)	9 (18)	12 (19)	0.813 ^b
Overweight	46 (40)	22 (42)	24 (39)	0.706 ^b
Obesity	47 (41)	21 (40)	26 (42)	1.0 ^b
Persistent AF	30 (27)	12 (23)	18 (29)	0.526 ^b
History of hypertension	68 (60)	31 (60)	37 (60)	1.0 ^b
History of diabetes mellitus	9 (8)	4 (8)	5 (8)	1.0 ^b
History of cerebrovascular accident	6 (5)	4 (8)	2 (3)	0.409 ^b
History of asymptomatic CAD	14 (12)	6 (12)	8 (13)	1.0 ^b
CHA2DS2-VASc score, median (IQR)	2 (1–3)	1 (0–2.75)	2 (1–3)	0.876 ^c
Antiarrhythmic use				0.02 ^b
None	30 (27)	20 (39)	10 (16)	
Class I	44 (39)	15 (29)	29 (47)	
Class III	39 (34)	17 (32)	22 (35)	
Anticoagulant use				0.23 ^b
None	2 (2)	2 (4)	0	
VKA	24 (21)	9 (17)	15 (24)	
NOAC	87 (77)	41 (79)	47 (76)	
Other medication use				
ACE/ARB	67 (59)	24 (46)	43 (69)	0.013 ^b
Statins	42 (37)	20 (38)	22 (35)	0.845 ^b

Data are presented as number (percentage) of patients unless otherwise indicated.

^aStudent t-test. ^bFisher's exact test. ^cMood's median test.

Abbreviations: ACEI, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; IQR, interquartile range; NOAC, non vitamin K antagonists oral anticoagulants; SD, standard deviation; VKA, vitamin K antagonist

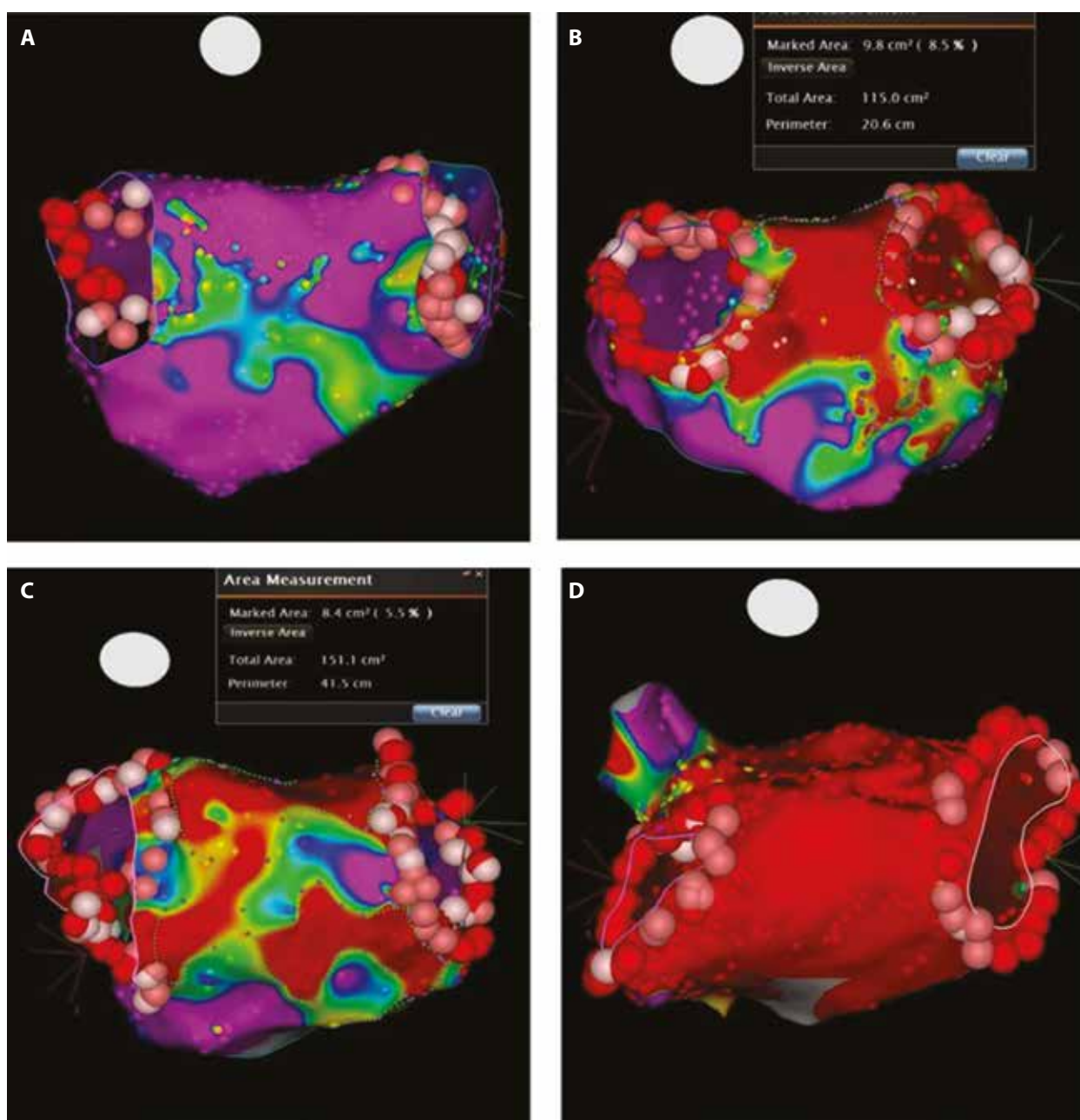


Figure 1. Examples of left atrium electro-anatomical voltage maps from 4 patients with different extent of fibrosis. **A.** No significant fibrosis. **B.** One area of severe fibrosis. **C.** Two areas of severe fibrosis. **D.** Diffuse severe fibrosis

patients with apparent fibrosis. The mean (SD) LA body volume, measured by standard two-dimensional echocardiography, was 56 (19) cm³ in the no fibrosis group and 62 (22) cm³ in the fibrosis group, but when measured by three-dimensional mapping software it was 127 (3) cm³ in the no fibrosis group and 128 (2) cm³ in the fibrosis group. The mean (SD) LA surface area was 149.8 (27) cm² in the no fibrosis group and 151.6 (35) cm² in the fibrosis group. LVZs were found in 86 (76%) patients, though 62 (54%) patients had LVZs in $\geq 5\%$ of the LA surface which is usually considered to be significant. Patients with LVZs had up to 9 areas, with a median of 2 and an IQR of 0–3. In 15 (13%) patients, LVZs were found in 100% of the LA body surface indicating advanced atrial fibrosis. The median total LVZ area for all

patients was 27.3 cm² with an IQR of 0.1–30.3 cm² (0.1%–19.9%). Examples of EAVM from 4 patients with different extent of left atrial fibrosis are shown in [Figure 1](#).

Association of LVZs and BMI

In the current cohort we assessed the association between BMI and groups of patients with and without significant (<5%) fibrosis ([Figure 2](#)). Patients without significant fibrosis had a mean BMI (SD) of 29.3 (4.5) kg/m², while patients with significant fibrosis had a mean BMI (SD) amounting to 28.9 (4.3) kg/m². After adjusting for age, sex, hypertension, diabetes, and persistent AF, we found that no association remained statistically significant ($P = 0.84$). We further assessed the association between BMI and four groups of

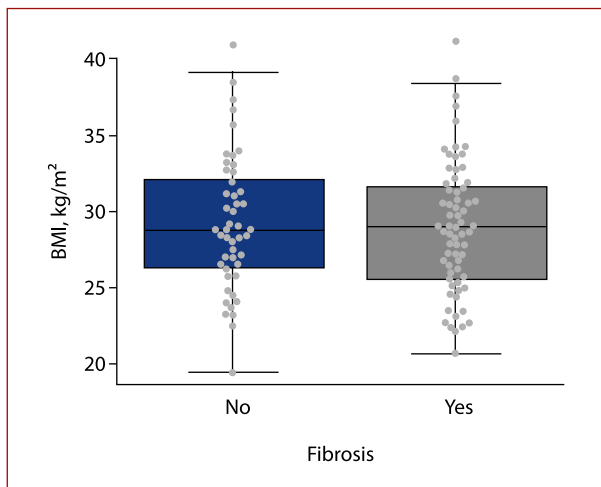


Figure 2. Box plot showing the distribution of body mass index (BMI) in two groups of patients based on the presence of significant fibrosis: NO — a group of patients in whom fibrosis was less than 5%; YES — a group of patients in which fibrosis was above 5%. The lower and upper boundaries of the boxplots indicate the first and third quartile, the middle notch indicates the median, and whiskers include all data points that fall within $1.5 \times$ interquartile range. ANCOVA adjusted for age, sex, and the presence of hypertension, diabetes and persistent atrial fibrillation showed no difference between groups ($P = 0.84$)

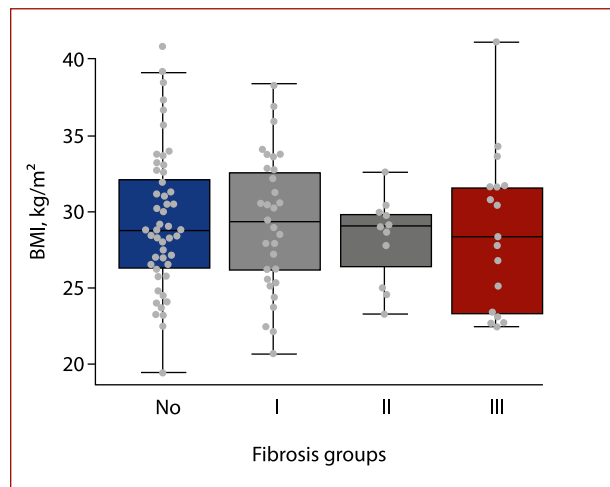


Figure 3. Box plot showing the distribution of body mass index (BMI) in four groups of patients stratified by percentage of fibrotic area: NO — group of patients in which fibrosis was less than 5%; I — group of patients in which fibrosis was 5%–20%; II — group of patients in which fibrosis was 20%–35%; III — group of patients in which fibrosis was above 35%. The lower and upper boundaries of the boxplots indicate first and third quartile, the middle notch indicates the median, and whiskers include all data points that fall within $1.5 \times$ interquartile range. ANCOVA adjusted for age, sex, and the presence of hypertension, diabetes, and persistent atrial fibrillation showed no difference between groups ($P = 0.57$)

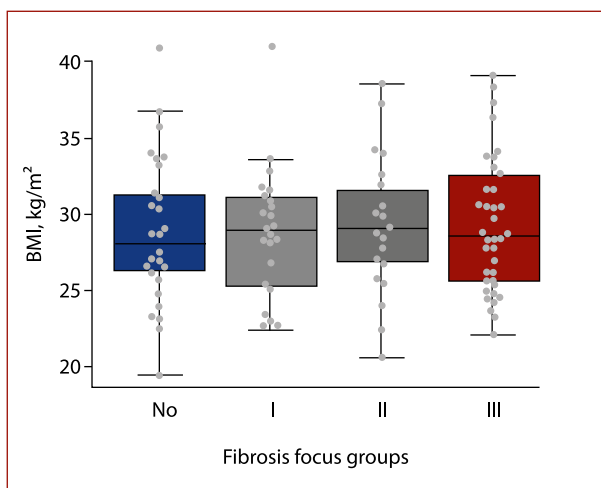


Figure 4. Box plot showing the distribution of body mass index (BMI) in four groups of patients based on the number of fibrotic areas: NO — a group of patients with no fibrotic areas; I — a group of patients with 1 fibrotic area; II — a group of patients with 2 fibrotic areas; III — a group of patients with 3 and more fibrotic areas. The lower and upper boundaries of the boxplots indicate the first and third quartile, the middle notch indicates the median, and whiskers include all data points that fall within $1.5 \times$ interquartile range. ANCOVA adjusted for age, sex, and the presence of hypertension, diabetes, and persistent atrial fibrillation showed no difference between groups ($P = 0.64$)

patients stratified by percentage of fibrotic area: NO for fibrosis <5%, I 5%–20%, II 20%–35%, and III above 35%. The mean (SD) BMI in these four groups was 29.2 (4.5) kg/m², 29.3 (4.4) kg/m², 28.2 (2.8) kg/m², and 28.7 (5.2) kg/m², respectively (Figure 3). After adjusting for age, sex, hyperten-

sion, diabetes, and persistent AF, BMI was not significantly different between the groups ($P = 0.57$).

Similarly, no association was found between BMI and four groups of patients stratified by the number of fibrotic areas: NO if a patient was without fibrosis, I for 1, II for 2 and III for 3 and more (Figure 4). Mean BMI (SD) in the four groups was 28.8 (4.7) kg/m², 28.6 (4.3) kg/m², 29.3 (4.4) kg/m², and 29.5 (4.4) kg/m², respectively ($P = 0.64$).

A subgroup of 21 (18%) patients with normal BMI was additionally analyzed. In this group, 14 (67%) patients had significant fibrosis of the LA. Patients with normal BMI and significant LA fibrosis had a median CHA₂DS₂-VASc score of 2.5 with IQR 2–3. Persistent AF was found in 4 (29%) patients, arterial hypertension in 9 (64%) patients, and 7 (50%) patients had diffuse LVZ covering $\geq 90\%$ of the LA surface.

DISCUSSION

To our knowledge, this study is the first to investigate the association between excess body weight and LA fibrosis in humans. The main result of this study is that no association was found between the prevalence and the extent of LA fibrosis and BMI in patients undergoing PVI.

In our study, only 18% of patients were of normal weight, while 41% of patients were obese. The high prevalence of obesity in the investigated cohort could partly explain why 60% of patients had hypertension, 8% had diabetes, 12% had asymptomatic coronary artery disease, and 5% had a history of cerebral vascular incidents. There is no evidence of any association between these co-morbidities and atrial fibrillation. Weight loss results in a significant reduction of the AF burden, comparable with PVI results.

However, we found no correlation between obesity and atrial fibrosis, which is the strongest risk factor for AF recurrence after PVI, suggesting other possible mechanisms for the higher AF burden in obese and overweight patients. There is strong evidence of a correlation between LA fibrosis and a worse prognosis for AF in terms of the progression of the disease and ineffective invasive therapy. Previous studies showed a strong correlation between AF and risk factors such as advanced age, hypertension, diabetes, obesity, and obstructive sleep apnoea. However, studies investigating some of these factors and the presence of left atrial fibrosis showed no correlation, suggesting a new idiopathic entity — fibrotic atrial cardiomyopathy.

There are some indications of a possible pro-inflammatory, thus a profibrotic effect of obesity on left atrial tissue, but no correlation has been established. Important findings from the ovine model have been published by Abed et al. [23]. In this study, animals were on a high-calorie diet that resulted in weight gain. The animals underwent electrophysiological studies, cardiac magnetic resonance imaging, and histology at baseline, 4- and 8-monthly intervals. Weight gain resulted in progressive remodeling characterized by conduction heterogeneity, bi-atrial enlargement, and increased pericardial fat volumes. Histology showed increased atrial interstitial fibrosis and inflammation [23].

Apart from the role of cardio-metabolic factors associated with obesity in promoting AF, several other factors have been observed and investigated. Diastolic function impairment has a strong correlation with the risk for AF onset [24, 25]. Possible mechanisms include enlargement of the LA area with consequent changes in the electrical properties of the tissue that promotes re-entry. Cardiac fat deposits overlying the LA also seem to be an important factor in promoting AF in obese patients. Investigators from the Framingham Heart Study Offspring and Third Generation Cohorts analyzed 2317 patients and showed an association of total pericardial fat volume measured by computed tomography and prevalence of AF [26]. Wong et al. [27] showed that pericardial fat, measured by magnetic resonance in this study, is also a predictor of AF recurrence after PVI. Possible mechanisms are local inflammation mediated by paracrine mediators and the arrhythmogenicity of interpolated fat tissue [28].

Strengths and limitations of the study

A high number of patients with excess body weight was included in this study, giving strength to evidence on LA fibrosis within this population. However, the proportion of these patients is not consistent with other studies investigating the extent of LA fibrosis. Body mass index is strongly correlated with the development of AF [19], progression from paroxysmal to persistent AF, [20] and with AF burden, [21] and was the only parameter of general obesity used in this study. Epicardial adipose tissue (EAT) emerged as an important factor in AF pathogenesis in recent studies.

Metaanalysis showed a highly significant correlation between BMI and EAT, but the correlation was even greater between EAT and waist circumference and between EAT and visceral adipose tissue [29]. These indices of obesity should also be included in future research on left atrial fibrosis. This study investigated the extent of LA fibrosis only in patients with AF, therefore the results could not be extrapolated to the healthy population. Although a correlation between low voltage zones in the LA and histological findings of fibrosis has been confirmed, exact voltage cut-off values have not been established yet. Commonly used voltage cut-off values in most of the studies for normal tissue, moderate fibrosis, and severe fibrosis are ≥ 1.5 mV, 0.5–1.5 mV, and ≤ 0.5 mV, respectively. In this study, we observed only areas of severe fibrosis (≤ 0.5 mV). Areas of moderate fibrosis were not analyzed in this study but might also play an important role in the development of FACM.

Electro-anatomical voltage mapping can give inconsistent results. Various catheters are used in studies to collect voltage points within the body of the LA. Multi-polar catheters can collect a greater number of voltage points over the same period of time than bipolar catheters, resulting in more detailed EAVM. Multipolar catheters use tissue impedance for contact assurance, while new generation bipolar catheters use contact force criteria (≥ 5 g/mm²).

In this study, 76% of patients had LVZs and 54% of the patients had fibrosis in more than 5% of the LA surface, which was considered significant in most previous studies. The exact proportion of left atrial fibrosis significant for developing AF has not been established. It is also not clear whether the number of LVZs would be a better predictor of AF recurrence after PVI than the proportion of LA fibrosis. Therefore, we decided to investigate if there was a difference in BMI between patients with and without fibrosis, and also with different proportions of fibrotic areas and with different numbers of fibrotic areas. This multiple hypothesis approach would lessen the strength of scientific proof in case of a positive result, but in our study the results were negative — we found no difference in BMI among the groups of patients. This study aimed to investigate only the correlation between BMI and LA fibrosis. Obesity has other well-established links with AF independent of LA fibrosis including associated co-morbidities such as arterial hypertension, diabetes mellitus, coronary artery disease, and obstructive sleep apnea, together with ventricular adaptation, diastolic dysfunction, and epicardial adipose tissue.

CONCLUSIONS

In conclusion, our study did not find a correlation between fibrosis of the LA, as the strongest predictor of AF recurrence after PVI, and BMI. There was no significant difference in BMI between groups of patients stratified by the presence and the extent of LA fibrosis, and the number of fibrotic areas. Further studies comparing the AF burden, the presence and the extent of LA fibrosis, and AF recurrence

after PVI including different indices of obesity, particularly abdominal obesity, are needed to clarify if PVI could be routinely planned regardless of BMI. The exact criteria for measurement of LA fibrosis and the clinical significance of different stages, proportions, and numbers of fibrotic areas should be set by future research.

Article information

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Conflict of interest: None declared.

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