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Research article

Association between body size and atrial myopathy: Investigation using the prevalence of left atrial low-voltage areas

Yasuhiro Matsuda, Masaharu Masuda *, Hiroyuki Uematsu, Ayako Sugino, Hirotaka Ooka, Satoshi Kudo, Subaru Fujii, Mitsutoshi Asai, Shin Okamoto, Takayuki Ishihara, Kiyonori Nanto, Takuya Tsujimura, Yosuke Hata, Naoko Higashino, Sho Nakao, Masaya Kusuda, Toshiaki Mano

Kansai Rosai Hospital Cardiovascular Center, 3-1-69 Inabaso, Amagasaki, Hyogo, 660-8511, Japan

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ABSTRACT

Background: Left atrial low-voltage areas (LVAs) are known to be associated with atrial myopathy and atrial fibrillation (AF) recurrence after catheter ablation. However, the association between body size and prevalence of LVAs has not been fully elucidated. The purpose of this study was to clarify the association between body size and the prevalence of LVAs in patients with AF ablation.
Methods: In total, 1,479 (age, 68 ± 10 years; female, 500 [34 %]) consecutive patients who underwent initial AF ablation were enrolled. Body mass index (BMI), height and body weight were used as indicators of body size. BMI was divided into four groups, namely <18.5 kg/m^2, 18.5–25.0 kg/m^2, 25.0–30.0 kg/m^2, ≥30.0 kg/m^2. LVAs were defined as areas with bipolar voltage of <0.5 mV covering ≥5 cm^2 of left atrium. Rhythm outcome following the catheter ablation procedure was followed for 24 months.
Results: LVAs were found in 349 (24 %) patients. A J-curve phenomenon was found between BMI or body weight and the prevalence of LVAs. In particular, BMI <18.5 kg/m^2 was an independent predictor of LVAs (odds ratio, 1.9; 95 % confidence interval: 1.01–3.5; p = 0.046). Conversely, the prevalence of LVAs increased with decreasing height. For rhythm outcome, there was a significant difference in freedom from AF recurrence among groups stratified by BMI (p = 0.001).
Conclusions: A J-curve phenomenon existed between BMI or body weight and the prevalence of LVAs, which reflects atrial myopathy, in patients with AF ablation. In contrast, the prevalence of LVAs increased with decreasing height.

1. Introduction

Recently, catheter ablation has been positioned as an effective treatments for atrial fibrillation (AF) [1,2]. However, some patients experience AF recurrence after catheter ablation [1,2]. It has been reported that left atrial low-voltage areas (LVAs) reflect left atrial myopathy and consequent left atrial remodeling, such as atrial fibrosis and loss of myocardial fibers, and that LVAs influence AF recurrence [3,4]. In addition, atrial myopathy as assessed by LVA is also associated with the development of heart failure, stroke, and poor life prognosis [5]. Although patients with underweight and obesity are more likely to have recurrent AF [6,7], the mechanism is

* Corresponding author. Kansai Rosai Hospital Cardiovascular Center, 3-1-69 Inabaso, Amagasaki-shi, Hyogo, 660-8511, Japan.
E-mail address: masuda-masaharu@kansaih.johas.go.jp (M. Masuda).

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not completely clarified; and to our knowledge, the relationship between body size and LVAs is also unclear. We hypothesized that LVAs would be more prevalent in patients with abnormal body size than in those with normal body size. The purpose of this study was to clarify the relationship between body size and the prevalence of LVAs in patients undergoing AF ablation.

2. Methods

2.1. Patient enrollment

A total of 1,479 consecutive patients who underwent initial AF at our hospital from December 2014 to March 2022 were enrolled. Consistent with AF classification in current guidelines, paroxysmal AF was defined as AF that stopped within 7 days, and persistent AF as AF that lasted longer than 7 days [1,2].

Body mass index (BMI), height and body weight were used as indicators of body size. BMI was calculated by dividing body weight in kilograms by the square of height in meters. Patients without height or body weight data were excluded. Patients who could not undergo voltage mapping, mainly due to AF with resistance to cardioversion after pulmonary vein isolation, were also excluded. Other exclusion criteria were patients who had undergone previous catheter ablation for AF, or had undergone MAZE surgery. BMI was divided into 4 groups: $<$18.5 kg/m^2, 18.5–25.0 kg/m^2, 25.0–30.0 kg/m^2, and $\geq$30.0 kg/m^2, based on previous Japanese reports [8,9]. This study complied with the Declaration of Helsinki, and the protocol of this study was approved by Kansai Rosai Hospital Institutional Review Board (Reference number: 23D062g; approved October 18, 2023). Written informed consent for catheter ablation and the use of data in this study was obtained from all patients.

2.2. Catheter ablation

Catheter ablation and electrophysiologic studies for atrial fibrillation were performed by experienced cardiologists. Intraoperative sedation was conducted with dexmedetomidine or propofol, and analgesia with pentazocine or fentanyl. Intraoperative respiratory management was performed with noninvasive positive pressure ventilation or mechanical ventilation with a laryngeal mask airway. The 3-D mapping systems used for catheter ablation were Carto 3 (Biosense Webster, Inc., Diamond Bar CA, USA), Ensite NavX (Abbott, Abbott Park IL, USA) or Rhythmia (Boston Scientific, Boston MA, USA), selected at the discretion of the operator.

From December 2014 to March 2016, only radiofrequency catheter ablation was performed; from March 2016 to March 2022, cryoballoon ablation was performed in patients with paroxysmal AF and a short duration ($<$1 year) of AF. In cases where cryoballoon ablation was considered challenging, such as patients with a common pulmonary vein or wide right pulmonary vein carina, radiofrequency catheter ablation was performed. Laser balloon ablation was performed only in two cases of paroxysmal AF in August 2018.

For radiofrequency catheter ablation, a long Agilis sheath (Abbott), Vizigo sheath (Biosense Webster) or Swartz SL0 sheath (Abbott) was used at the operator's judgment. Bilateral extensive pulmonary vein isolation was performed. The ablation catheter used was an open-irrigated linear ablation catheter with a 3.5-mm tip. Each site was ablated at a power between 25 W and 35 W for 10–30 s. The radiofrequency ablation catheter parameters were set to a maximum temperature of 42 °C and a flow rate of 8–17 mL/min. To predict ablation lesion size, the ablation index (Biosense Webster) was used from February 2018 to March 2022 for cases performed with Carto 3, and the lesion size index (Abbott) was used from August 2018 to March 2022 for cases performed with Ensite NavX [10,11].

For cryoballoon ablation, individual isolation of pulmonary veins was performed using the Arctic Front Advance cryoballoon catheter with a 28-mm balloon size (Medtronic, Inc., Minneapolis MN, USA). Balloon cooling time was set at 180 or 120 s from time-to-isolation, but was shortened in areas adjacent to the esophagus [12]. Contrast was used to confirm the balloon occlusion of each pulmonary vein. However, saline and intracardiac echocardiography were used in patients with impaired renal function or contrast allergy.

Laser balloon ablation was performed using a visually guided laser balloon ablation system (Heartlight™; CardioFocus, Marlborough, MA, USA and Japan Lifeline Co., Ltd, Tokyo, Japan). The laser balloon was inserted into each pulmonary vein under fluoroscopic and 3-D mapping guidance. The sites of laser energy application were the ostium of the pulmonary veins observed on endoscopic images, and laser energy application was avoided in regions overlapping with stagnant blood. The degree of legion overlap and the dose and duration of laser energy application were operator-dependent.

The disappearance of pulmonary vein potentials was confirmed with a multi-electrode mapping catheter or circular catheter, and supplemented with additional radiofrequency catheter ablation if isolation of the pulmonary vein was difficult with balloon ablation.

Empirical additional ablation other than pulmonary vein isolation was also performed at the judgment of the operator. Spontaneously occurring or atrial burst stimuli, and AF triggers or frequent atrial premature beats originating from non-pulmonary vein foci induced by isoproterenol infusion were also ablated.

2.3. Methods of voltage mapping

Left atrial voltage mapping was conducted after pulmonary vein isolation immediately after pulmonary vein isolation, before additional ablation other than pulmonary vein isolation. Voltage mapping was performed under sinus rhythm or pacing from the high right atrium using an ablation catheter with a 3.5-mm tip or a multi-electrode mapping catheter [13].

In accordance with our previous study [13], mapping points were obtained to remove all color gaps on the voltage map in the 3-D mapping system. The target number of mapping points was $\geq$100 points with the 3.5-mm tip ablation catheter and $\geq$1,000 points with the multi-electrode mapping catheter. Sufficient contact with the left atrial endocardium was ensured by distance to the geometry

surface and a stable intracardiac electrogram as detected by the mapping catheter. The sites of LVAs were assessed using the confidence module (Carto 3) and Ensite Automap (Ensite NavX) to accurately depict the area. Fill thresholds were 15 mm (Carto 3) and 20 mm (Ensite NavX), and color interpolation thresholds were 20 mm (Carto 3) and 7 mm (Ensite NavX). Respective interpolation threshold and confidence mask settings when Rhythmia was used were 5 mm and 0.03 mV.

High-pass and low-pass signal filters were set to 30 and 500 Hz, and the obtained peak-to-peak voltage of intracardiac electrogram among mapping points was assessed. Normal regions were defined as areas with a bipolar voltage $\geq$0.5 mV, and low-voltage regions as areas with $<$0.5 mV. With respect to the regions near the pulmonary vein isolation lines, areas with bipolar voltage $<$0.2 mV were defined as scarred regions, and scarred regions were excluded from LVAs measurement [13]. LVAs were defined as low-voltage regions which covered $\geq$5 cm^2 of left atrial endocardium [13]. Regarding the location of LVAs, the left atrium was divided into five regions: antero-septal, posterior, roof, inferior, and posterolateral [14].

2.4. Rhythm outcomes

AF recurrence following catheter ablation was assessed for 24 months. In general, routine follow-up with a 12-lead electrocardiogram was carried out at 1, 3, 6, 9, 12, 18, and 24 months after the ablation procedure. 24-hour Holter electrocardiography was performed 6 months after the ablation procedure.

If the patient felt symptoms suspicious of AF recurrence, additional follow-up was conducted, and a 12-lead electrocardiogram, 24-h Holter electrocardiography and/or event monitor recording were performed at the cardiologist's discretion.

AF recurrence was defined as follows: (1) atrial tachyarrhythmias detected on 12-lead electrocardiography or event monitor recording at $\geq$90 days after the ablation procedure; (2) atrial tachyarrhythmias lasting $>$30 s detected by 24-h Holter electrocardiography at $\geq$90 days after the ablation procedure; or (3) prescription of a class I and/or class III antiarrhythmic agent at $\geq$90 days after the procedure.

Irrespective of multiple ablation procedures and antiarrhythmic agent usage, cardiac rhythm at the most recent outpatient visit was also assessed over the 24-month follow-up.

2.5. Statistical methods

Categorical data are presented as absolute values and percentages, while continuous data are expressed as mean $\pm$ standard deviation or median (1st quintile to 3rd quartile). Tests for significance were conducted using the chi-squared test or the Fisher's exact test for categorical variables, and one-way analysis of variance or the Kruskal-Wallis test for continuous variables. The association between BMI and clinical risk scores (DR-FLASH score and SPEED score), which predict the presence of LVAs, was also examined [13, 15]. A quadratic approximation curve was delineated to estimate the association between the prevalence of LVA and BMI, height or body weight. Kaplan-Meier analysis and the log-rank test were used to investigate associations between AF recurrence and BMI. Logistic regression analysis was used to assess clinical risk factors associated with the prevalence of LVAs. Variables with a P value $<$ 0.05 in the univariate analyses were eligible for inclusion in the multivariate analysis. Statistical analyses in this study were performed using commercial software (SPSS ™, SPSS, Inc., Chicago IL, USA) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [16].

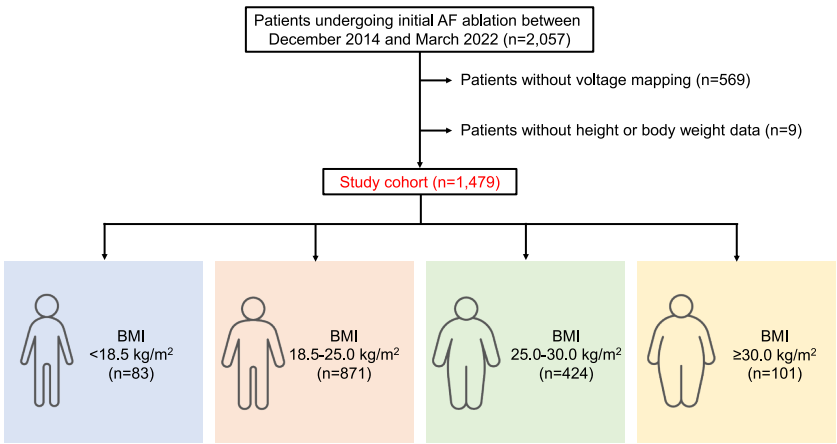

Fig. 1. Patient flowchart. Of the 2,057 patients who underwent initial AF ablation, 1,479 patients were enrolled after excluding 569 patients who did not undergo voltage mapping and 9 patients with missing height or body weight data. Patients were classified by BMI into four groups: $<$18.5 kg/m^2, 18.5–25.0 kg/m^2, 25.0–30.0 kg/m^2, and $\geq$30.0 kg/m^2. AF, atrial fibrillation; BMI, body mass index.

3. Results

3.1. Patient characteristics

Of the 2,057 patients who underwent initial AF ablation, 569 patients who did not undergo voltage mapping and 9 patients with missing height or body weight data were excluded, leaving 1,479 patients for enrollment. Based on BMI, patients were classified into four groups: <18.5 kg/m^2 (n = 83), 18.5–25.0 kg/m^2 (n = 871), 25.0–30.0 kg/m^2 (n = 424), and ≥30.0 kg/m^2 (n = 101) (Fig. 1).

Pulmonary vein isolation was achieved in all patients. The 3-D mapping system used was Carto 3 in 1,269 (86 %) patients, EnSite NavX in 164 (11 %), and Rhythmia in 46 (3 %). Patient characteristics are shown in Table 1. Mean BMI was 24.1 ± 4.0 kg/m^2. Patients with a BMI <18.5 kg/m^2 were older, more frequently female, and had lower albumin than those with a higher BMI. Patients with a BMI <18.5 kg/m^2 also had a higher prevalence of paroxysmal AF and N-terminal pro-brain natriuretic peptide compared to those with a higher BMI. In contrast, as BMI increased, patients had a higher prevalence of hypertension and diabetes mellitus, and a larger left atrial diameter.

Mean DR-FLASH score was 3.6 ± 1.3 points, and mean SPEED score was 2.2 ± 1.2 points. There were significant differences between BMI and DR-FLASH score or SPEED score.

3.2. Procedural characteristics and voltage mapping

Procedural characteristics are shown in Table 2. In total, LVAs were found in 349 (24 %) patients. Mean area of left atrium was 147 ± 50 cm^2, and median total number of mapping points was 943 (177–1,365) points.

A J-curve phenomenon existed between BMI and the prevalence of LVAs, and a significant difference in the prevalence of LVAs was seen among groups stratified by BMI (Fig. 2). This J-curve phenomenon between BMI and the prevalence of LVAs was present even on stratification by gender and AF type. Although a J-curve phenomenon was also found between body weight and the prevalence of LVAs, the prevalence of LVAs increased with decreasing height (Fig. 3).

In patients with LVAs, median LVA area was 11 (8–24) cm^2, and no significant difference in the size of LVAs was seen among groups stratified by BMI. With regard to the location of LVAs, LVAs existed in the anterior-septal region in 308 (88 %) patients, roof region in 158 (45 %), posterior region in 117 (34 %), inferior region in 66 (19 %), and posterolateral region in 31 (9 %) patients. In patients with low BMI, the prevalence of LVAs in the anterior-septal region and roof region was significantly higher than those with high BMI

Table 1
Patient characteristics.

Variable	All (n = 1,479)	BMI <18.5 kg/m^2 (n = 83)	BMI 18.5–25.0 kg/m^2 (n = 871)	BMI 25.0–30.0 kg/m^2 (n = 424)	BMI ≥30.0 kg/m^2 (n = 101)	P
Age, years	68 ± 10	73 ± 8	69 ± 10	67 ± 11	65 ± 11	<0.001
Female, n (%)	500 (34)	53 (64)	291 (33)	114 (27)	42 (42)	<0.001
Persistent atrial fibrillation, n (%)	899 (61)	43 (52)	502 (58)	281 (66)	73 (72)	0.001
BMI, kg/m^2	24 ± 4	17 ± 1	22 ± 2	27 ± 1	34 ± 4	<0.001
CHA_2DS_2-VASc score	2.5 ± 1.5	3.1 ± 1.3	2.5 ± 1.5	2.4 ± 1.4	2.8 ± 1.5	<0.001
DR-FLASH score	3.6 ± 1.3	3.6 ± 1.1	3.4 ± 1.2	3.7 ± 1.3	4.2 ± 1.3	<0.001
SPEED score	2.2 ± 1.2	2.7 ± 1.1	2.2 ± 1.1	2.2 ± 1.2	2.6 ± 1.2	<0.001
Congestive heart failure, n (%)	319 (22)	24 (29)	181 (21)	76 (18)	38 (38)	<0.001
Hypertension, n (%)	831 (56)	33 (40)	455 (52)	275 (65)	68 (67)	<0.001
Diabetes mellitus, n (%)	266 (18)	8 (10)	126 (15)	99 (23)	33 (33)	<0.001
Thromboembolism, n (%)	116 (8)	9 (11)	72 (8)	28 (7)	7 (7)	0.52
Vascular disease, n (%)	133 (9)	7 (8)	80 (9)	33 (8)	13 (13)	0.44
Hemoglobin, g/dL	14.0 ± 1.6	12.7 ± 1.8	13.8 ± 1.5	14.4 ± 1.5	14.3 ± 1.6	<0.001
eGFR, mL/min/1.73 m^2	63 ± 18	55 ± 22	63 ± 18	64 ± 17	59 ± 19	<0.001
BNP, pg/ml	110 (47–228)	180 (72–361)	107 (40–225)	107 (46–209)	144 (50–217)	0.07
NT-proBNP, pg/ml	541 (154–1032)	842 (434–1903)	503 (140–1071)	558 (168–973)	603 (187–947)	0.001
Elevated BNP/NT-proBNP[a], n (%)	881 (60)	60 (77)	499 (59)	258 (62)	64 (65)	0.01
Albumin, g/dL	4.1 ± 0.4	3.9 ± 0.4	4.1 ± 0.4	4.1 ± 0.3	4.1 ± 0.3	0.001
Left ventricular ejection fraction, %	61 ± 12	59 ± 14	61 ± 12	62 ± 11	59 ± 12	0.12
Left ventricular mass index, g/m^2	107 ± 30	101 ± 41	105 ± 29	109 ± 29	117 ± 33	<0.001
Left atrial diameter, mm	41 ± 7	35 ± 7	39 ± 7	43 ± 6	46 ± 7	<0.001
E/e'	11 ± 5	11 ± 6	11 ± 5	11 ± 4	12 ± 5	0.046
Deceleration time, msec	170 ± 51	163 ± 52	171 ± 51	171 ± 51	170 ± 47	0.64

BMI: Body mass index, eGFR: Estimated glomerular filtration rate, BNP: Brain natriuretic peptide.
NT-proBNP: N-terminal pro-brain natriuretic peptide.
[a] BNP ≥100 pg/ml or NT-proBNP ≥400 pg/ml.

Table 2
Procedural characteristics.

Variable	All (n = 1,479)	BMI <18.5 kg/m^2 (n = 83)	BMI 18.5–25.0 kg/m^2 (n = 871)	BMI 25.0–30.0 kg/m^2 (n = 424)	BMI ≥30.0 kg/m^2 (n = 101)	P
Procedural time, min	101 ± 34	104 ± 34	99 ± 33	100 ± 35	115 ± 37	<0.001
Fluoroscopy time, min	20 ± 10	22 ± 11	20 ± 10	20 ± 9	24 ± 13	<0.001
Balloon ablation, n (%)	321 (22)	27 (33)	198 (23)	81 (19)	15 (15)	0.01
Prevalence of LVAs, n (%)	349 (24)	38 (46)	208 (24)	79 (19)	24 (24)	<0.001
Total LVAs in patients with LVAs, cm^2	13 (8–22)	14 (8–25)	13 (8–22)	13 (8–22)	11 (7–17)	0.57
Regions with LVAs						
Antero-septal region, n (%)	429 (29)	45 (54)	259 (30)	98 (23)	27 (27)	<0.001
Roof region, n (%)	202 (14)	25 (30)	116 (14)	53 (13)	8 (8)	<0.001
Posterior region, n (%)	163 (11)	15 (18)	98 (12)	42 (10)	8 (8)	0.13
Inferior region, n (%)	84 (6)	10 (12)	47 (6)	22 (5)	5 (5)	0.13
Posterolateral region, n (%)	34 (2)	3 (4)	26 (3)	4 (1)	1 (1)	0.053
Total area of left atrium, cm^2	147 ± 50	136 ± 40	143 ± 48	150 ± 50	173 ± 62	<0.001
Total mapping points of left atrium, points	943 (177–1365)	935 (212–1459)	922 (175–1321)	978 (164–1413)	1058 (193–1491)	0.28
Additional ablation						
CTI linear ablation, n (%)	232 (16)	9 (11)	151 (17)	61 (14)	11 (11)	0.14
SVC isolation, n (%)	25 (2)	0 (0)	15 (2)	10 (2)	0 (0)	0.32
Non-pulmonary vein trigger ablation, n (%)	57 (4)	5 (6)	29 (3)	21 (5)	2 (2)	0.25
Left atrial linear ablation, n (%)	121 (8)	10 (12)	70 (8)	31 (7)	10 (10)	0.48
LVAs ablation, n (%)	132 (9)	13 (16)	76 (9)	30 (7)	13 (13)	0.04
CFAE ablation, n (%)	26 (2)	3 (4)	14 (2)	8 (2)	1 (1)	0.50

BMI: Body mass index, LVAs: Low-voltage areas, eGFR: Estimated glomerular filtration rate, BNP: Brain natriuretic peptide.
NT-proBNP: N-terminal pro-brain natriuretic peptide, CTI: Cavo-tricuspid isthmus, SVC: Superior vena cava.
CFAE: Complex fractionated atrial electrogram.† BNP ≥100 pg/ml or NT-proBNP ≥400 pg/ml.

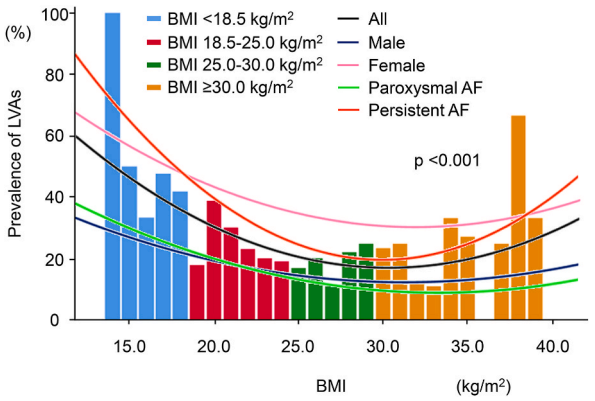

Fig. 2. Association between BMI and prevalence of LVAs A J-curve phenomenon was seen between BMI and the prevalence of LVAs. Prevalence of LVAs significantly differed among groups stratified by BMI. P values indicate significance level for the relationship between the prevalence of LVAs and groups stratified by BMI. Even on stratification by gender and AF type, the J-curved phenomenon is seen between BMI and prevalence of LVAs. The parameters of the quadratic approximation curve were $y = 0.001x^2$-$0.076x$+1.312, $R^2 = 0.019$, $p < 0.001$ (all); $y = 0.001x^2$-$0.035x$+0.664, $R^2 = 0.005$, $p = 0.10$ (male); $y = 0.001x^2$-$0.059x$+1.237, $R^2 = 0.015$, $p = 0.02$ (female); $y = 0.001x^2$-$0.042x$+0.781, $R^2 = 0.014$, $p = 0.02$ (paroxysmal AF) and $y = 0.002x^2$-$0.12x$+1.996, $R^2 = 0.035$, $p < 0.001$ (persistent AF). BMI, body mass index; LVAs, left atrial low-voltage areas, AF, atrial fibrillation.

(Table 2).

3.3. Predictors of LVAs

In univariate analysis, elderly, female, persistent AF, low BMI, CHA_2DS_2-VASc score, congestive heart failure, diabetes mellitus, thromboembolism, lower hemoglobin, lower albumin, and lower estimated glomerular filtration rate, higher brain natriuretic peptide higher N-terminal pro-brain natriuretic peptide, higher left ventricular mass index, higher left atrial diameter, higher E/e' and lower deceleration time were significantly associated with the prevalence of LVAs.

In multivariate analysis including these variables, independent predictors of the prevalence of LVAs included BMI <18.5 kg/m^2,

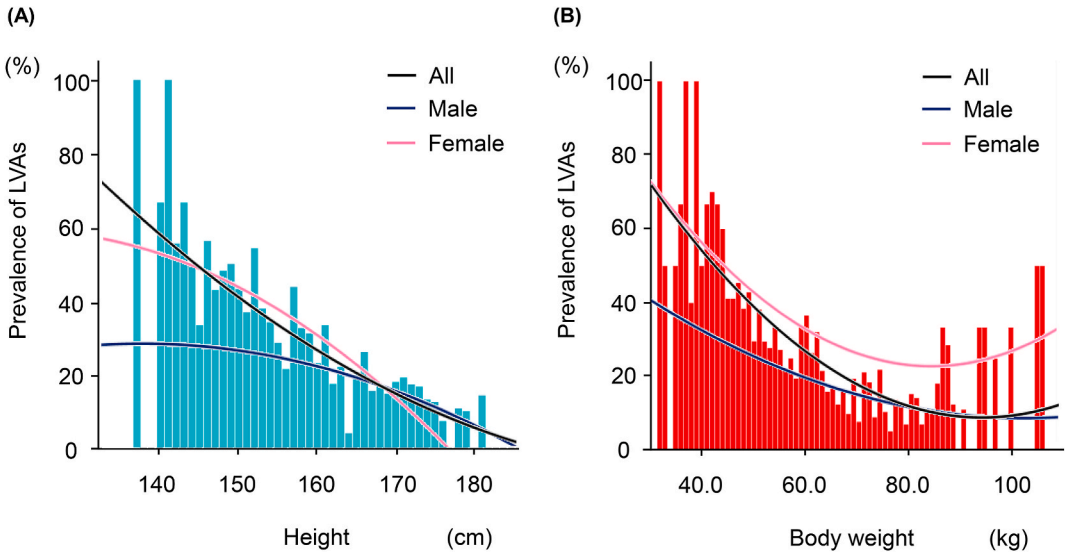

Fig. 3. Association between height or body weight and prevalence of LVAs A J-curve phenomenon was seen between body weight and the prevalence of LVAs. In contrast, the prevalence of LVAs increased with decreasing height. The parameters of the quadratic approximation curve in body weight were $y = 0.0002x^2$-$0.029x$+1.435, $R^2 = 0.070$, $p < 0.001$ (all); $y = 0.00006x^2$-$0.012x$+0.721, $R^2 = 0.014$, $p = 0.001$ (male) and $y = 0.0002x^2$-$0.029x$+1.439, $R^2 = 0.037$, $p < 0.001$ (female). The parameters of the quadratic approximation curve in height were $y = 0.0001x^2$-$0.054x$+5.621, $R^2 = 0.082$, $p < 0.001$ (all); $y = -0.0001x^2$+$0.034x$-2.046, $R^2 = 0.019$, $p < 0.001$ (male) and $y = -0.0002x^2$+$0.50x$-2.451, $R^2 = 0.029$, $p = 0.001$ (female). LVAs, left atrial low-voltage areas.

Table 3
Predictors of LVAs.

Variable	All (n = 1,479)	LVAs		Univariate analysis		Multivariate analysis	
		With (n = 349)	Without (n = 1,130)	OR [95 % CI]	P	OR [95 % CI]	P
Age,/10 years	6.8 ± 1.0	7.3 ± 0.7	6.7 ± 1.0	2.5 [2.1, 2.9]	<0.001	2.3 [1.9, 2.9]	<0.001
Female, n (%)	500 (34)	194 (56)	306 (27)	3.4 [2.6, 4.3]	<0.001	2.9 [2.1, 4.0]	<0.001
Persistent atrial fibrillation, n (%)	899 (61)	258 (74)	641 (57)	2.2 [1.7, 2.8]	<0.001	2.6 [1.7, 4.0]	0.003
BMI, kg/m^2	24 ± 4	23 ± 4	24 ± 4	0.94 [0.91, 0.97]	<0.001	–	–
BMI <18.5 kg/m^2, n (%)	83 (6)	38 (11)	45 (4)	2.9 [1.9, 4.6]	<0.001	1.9 [1.01, 3.5]	0.046
CHA_2DS_2-VASc score	2.5 ± 1.5	3.3 ± 1.4	2.3 ± 1.4	1.7 [1.5, 1.8]	<0.001	–	–
Congestive heart failure, n (%)	319 (22)	104 (30)	215 (19)	1.8 [1.4, 2.4]	<0.001	1.2 [0.8, 1.8]	0.31
Diabetes mellitus n (%)	266 (18)	85 (24)	181 (16)	1.7 [1.3, 2.3]	<0.001	1.6 [1.1, 2.3]	0.02
Thromboembolism, n (%)	116 (8)	38 (11)	78 (7)	1.6 [1.1, 2.5]	0.02	1.6 [1.1, 2.3]	0.12
Hemoglobin, g/dL	14.0 ± 1.6	13.4 ± 1.7	14.2 ± 1.5	0.73 [0.7, 0.8]	<0.001	0.8 [0.7, 0.9]	0.002
Albumin, g/dL	4.1 ± 0.4	4.0 ± 0.4	4.1 ± 0.4	0.5 [0.4, 0.7]	<0.001	1.6 [0.97, 2.5]	0.07
eGFR,/10 ml/min/1.73 m^2	6.3 ± 1.8	5.8 ± 1.9	6.4 ± 1.8	0.86 [0.8, 0.9]	<0.001	1.05 [0.95, 1.1]	0.33
BNP,/100 pg/dL	1.1 (0.5–2.3)	1.9 (1.0–3.3)	0.9 (0.4–2.0)	1.1 [1.04, 1.2]	0.003	–	–
NT-proBNP,/1000 pg/dL	0.54 (0.15–1.03)	0.86 (0.45–1.69)	0.44 (0.12–0.91)	1.04 [1.01, 1.07]	0.005	–	–
Elevated BNP/NT-proBNP[a], n (%)	881 (61)	268 (80)	613 (56)	3.1 [2.4, 4.2]	<0.001	1.5 [0.997, 2.3]	0.052
Left ventricular mass index,/10 g/m^2	10.7 ± 3.0	11.0 ± 3.4	10.6 ± 2.9	1.05 [1.01, 1.1]	0.03	1.01 [0.95, 1.07]	0.74
Left atrial diameter,/10 mm	4.1 ± 0.7	4.2 ± 0.7	4.0 ± 0.7	1.5 [1.3, 1.8]	<0.001	1.2 [0.9, 1.6]	0.20
E/e'	11 ± 5	13 ± 6	11 ± 4	1.1 [1.06, 1.12]	<0.001	1.02 [0.98, 1.06]	0.38
Deceleration time,/10 msec	17.0 ± 5.1	16.3 ± 5.0	17.3 ± 5.1	0.96 [0.93, 0.98]	0.002	0.98 [0.94, 1.01]	0.14

LVAs: Low-voltage areas, OR: Odds ratio, CI: Confidence interval, BMI: Body mass index, eGFR: Estimated glomerular filtration rate.
BNP: Brain natriuretic peptide, NT-proBNP: N-terminal pro-brain natriuretic peptide.
Variables with p value < 0.05 on univariate analysis were included in the multivariate analysis.
[a] BNP ≥100 pg/ml or NT-proBNP ≥400 pg/ml.

elderly, female, persistent AF, diabetes mellitus, and low hemoglobin (Table 3).

3.4. Rhythm outcome following AF ablation

AF recurrence developed in 409 (28 %) patients during the observation period following AF ablation.

A significant difference in freedom from AF recurrence was seen among groups stratified by BMI (Fig. 4). In particular, freedom from AF recurrence was significantly lower in patients with BMI <18.5 kg/m^2 or ≥30.0 kg/m^2 than in those with 18.5–25.0 kg/m^2. On classification by the presence or absence of LVAs, there were no significant differences in freedom from AF recurrence among groups stratified by BMI in patients without LVAs (Fig. 5A). Conversely, in patients with LVAs, a significant difference in freedom from AF recurrence was seen among groups stratified by BMI (Fig. 5B).

Sub-group analyses stratified by AF type were also performed. There was a significant difference in freedom from AF recurrence among groups stratified by BMI, irrespective of AF type (Fig. 6A and B) In patients with paroxysmal AF, freedom from AF recurrence was similar among groups stratified by BMI irrespective of the prevalence of LVAs (Fig. 7A and B). In patients with persistent AF, a significant difference among groups stratified by BMI was seen only in patients with LVAs (Fig. 8A and B).

Even after receiving multiple procedures (second ablation: 264 [18 %], third or later ablation: 50 [3 %]), a significant difference in the number of patients who maintained sinus rhythm was seen among groups stratified by BMI. In persistent AF, there was a significant difference in the number of patients who maintained sinus rhythm even after receipt of multiple procedures among groups stratified by BMI; conversely, the number of patients who maintained sinus rhythm after multiple procedures was similar among groups stratified by BMI in paroxysmal AF (Table 4).

4. Discussion

In this study of the association between body size and prevalence of LVAs or rhythm outcome, we detected LVAs in 349 (24 %) of 1,479 patients enrolled after initial AF ablation. A J-curve phenomenon existed between BMI or body weight and prevalence of LVAs. In particular, BMI <18.5 kg/m^2 was an independent predictor of LVAs. In contrast, the prevalence of LVAs increased with decreasing height. Regarding rhythm outcomes, we found a significant difference in freedom from AF recurrence among groups stratified by BMI. These main results of this study have been summarized in the Graphical Abstract. To our knowledge, this is the first clinical research to clarify the association between body size and prevalence of LVAs, which reflects atrial myopathy.

4.1. Body size and the prevalence of LVAs

A J-curve phenomenon was identified between BMI or body weight and the prevalence of LVAs in our study. In terms of histological changes in atrium, pathological evaluation of atrial myocardium has shown that LVAs are caused by loss of myocardial fibers, decreased number of nuclei, fibrosis, and an increase in the size of intercellular spaces [3]. Underweight or obesity may induce these factors, leading to an increase of LVAs.

In underweight patients, the expression of myocardial contractile genes, which are involved in degeneration and necrosis of the myocardium, and of ribosomal proteins, which are involved in apoptosis and fibrosis of the myocardium, are suppressed [17–22]. Consequently, the loss of myocardial fibers, reduction in the number of myocardial nuclei, and fibrosis may occur, resulting in an increase in LVAs [3]. In addition, it has been reported that the pressure of the ascending aorta on the left atrium is stronger and that LVAs in contact with aorta are larger in patients with lower BMI than those without [23]. These findings are consistent with our present

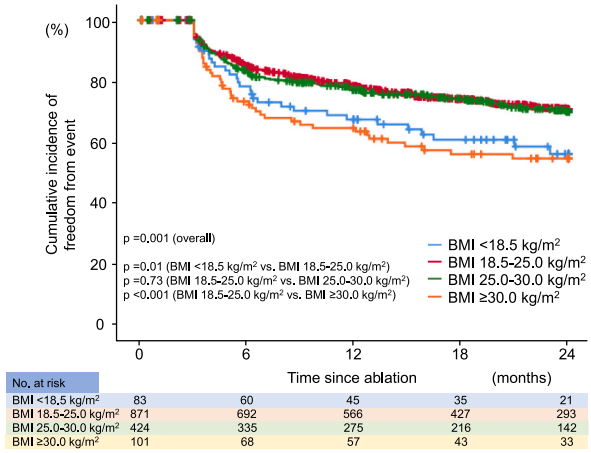

Fig. 4. Rhythm outcome following AF ablation in patients stratified by BMI Freedom from AF recurrence significantly differed among groups stratified by BMI. In particular, freedom from AF recurrence was significantly lower in patients with BMI <18.5 kg/m^2 or BMI ≥30.0 kg/m^2 than in those with 18.5–25.0 kg/m^2. AF, atrial fibrillation; BMI, body mass index.

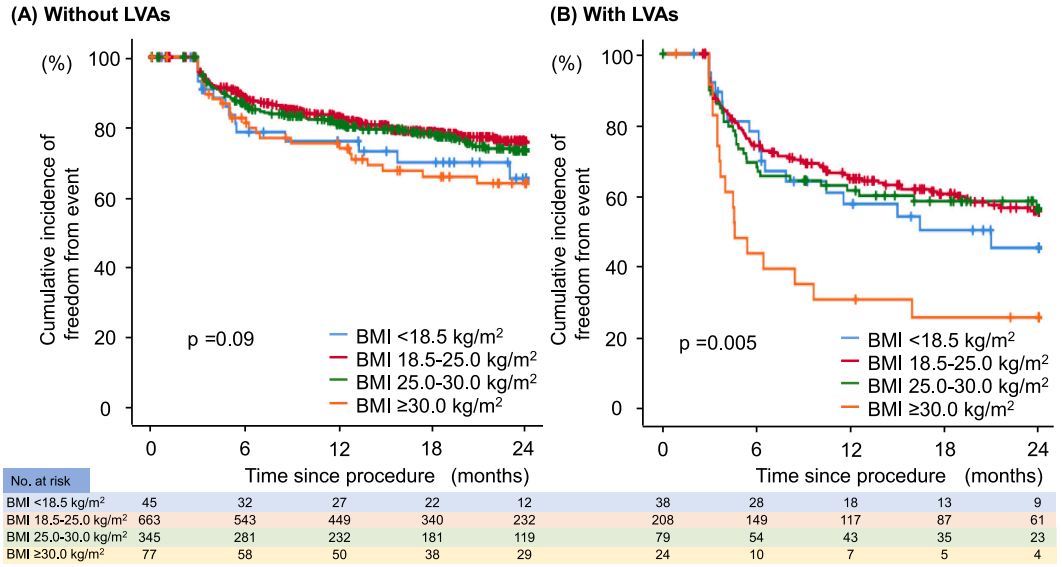

Fig. 5. Rhythm outcome following AF ablation in patients with or without LVAs (A) In patients without LVAs, freedom from AF recurrence did not significantly differ among groups stratified by BMI. (B) In patients with LVAs, freedom from AF recurrence significantly differed among groups stratified by BMI. AF, atrial fibrillation; LVAs, left atrial low-voltage areas; BMI, body mass index.

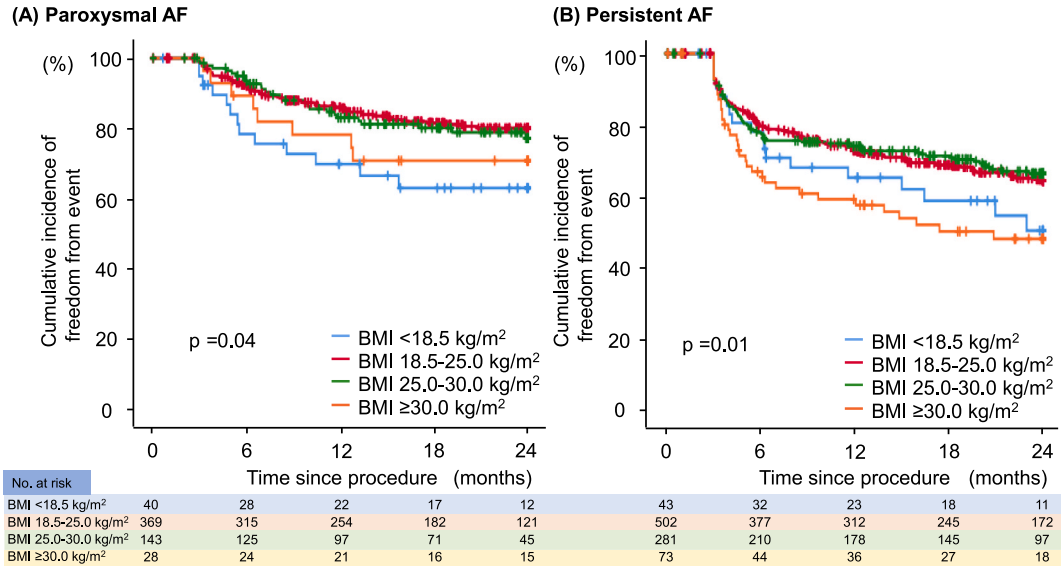

Fig. 6. Rhythm outcome following AF ablation stratified to AF type (A) In patients with paroxysmal AF, freedom from AF recurrence significantly differed among groups stratified by BMI. (B) In patients with persistentAF, freedom from AF recurrence significantly differed among groups stratified by BMI. AF, atrial fibrillation; BMI, body mass index.

findings of more LVAs in the antero-septal and roof regions, which are adjacent to the ascending aorta, in underweight patients. We speculate that mechanical compression stress in the limited space of the thorax may cause fibrosis, which is associated with progression of atrial myopathy, leading to the formation of LVAs [23,24].

In contrast, obesity has also been shown to suppress the expression of genes involved in myocardial contraction, which may result in LVAs due to the loss of myocardial fibers and decrease in the number of myocardial nuclei [17]. Moreover, obesity is associated with increased epicardial adipose tissue, which is associated with atrial interstitial fibrosis mediated by the paracrine effect, and may be the cause of the increase in LVAs [25,26].

Previous studies have not found that BMI or body weight is an independent predictor of LVAs [14,15,27]. This may be because the relationship between BMI or body weight and the presence of LVAs is not monophasic, but rather represents a J-curve phenomenon. Therefore, the absolute value of BMI or body weight might not be predictive. This study was conducted in Japan, where many patients

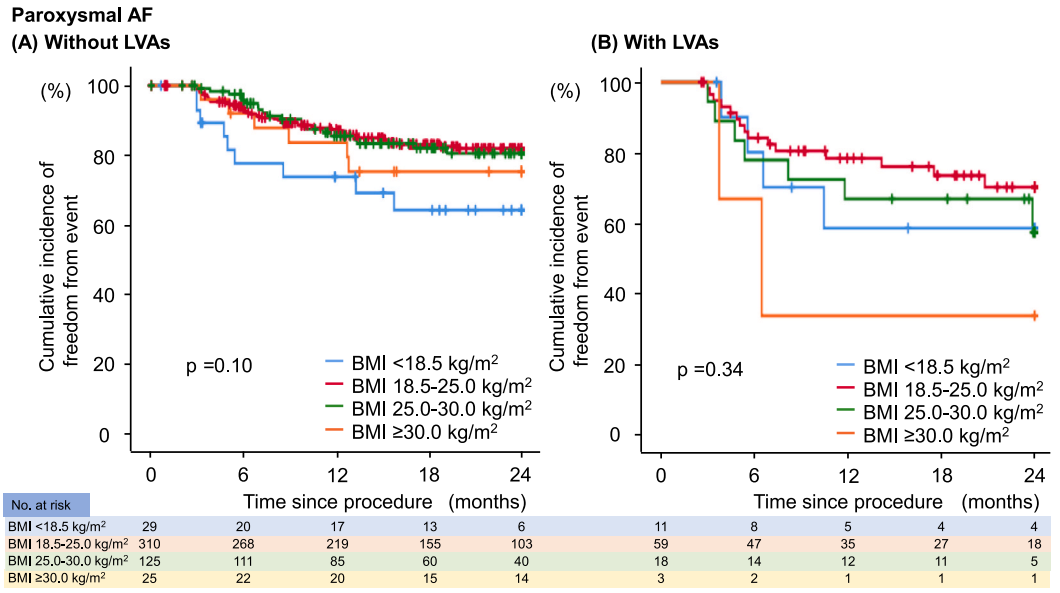

Fig. 7. Rhythm outcome following AF ablation in patients with paroxysmal AF (A) In patients without LVAs, freedom from AF recurrence did not significantly differ among groups stratified by BMI. (B) In patients with LVAs, freedom from AF recurrence did not significantly differ among groups stratified by BMI. AF, atrial fibrillation; LVAs, left atrial low-voltage areas; BMI, body mass index.

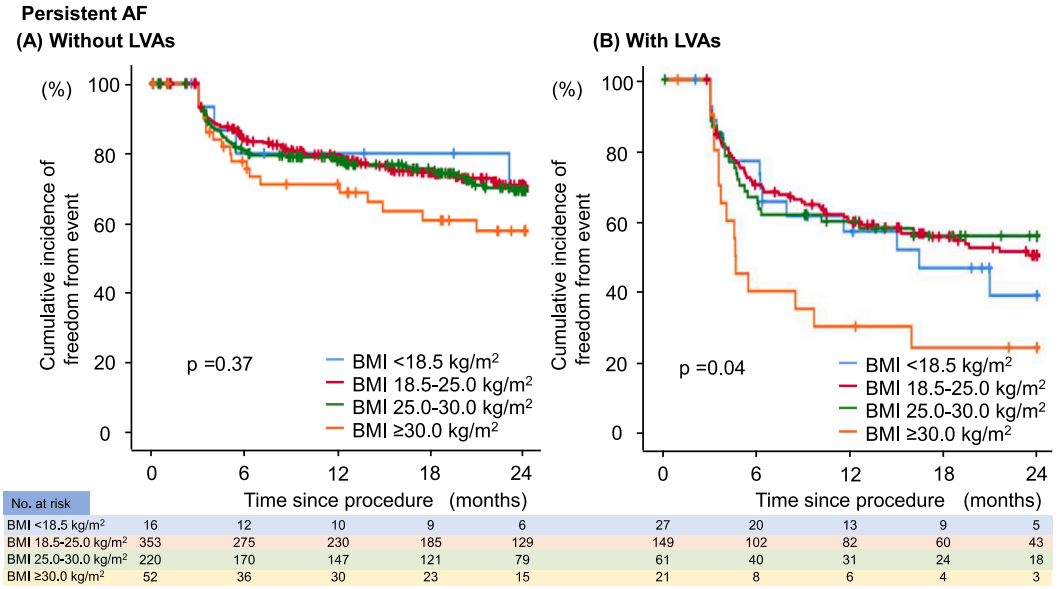

Fig. 8. Rhythm outcome following AF ablation in patients with persistent AF. (A) In patients without LVAs, freedom from AF recurrence did not significantly differ among groups stratified by BMI. (B) In patients with LVAs, freedom from AF recurrence significantly differed among groups stratified by BMI. AF, atrial fibrillation; LVAs, left atrial low-voltage areas; BMI, body mass index.

are underweight [28,29], and the relatively large number of participants accordingly allowed us to examine the impact of underweight on the prevalence of LVAs.

While many previous studies have shown tallness to be a risk for AF [30–32], the prevalence of LVAs increased with decreasing height in the present study. The *Pitx2c* gene, which is involved in the growth pathway, has been shown to increase the number of extrasystoles and to be a risk factor for AF [31,33], suggesting that tallness may be a cause of AF regardless of atrial remodeling. Moreover, given that cardiomyocyte size is positively correlated with height [34], short patients might have small cardiomyocytes, resulting in the development of LVAs [35].

Table 4
Rhythm outcomes after the most recent ablation procedure.

Variable	Sinus rhythm at the most recent outpatient visit					Follow-up periods (months)	P
	All	BMI	BMI	BMI	BMI		
	(n = 1,448) [a]	<18.5 kg/m^2 (n = 82)	18.5–25.0 kg/m^2 (n = 855)	25.0–30.0 kg/m^2 (n = 415)	≥30.0 kg/m^2 (n = 96)		
All	1335 (92)	75 (92)	794 (93)	389 (94)	77 (80)	23 (15–31)	0.002
Paroxysmal AF	550 (98)	38 (95)	348 (97)	140 (100)	24 (92)	22 (14–27)	0.12
Persistent AF	785 (89)	37 (88)	446 (90)	249 (91)	53 (76)	24 (15–33)	0.03

AF: Atrial fibrillation.
[a] In 31 (2 %) of the patients, there was no data on the cardiac rhythm at the most recent outpatient visit.

4.2. Impact of BMI and LVAs on rhythm outcomes following AF ablation

The present study showed that there was a significant difference in freedom from AF recurrence among groups stratified by BMI. The main reason why AF recurrence was more frequent in patients with abnormal BMI, namely underweight and obesity, might be atrial remodeling subsequent to atrial myopathy, which is indicated by the prevalence of LVAs [3]. In clinical settings, atrial remodeling includes (1) electrical remodeling, which is evaluated by LVAs, and (2) volumetric remodeling, which is evaluated by left atrial enlargement [36]. Histological assessment has shown that atrial remodeling is also indicated by the existence of LVAs [3]. In the present study, there was a significant difference in AF recurrence between groups classified by BMI only in patients with LVAs, indicating that left atrial enlargement alone has only a minor influence on AF recurrence, and that tissue degeneration of the atrium may impact AF recurrence in patients with abnormal BMI.

In a subanalysis by AF type, we found a significant difference in AF recurrence between groups classified by BMI in patients with LVAs and persistent AF. In contrast, we found no significant difference between groups classified by BMI in paroxysmal AF, even if LVAs were present. In paroxysmal AF, the main cause of AF is triggered activity [37], and left atrial remodeling itself may not have sufficient impact to increase AF recurrence in patients with abnormal BMI.

The difficulty of the ablation procedure in patients with abnormal BMI may also be a reason for the high incidence of AF recurrence. Patients with underweight are a high-risk group that requires careful ablation, as they often have chronic diseases and undernutrition due to aging [38]. Additionally, patients with underweight are known to have a high incidence of cardiac tamponade during AF ablation [9]. Obese patients are also known to have unstable respiration and long operative times in AF ablation [39,40]. It is possible that the difficulty in performing catheter ablation procedures with high quality in patients with abnormal BMI may have led to a higher incidence of recurrences.

4.3. Clinical implications

Prediction of LVAs by body size before the procedure is simple and noninvasive. Additionally, given that atrial myopathy is a progressive disease [41,42], maintenance of an optimal body size may be important in postoperative management to reduce the progression of atrial myopathy and thereby prevent AF recurrence. In terms of rhythm outcomes, patients with abnormal BMI and LVAs have a high AF recurrence rate and may require careful follow-up.

4.4. Limitations

This study has some limitations which warrant consideration. First, although there are many causes of abnormal body size, such as undernutrition, chronic disease, and changes in body composition such as osteoporosis, dehydration, and fluid congestion, we may not have sufficiently evaluated the causes of this abnormality in this study [38,43]. Second, while body weight, which is also a component of BMI, is an index that changes constantly, we measured this variable here at only a single point in the period prior to the procedure. Third, follow-up was limited to 12-lead electrocardiography, 24-h Holter electrocardiography and event monitor recording, and AF recurrence was accordingly not well evaluated in comparison with the use of an implantable cardiac monitor or cardiac-implantable electric device. Fourth, given that body composition differs among races [44], the results of this study, which were limited to a Japanese population, may not be applicable to all racial groups. Fifth, given that the study was conducted under an observational study design, patient characteristics, ablation devices, additional ablation strategy other than pulmonary vein isolation, and mapping catheter types were not similar. As a result, some analyses may be affected. For example, the size of the LVA may be underestimated by the use of different mapping catheters [45]. Finally, the number of patients in some subgroups, such as patients with BMI <18.5 kg/m^2, patients with BMI ≥30.0 kg/m^2 or patients who received a third or later ablation, was not large. Therefore the power of some statistical analyses may be weakened. For instance, in patients with paroxysmal AF and LVAs, freedom from AF recurrence was statistically similar among groups stratified by BMI because of the small number of patients with BMI ≥30.0 kg/m^2.

Empirical additional ablation other than pulmonary vein isolation was also performed at the judgment of the operator. Spontaneously occurring or atrial burst stimuli, and AF triggers or frequent atrial premature beats originating from non-pulmonary vein foci induced by isoproterenol infusion were also ablated.

5. Conclusions

In patients with AF ablation, this study revealed the presence of a J-curve phenomenon between BMI or body weight and the prevalence of LVAs, which reflect the presence of atrial myopathy. In particular, BMI <18.5 kg/m^2 was an independent predictor of LVAs. Conversely, the prevalence of LVAs increased with decreasing height. With regard to rhythm outcomes following AF ablation, a significant difference in AF recurrence was seen among groups stratified by BMI.

CRediT authorship contribution statement

Yasuhiro Matsuda: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Masaharu Masuda:** Writing – review & editing, Supervision, Conceptualization. **Hiroyuki Uematsu:** Writing – review & editing, Data curation. **Ayako Sugino:** Writing – review & editing, Data curation. **Hirotaka Ooka:** Writing – review & editing, Data curation. **Satoshi Kudo:** Writing – review & editing, Data curation. **Subaru Fujii:** Writing – review & editing, Data curation. **Mitsutoshi Asai:** Writing – review & editing. **Shin Okamoto:** Writing – review & editing. **Takayuki Ishihara:** Writing – review & editing. **Kiyonori Nanto:** Writing – review & editing. **Takuya Tsujimura:** Writing – review & editing. **Yosuke Hata:** Writing – review & editing. **Naoko Higashino:** Writing – review & editing. **Sho Nakao:** Writing – review & editing. **Masaya Kusuda:** Writing – review & editing. **Toshiaki Mano:** Writing – review & editing, Supervision.

IRB information

Kansai Rosai Hospital Institutional Review Board. Reference number: 23D062g.

Ethics and consent

The protocol of this study was approved by Kansai Rosai Hospital Institutional Review Board (Reference number: 23D062g; approved October 18, 2023). Written informed consent for catheter ablation and the use of data in this study was obtained from all patients.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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