



HAL
open science

Left Atrial Low-Voltage Zone Assessment and Voltage-Guided Ablation Outcome in Patients With Atrial Fibrillation-Induced Tachycardiomyopathy

Halim Marzak, Justine Hammann, Kensuke Matsushita, Romain Ringele, Simon Fitouchi, François Séverac, Thomas Cardi, Mohamad Kanso, Alexandre Schatz, Patrick Ohlmann, et al.

► To cite this version:

Halim Marzak, Justine Hammann, Kensuke Matsushita, Romain Ringele, Simon Fitouchi, et al.. Left Atrial Low-Voltage Zone Assessment and Voltage-Guided Ablation Outcome in Patients With Atrial Fibrillation-Induced Tachycardiomyopathy. *Circulation Journal*, 2024, Online ahead of print. 10.1253/circj.cj-24-0079 . hal-04839610

HAL Id: hal-04839610

<https://hal.science/hal-04839610v1>

Submitted on 16 Dec 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License



Left Atrial Low-Voltage Zone Assessment and Voltage-Guided Ablation Outcome in Patients With Atrial Fibrillation-Induced Tachycardiomyopathy

Halim Marzak, MD; Justine Hammann, MD; Kensuke Matsushita, MD;
Romain Ringele, MD; Simon Fitouchi, MD; François Severac, MD;
Thomas Cardi, MD; Mohamad Kanso, MD; Alexandre Schatz, MD;
Patrick Ohlmann, MD, PhD; Olivier Morel, MD, PhD; Laurence Jesel, MD, PhD

Background: Persistent atrial fibrillation (AF) patients with tachycardia-induced cardiomyopathy (TIC) undergoing catheter ablation have similar or even better outcomes than patients without TIC. Data regarding atrial substrate remodeling are scarce in cases of TIC. We assessed regional distribution of left atrial (LA) bipolar voltage, the extent of low-voltage zones (LVZs), and outcomes of voltage-guided ablation in AF patients with and without TIC.

Methods and Results: In all, 139 patients with persistent AF presenting for a first voltage-guided catheter ablation were enrolled, 61 with TIC and 78 with structurally normal hearts. LA voltage maps were obtained using a 3-dimensional electroanatomical mapping system in sinus rhythm. LVZ was defined as <0.5 mV. Compared with non-TIC patients, TIC patients had a lower indexed LA volume (median [interquartile range] 58.6 [50.6–68.7] vs. 63.4 [60.1–76.1] mL/m²; $P<0.01$) and higher LA voltage (2.3 [1.5–2.8] vs. 1.7 [1–2.6] mV; $P=0.02$). LVZs were less frequently found in patients with than without TIC (8 [13.1%] vs. 30 [39%]; $P<0.01$). There was no significant difference in atrial tachyarrhythmia (AT)-free survival rate over a 36-month follow-up between the 2 groups (log-rank test, $P=0.176$). No predictor of AT recurrence was identified.

Conclusions: TIC patients exhibit less LA substrate remodeling with a smaller LA volume, higher bipolar voltage, and fewer LVZs than non-TIC patients. They have a similar favorable outcome after a single procedure.

Key Words: Atrial fibrillation; Bipolar voltage map; Catheter ablation; Low-voltage zone; Tachycardia-induced cardiomyopathy

Tachycardia-induced cardiomyopathy (TIC) is a reversible cardiomyopathy characterized by left ventricular (LV) systolic dysfunction (LVSD) induced by tachyarrhythmia. Atrial fibrillation (AF) is frequently considered as a primary cause of TIC. When TIC is mediated by AF, LVSD arises from rapid and/or irregular and/or asynchronous ventricular contraction.¹ Heart rate control during AF without sinus conversion can lead to partial recovery of LV ejection fraction (LVEF) in TIC.² AF catheter ablation (CA) is a widespread, safe, and effective alternative to anti-arrhythmic medication and is therefore recommended in AF patients where TIC is strongly suspected.³

Recent studies have confirmed the importance of CA restoration of sinus rhythm (SR) for enhancing LVEF,

improving quality of life, and reducing heart failure hospitalizations and total mortality.⁴ TIC patients undergoing CA for persistent AF have demonstrated comparable or even superior outcomes to those seen in patients with structurally normal hearts.^{5,6}

However, the underlying pathophysiological mechanisms driving this favorable outcome in TIC patients post-CA remain poorly understood. Notably, left atrial (LA) electrophysiological remodeling has not yet been extensively investigated in TIC patients. The presence of low-voltage zones (LVZs) indicative of LA remodeling is recognized as a robust predictor of recurrence following AF ablation.^{7–9}

Pulmonary vein isolation (PVI), combined with LVZ-guided ablation, holds promise for a better outcome in

Received January 28, 2024; revised manuscript received August 2, 2024; accepted August 12, 2024; J-STAGE Advance Publication released online September 28, 2024 Time for primary review: 28 days

Division of Cardiovascular Medicine, Nouvel Hôpital Civil (H.M., J.H., K.M., R.R., S.F., T.C., M.K., A.S., P.O., O.M., L.J.), Public Health Service, Groupe Méthodes en Recherche Clinique (GMRC) (F.S.), Strasbourg University Hospital, Strasbourg; UR 3074 Translational CardioVascular Medicine CRBS, Strasbourg (K.M., O.M., L.J.), France

The first two authors contributed equally to this work (H.M., J.H.).

Mailing address: Halim Marzak, MD, Pôle d'activité médico-chirurgicale cardio-vasculaire, Nouvel Hôpital Civil, CHU de Strasbourg, 1, place de l'Hôpital, F-67091 Strasbourg cedex, France. email: halim.marzak@chru-strasbourg.fr

All rights are reserved to the Japanese Circulation Society. For permissions, please email: cj@j-circ.or.jp

ISSN-1346-9843



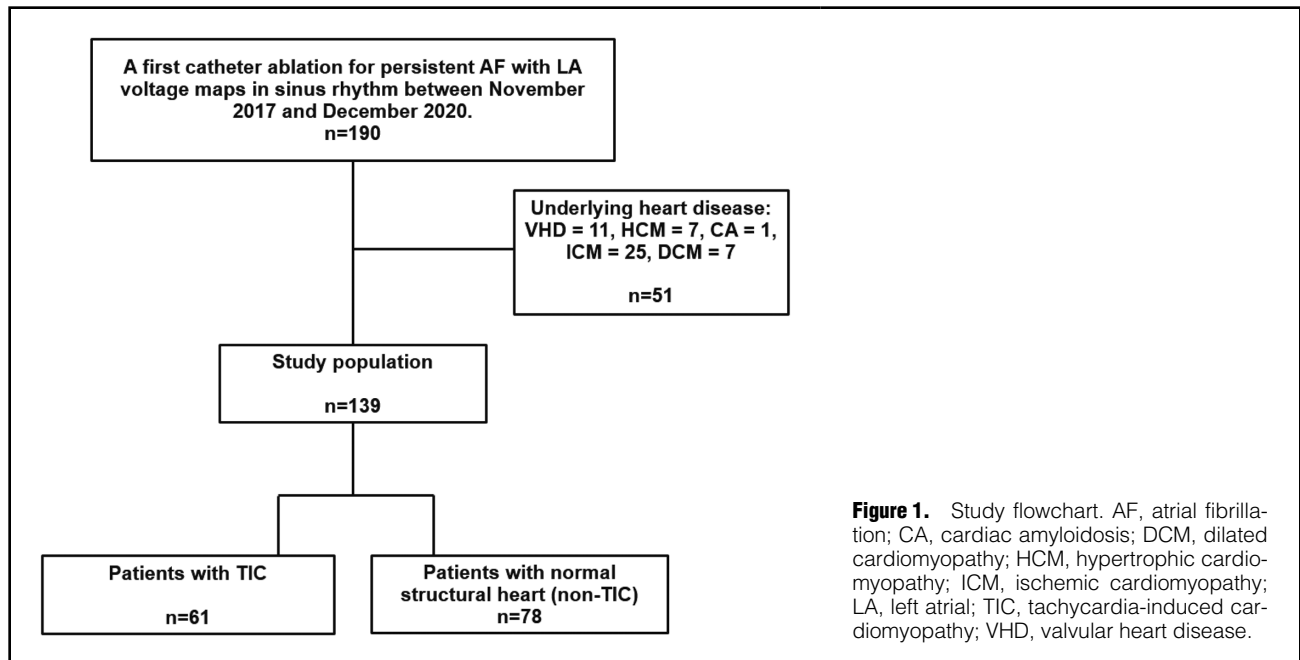


Figure 1. Study flowchart. AF, atrial fibrillation; CA, cardiac amyloidosis; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ICM, ischemic cardiomyopathy; LA, left atrial; TIC, tachycardia-induced cardiomyopathy; VHD, valvular heart disease.

cases of persistent AF, which are frequently associated with a long-term recurrence rate of up to 50%.¹⁰

The purpose of this study was to evaluate the extent of LVZs in LA and the regional distribution of LA bipolar voltage in a cohort of patients with persistent AF and TIC, comparing them to patients with structurally normal hearts. In addition, we assessed the 36-month outcomes of LA voltage-guided substrate ablation in addition to PVI, and searched for predictors of LVZ and AF recurrence after CA in both TIC and non-TIC patients.

Methods

Study Population

After a retrospective analysis of persistent AF ablation procedures from November 2017 to December 2020, we included 190 consecutive patients undergoing a first CA for persistent AF with an LA voltage map in SR. After excluding 51 patients with structural heart disease, 139 patients were finally analyzed (**Figure 1**). The excluded patients were patients with structural heart disease (n=43) or patients who showed partial or no improvement in LVEF after the ablation (n=8). Structural heart disease was defined by a previous diagnosis of ischemic heart disease, valve dysfunction (\geq moderate), or primary myocardial structural disease, including dilated or hypertrophic cardiomyopathies. Some patients who described experiencing episodes of paroxysmal AF in the past before developing persistent AF were classified as having “a history of paroxysmal AF”. A diagnosis of TIC could only be established retrospectively in AF patients with postablation normalization of LVEF.¹¹ After careful examination of the medical reports, 61 patients with TIC and 78 patients with persistent AF and structurally normal hearts (non-TIC patients) were identified. Transthoracic echocardiography was performed in patients with TIC as for other patients at the time of AF diagnosis and before ablation. Usually, if maintaining SR after cardioversion was possible with anti-

arrhythmic drugs (AADs), a non-emergency CA procedure was performed in our center.

Information on patient demographics and baseline clinical characteristics was collected, including sex, age, medical history, cardiovascular risk factors, medications, echocardiographic parameters, and electrocardiogram results at the time of admission and after follow-up.

The study protocol was approved by the Institutional Review Board of Strasbourg University (CE-2023-113). All patients provided written informed consent for the ablation procedure and their participation in this study.

Propensity Score (PS)-Matched Cohort Study

The PS model included the following covariates: AF duration, time to treatment (time from first clinical diagnosis of AF to ablation procedure), age, body mass index (BMI), CHA₂DS₂-VASc score, hypertension, dyslipidemia, diabetes, obstructive sleep apnea, history of paroxysmal AF, use of β -blockers, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEi/ARB), aldosterone receptor antagonists (ARA), estimated glomerular filtration rate (eGFR), pre-procedural LA intracavitary volume (LAIV), and preprocedural LA intracavitary volume index (LAIVI). A nearest-neighbor algorithm was used to match sex differences in a 1 : 1 ratio, with a caliper width equal to 0.2 of the standard deviation of the logit of the PS. The PS-matched cohort included a total of 64 patients (32 TIC patients, 32 non-TIC patients). Patient demographics and baseline clinical characteristics are presented in **Table 1**.

Procedure Preparation

Patients were efficiently anticoagulated for at least 3 weeks. Before the procedure, AADs were interrupted for \geq 5 half-lives. Amiodarone was discontinued 3 weeks before the procedure. CA procedures were performed under general anesthesia under the guidance of a 3-dimensional electroanatomical mapping (3D-EAM) system (CARTO 3 [Biosense

	Before PS matching			After PS matching		
	Non-TIC (n=78)	TIC (n=61)	P value	Non-TIC (n=32)	TIC (n=32)	P value
Age (years)	67 [62–72]	62 [56–68]	<0.01	64 [59–69]	64 [58–70]	1.00
Female sex	26 (33.33)	16 (26.23)	0.47	8 (25)	10 (31)	0.58
Weight (kg)	87 [77–95]	100 [84–111]	<0.01			
BMI (kg/m ²)	28.8 [25.3–31.4]	30.7 [27.7–34.1]	0.01	30.7 [27.6–33.9]	30.9 [27.8–34.1]	0.60
Dyslipidemia	23 (29.49)	27 (44.26)	0.1	11 (35)	15 (47)	0.31
Hypertension	48 (61.54)	38 (62.3)	1	26 (82)	22 (69)	0.292
Diabetes	11 (14.1)	15 (24.59)	0.18	7 (22)	7 (22)	1.00
Current smoker	9 (11.54)	12 (19.67)	0.28	6 (19)	6 (19)	1.00
OSA	27 (34.62)	15 (24.59)	0.28	13 (41)	7 (22)	0.11
AF on admission before the procedure	26 (33.3)	18 (29.5)	0.77			
History of paroxysmal AF	38 (48.72)	11 (18.03)	<0.01	8 (25)	7 (22)	1.00
Sinus node dysfunction	8 (10.26)	2 (3.28)	0.19	3 (9)	1 (3)	0.61
Time to treatment ^A (days)	1,059 [441–2,236]	257 [165–840]	<0.01	766 [302–2,234]	448 [183–2,162]	0.23
Reported AF duration (months)			0.27			
<3	55 (71.43)	53 (86.89)				
≥3 to <6	11 (14.29)	4 (6.56)				
≥6 to <9	6 (7.79)	3 (4.92)				
≥9 to <12	2 (2.6)	0 (0)				
≥12	3 (3.9)	1 (1.64)				
CHA ₂ DS ₂ -VASc score	2.24±1.57	2.39±1.36	0.37	2±2	2±1	0.87
CHA₂DS₂-VASc score			0.68			
0	9 (11.54)	4 (6.56)				
1	19 (24.36)	15 (24.59)				
2	21 (26.92)	13 (21.31)				
3	12 (15.38)	14 (22.95)				
≥4	17 (21.79)	15 (24.59)				
Medications						
β-blocker	57 (73.08)	58 (95.08)	<0.01	30 (94)	30 (94)	1.00
ACEi/ARB	39 (50)	47 (77.05)	<0.01	21 (65)	22 (69)	0.79
Aldosterone receptor antagonist	7 (8.97)	22 (36.07)	<0.01	5 (16)	4 (13)	1.00
P-wave duration (ms)	123±27.07	116.4±19.88	0.25			
eGFR (mL/min/1.73m ²)	82 [69–94]	77 [66–93]	0.39	85 [74–96]	77 [67–94]	0.12
LVEF at AF diagnosis (%)	60 [55–65]	31 [25–35]	<0.01			
LVEF before AF ablation (%)	63 [58–69]	51 [46–60]	<0.01			
TTE LA volume index (mL/m ²)	42 [34–53]	40 [30–48]	0.17			
Preprocedural LAIV excluding LAA (mL)	140 [120–160]	127 [100–140]	0.03	140 [125–160]	130 [111–140]	0.12
Preprocedural LAIVl excluding LAA (mL/m ²)	63 [60–76]	59 [51–69]	<0.01	64 [61–75]	62 [53–67]	0.15

Unless indicated otherwise, data are presented as n (%) for categorical variables and as the median [interquartile range] or mean±SD for continuous variables. Two-tailed P<0.05 was considered significant. ^ATime to treatment is the time from the first clinical diagnosis of AF to the ablation procedure. ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; LA, left atrial; LAA, left atrial appendage; LAIV, left atrial intracavitary volume; LAIVl, left atrial intracavitary volume index; LVEF, left ventricular ejection fraction; OSA, obstructive sleep apnea; PS, propensity score; TIC, tachycardia-induced cardiomyopathy; TTE, transthoracic echocardiography.

Webster, Diamond Bar, CA, USA) or EnSite Velocity [Abbott, St. Paul, MN, USA]) and a deflectable decapolar circular mapping catheter (Lasso catheter of variable diameter size [15–25 mm; Biosense Webster] or a spiral multipolar pulmonary venous [PV] catheter [Afocus II; Abbott]).

Transesophageal echocardiography was performed during the procedure to exclude any LA thrombi, especially in the left atrial appendage (LAA), and to guide transseptal

puncture. A decapolar catheter (Inquiry steerable diagnostic catheter; Abbott) was inserted in the coronary sinus for LA activity recording and stimulation. Two transseptal sheaths (SLO™ and/or Agilis™; Abbott) were introduced into the LA via the femoral veins. A temperature probe was inserted into the esophagus for temperature monitoring during ablation. An activated clotting time was maintained between 250 and 350 s during the procedure.

LA Voltage Mapping

LA endocardial voltage mapping was obtained in SR prior to radiofrequency ablation. In patients with sustained AF at the beginning of the procedure, an electrical cardioversion was achieved to restore SR in order to obtain LA voltage mapping. Endocardial contact during point acquisition was validated by a stable contact signal for >2 beats. All points recorded in SR were checked to exclude mechanically induced premature beats. Any area with abnormal voltage resulting from inadequate contact between the circular catheter and LA tissue was carefully reanalyzed point by point with a 4-mm irrigated contact-force ablation catheter (ThermoCool® SmartTouch® [Biosense Webster] or TactiCath® [Abbott]) to avoid any mistakes.

The LA was divided into 6 anatomical regions: posterior, anterior, septal, lateral, LAA, and inferior. The roof was part of the anterior region, as described previously.¹² The bipolar voltage amplitude was recorded for every point and within each individual region. In all patients, the median LA and bipolar voltage measurements for each specific region were calculated. For each patient, the global LA voltage amplitude was obtained by calculating the median of the different atrial voltage amplitudes of all points recorded during LA mapping in SR. The regional LA voltage amplitudes were the medians of atrial voltage amplitudes of all points recorded in each LA region. The LAIV excluding LAA was obtained for each patient after LA anatomic reconstruction and expressed in milliliters. The LAIVI, corresponding to the LAIV indexed to body surface area, was expressed in milliliters per meters squared.

LVZs were defined as sites of >3 adjacent low-voltage points with a bipolar peak-to-peak voltage amplitude of <0.5 mV¹³ and covering >5% of the LA surface area (LVZ surface/LA surface >5%, excluding the PV antral region, LAA orifice, and mitral valve). This threshold value corresponds to the lowest degree of atrial fibrosis detected using late gadolinium enhancement magnetic resonance imaging.¹⁴ LVZ extent was categorized as Stage I (no or discrete LVZ; LVZ ≤5% of left atrial surface area), Stage II (%; >5 to ≤20%), Stage III (moderate; >20% to ≤35%), or Stage IV (severe; >35%) according to the Utah fibrosis classification.¹⁴ Each region involving an LVZ was considered as a low-voltage region (**Supplementary Figures 1,2**). The surface areas (cm²) of each atrial region and of the LVZ within each region were measured using the 3D-EAM software.

CA Procedure

Irrigated radiofrequency energy was delivered point by point with a target temperature of 43°C, an infusion rate of 17 mL/min via the irrigated ablation catheter, and a maximum power limit of 35 W (20–25 W for the posterior wall and 30–35 W for the anterior wall). The ablation protocol was the same in the 2 groups. PVI was performed in all patients with a wide encirclement around PVs with point-by-point applications using a 4-mm irrigated contact-force ablation catheter (ThermoCool® SmartTouch® [Biosense Webster] or TactiCath® [Abbott]) to create the contiguous lesions. The endpoint of PVI was a bidirectional conduction block between the LA and PVs. Then, we ablated by targeting LVZ if present, in addition to PVI. If the LA voltage map was normal, only PVs were isolated for Stage I patients, whereas an additional LVZ-guided ablation was performed for Stage II–IV patients. LVZ

homogenization or isolation was performed by radiofrequency ablation in patients with a mild or moderate LVZ. The endpoint for LVZ homogenization was reached with significant reduction in local atrial electrograms and loss of local atrial capture. Linear ablation across the LVZ was performed when the LVZ ablation area could be considered as a critical isthmus site for potential macroreentrant tachycardia. Linear lesions were also performed to isolate large LVZs from the rest of the LA tissue, such as a posterior box by a roof line and an inferoposterior line. Atrial burst pacing to refractoriness was conducted from the proximal coronary sinus after ablation. Inducible atrial tachycardias were ablated with its termination without reinducibility. In the case of induced AF, no additional ablation was performed.

Patient Follow-up

After ablation, all patients continued their AADs for at least 3 months to prevent early atrial tachyarrhythmia (AT) recurrences. Patients were reviewed at 3 months, then every 6 months until the 42nd month, by their cardiologist. At each visit, 12-lead electrocardiography (ECG) and routine 24-h ECG were recorded to document AT recurrence, which was defined as any documented AF, atrial flutter, and atrial tachycardia lasting for >30s. Arrhythmic episodes occurring within the first 3 months (blinking period) were not included in the evaluation of final success rates. AADs were gradually discontinued between 3 and 6 months after the ablation in the absence of AT recurrence, at the discretion of the attending physician.

Statistical Analysis

Categorical variables are presented as absolute values and percentages. The significance of differences in categorical variables between the 2 groups was tested using the Chi-squared test or Fischer's exact test.

Continuous variables are expressed as the mean ± SD for normally distributed data. Variables that were not normally distributed are presented as median values with the interquartile ranges (IQR). The Shapiro-Wilk test was used to determine the Gaussian distribution for each continuous variable. The significance of differences in continuous variables was analyzed using Student's t-test or the Wilcoxon test, depending on data distribution. Kaplan-Meier survival curves were used to analyze freedom from atrial arrhythmia recurrence, and TIC patients were compared to non-TIC patients using the log-rank test with Bonferroni correction. Kaplan-Meier survival curves were constructed for each group after an AF ablation procedure. Binomial logistic regression was used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) of independent variables associated with LVZs. Variables selected for testing in the multivariable analysis were those with P<0.10 in the univariable analysis. A stepwise variable selection procedure based on the Akaike information criterion was performed on the multivariable model to retain only those variables associated with LVZs.

Univariable and multivariable Cox proportional hazard regression were used to identify variables predictive of atrial arrhythmias over a 3-year follow-up after catheter ablation in both the TIC cohort and entire cohort. Results for atrial arrhythmias from the univariate Cox regression analyses are reported as hazard ratios (HRs) and 95% CIs. Variables selected for testing in the multivariable analysis were those with P<0.20 in the univariable analysis.

Table 2. Regional Distribution of Bipolar Voltage Amplitudes in Patients Without and With TIC Before and After PS Matching

Bipolar voltage amplitude (mV)	Before PS matching			After PS matching		
	Non-TIC (n=78)	TIC (n=61)	P value	Non-TIC (n=32)	TIC (n=32)	P value
Global left atrium	1.7 [1–2.6]	2.3 [1.5–2.8]	0.02	1.8 [1.2–2.7]	2.5 [1.3–2.9]	0.29
Anterior	1.5 [0.8–2.3]	1.9 [1.3–2.6]	0.01	1.6 [0.9–2.5]	1.9 [1.2–2.6]	0.23
Septal	1.4 [0.8–2.1]	1.7 [1.1–2.4]	0.05	1.1 [0.8–2.4]	1.6 [1.0–2.5]	0.26
Posterior	1.9 [0.8–2.7]	2.4 [1.5–3.3]	<0.01	2.0 [1.0–2.8]	2.5 [1.4–3.5]	0.06
Inferior	1.7 [1–2.6]	2 [1.2–2.8]	0.04	1.8 [1.1–2.5]	2.2 [1.5–3.1]	0.09
Lateral	2.1 [1.1–3]	2.3 [1.3–3]	0.32	2.2 [1.5–3.3]	2.3 [1.2–3.0]	0.75
Left atrial appendage	2.5 [1.4–3.4]	3 [2–3.9]	0.04	2.6 [1.9–3.5]	3.0 [1.8–4.2]	0.46

Unless indicated otherwise, data are presented as the median [interquartile range]. Two-tailed $P < 0.05$ was considered significant. Abbreviations as in Table 1.

Table 3. LVZs by Distribution and Extent in Patients Without and With TIC Before and After PS Matching

LVZ extent ^A	Before PS matching			After PS matching		
	Non-TIC (n=78)	TIC (n=61)	P value	Non-TIC (n=32)	TIC (n=32)	P value
No or discrete LVZ	48 (61)	53 (87)	<0.01	20 (62)	27 (84)	0.048
LVZ	30 (39)	8 (13)	<0.01	12 (38)	5 (16)	0.048
Mild LVZ	11 (14)	5 (8)	0.4	7 (22)	2 (6)	0.15
Moderate LVZ	11 (14)	1 (2)	0.02	5 (16)	1 (3)	0.20
Severe LVZ	8 (11)	2 (3)	0.18	0 (0)	2 (6)	0.49
No. patients with regional LVZs						
Anterior	31 (40)	10 (16)	<0.01	10 (31)	7 (22)	0.40
Septal	24 (31)	12 (20)	0.18	9 (28)	8 (25)	0.78
Posterior	18 (23)	2 (3)	<0.01	7 (22)	1 (3)	0.05
Inferior	6 (8)	2 (3)	0.3	1 (3)	2 (6)	1.00
Lateral	1 (1)	3 (5)	0.32	0 (0)	2 (6)	0.49
LAA	5 (7)	1 (2)	0.23	0 (0)	1 (3)	1.00
LVZ surface area (cm²) indexed to regional atrial surface area (cm²)						
LVZ/LA area (%)	0 [0–13]	0 [0–1]	<0.01	0 [0–9]	0 [0–1]	0.19
Anterior LVZ/anterior area (%)	0 [0–22]	0 [0–0]	<0.01	0 [0–17]	0 [0–0]	0.10
Septal LVZ/septal area (%)	0 [0–14]	0 [0–0]	<0.01	0 [0–11]	0 [0–2]	0.20
Posterior LVZ/posterior area (%)	0 [0–7]	0 [0–0]	<0.01	0 [0–32]	0 [0–0]	0.03
Inferior LVZ/inferior area (%)	0 [0–0]	0 [0–0]	0.03	0 [0–0]	0 [0–0]	0.46
Lateral LVZ/lateral area (%)	0 [0–0]	0 [0–0]	0.97	0 [0–7]	0 [0–3]	0.95
LAA LVZ/LAA area (%)	0 [0–0]	0 [0–0]	0.11	0 [0–0]	0 [0–0]	1.00

Unless indicated otherwise, data are presented as n (%) for categorical variables or as the median [interquartile range] for continuous variables. Two-tailed $P < 0.05$ was considered significant. ^ALVZ extent calculated as a percentage of LA surface area as follows: no or discrete LVZ, $\leq 5\%$ of LA surface area; mild, $>5\%$ to $\leq 20\%$; moderate, $>20\%$ to $\leq 35\%$; severe, $>35\%$. LVZ, low-voltage zone. Other abbreviations as in Table 1.

All statistical analyses were performed using SPSS statistical software, version 23.0 (IBM Corp.) for the unmatched cohort. Two-tailed $P < 0.05$ was considered statistically significant. The PS model was developed using logistic regression. For the matched cohort, all analyses were performed using R version 3.6.3.

Results

Baseline Characteristics

The study population included 139 patients with persistent AF (61 TIC patients, 78 non-TIC patients). Compared with the non-TIC group, patients in the TIC group were younger ($P < 0.01$), more likely to be obese ($P = 0.01$) and

had a smaller indexed LA volume ($P < 0.01$). In addition, a significantly higher proportion of TIC patients were treated with β -blockers, ACEi/ARB, and ARA ($P < 0.01$). There were no significant differences in major risk factors associated with AF between the 2 groups. For TIC patients, re-evaluation transthoracic echocardiography was systematically performed before CA, with a significant improvement of LVEF in SR compared with at the time of AF diagnosis ($P < 0.01$). Patient characteristics before and after PS matching of the primary cohort are summarized in **Table 1**.

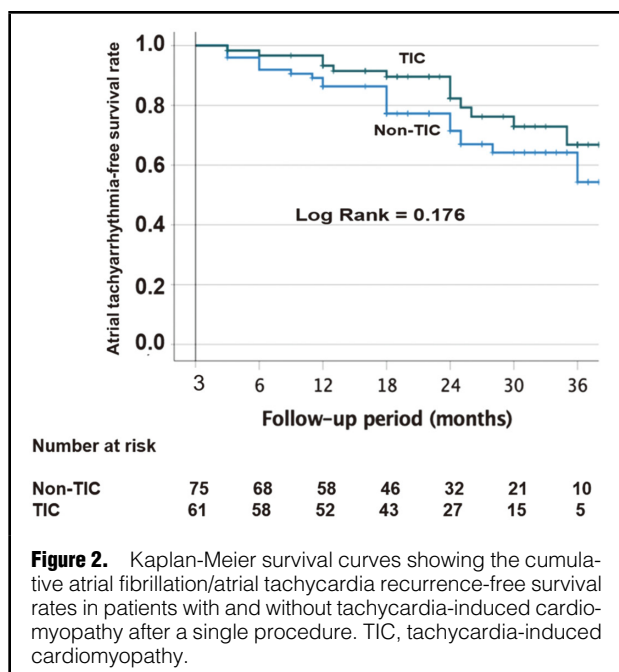
LA Bipolar Voltage Assessment

In the unmatched cohort, global LA bipolar voltage was

Table 4. Univariate and Multivariate Analyses for Prediction of LVZs After Catheter Ablation in the Whole Cohort

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Female sex	7.48	3.24–17.30	<0.001	11.55	2.52–52.87	0.002
Age	1.20	1.11–1.29	<0.001	1.13	1.02–1.26	0.02
AF duration >6 months	0.39	0.12–1.26	0.116	–	–	–
Time to treatment ^A	1.000	1.000–1.001	0.059	–	–	–
BMI	0.89	0.81–0.97	0.006	–	–	–
Dyslipidemia	0.92	0.42–2.02	0.843	–	–	–
Hypertension	0.51	0.22–1.17	0.112	–	–	–
Diabetes	0.80	0.31–2.03	0.632	–	–	–
OSA	1.87	0.77–4.53	0.167	–	–	–
History of paroxysmal AF	0.43	0.20–0.94	0.034	–	–	–
Sinus node dysfunction	0.34	0.09–1.24	0.102	–	–	–
eGFR	0.96	0.94–0.99	0.002	–	–	–
LAIVI	1.09	1.04–1.14	<0.001	1.11	1.04–1.18	0.001
TIC	0.25	0.10–0.59	0.002	0.16	0.03–0.81	0.026
ACEi/ARB	1.35	0.628–2.92	0.439	–	–	–
Aldosterone receptor antagonist	0.96	0.38–2.42	0.937	–	–	–

Data are presented as OR with 95% CIs. Two-tailed $P < 0.05$ was considered significant. ^ATime to treatment is the time from the first clinical diagnosis of AF to the ablation procedure. CI, confidence interval; LVZ, low-voltage zone; OR, odd ratio. Other abbreviations as in Table 1.



higher in the TIC than non-TIC group ($P = 0.02$; **Table 2**). In addition, bipolar voltage amplitudes of TIC patients were higher in different atrial regions, except for the septal and lateral regions. After PS matching, no significant differences were observed for either global LA or each atrial region, except for the posterior wall, which was at the limit of significance ($P = 0.06$).

LVZ Assessment

LVZs were found in 38 (27.3%) patients in the whole cohort. In the unmatched cohort, LVZs were less frequent in the TIC group ($P < 0.01$), especially for anterior and

posterior atrial regions (**Table 3**). The LVZ surface/LA surface was more extensive in the non-TIC group and in different regions, except for the lateral wall and LAA. After PS matching, LVZs remained less frequent in the TIC group ($P = 0.048$).

Predictors of LVZs

To evaluate factors predictive of LVZ, univariate and multivariate analysis were performed in the unmatched cohort. Female sex, age, LA indexed volume, and TIC were selected as variables for multivariate analysis. Female sex (OR 11.55; 95% CI 2.52–52.87; $P = 0.002$), age (OR 1.13; 95% CI 1.02–1.26; $P = 0.023$), and LA indexed volume (OR 1.11; 95% CI 1.04–1.18; $P = 0.001$) were identified as independent predictors of LVZ. However, TIC (OR 0.16; 95% CI 0.03–0.81; $P = 0.026$) was a protective factor against LVZ in our study (**Table 4**).

Ablation Results

All PVs were successfully isolated during CA (**Supplementary Table**). PVI alone was performed in 100 (72.5%) patients in the overall cohort, whereas the remaining 38 (27.5%) patients had an additional LVZ-guided ablation. PVI alone was more frequently performed in TIC patients ($P = 0.01$) with less linear ablation ($P < 0.02$). Therefore, the total radiofrequency duration was lower in TIC patients ($P < 0.01$).

Long-Term Clinical Outcomes After a Single AF Ablation Procedure

After a median follow-up period of 37.2 months (IQR 33.9–40.5 months) in the unmatched cohort, ATs recurred in 39 of 139 (28.1%) patients in the whole cohort after a single procedure. There was no difference in the AT-free survival rate after 1 procedure between the 2 groups (log rank test, $P = 0.176$; **Figure 2**). In the TIC group, the maintenance of SR was associated with further improvement in LVEF at 1 year (median [IQR] 60% [50%–63%] vs. 51% [46%–60%]; $P = 0.03$).

Table 5. Univariate and Multivariate Cox Regression Analysis for the Prediction of ATs Recurrence During a 3-Year Follow-up After Catheter Ablation in the TIC Cohort

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Female gender	0.41	0.09–1.82	0.243	–	–	–
Age	0.99	0.95–1.04	0.787	–	–	–
AF duration >6 months	3.63	1.03–12.83	0.045	–	–	–
Time to treatment ^A	1.00	1.00–1.00	0.233	–	–	–
BMI	0.95	0.87–1.04	0.274	–	–	–
Dyslipidemia	1.43	0.58–3.53	0.438	–	–	–
Hypertension	0.60	0.24–1.47	0.260	–	–	–
OSA	0.66	0.19–2.29	0.515	–	–	–
History of paroxysmal AF	1.38	0.39–4.81	0.615	–	–	–
Sinus node dysfunction	2.22	0.29–17	0.443	–	–	–
CHA ₂ DS ₂ -VASc score ≥3	0.67	0.26–1.70	0.398	–	–	–
eGFR	0.99	0.97–1.01	0.433	–	–	–
LAIV	1.00	0.99–1.02	0.782	–	–	–
LAIVI	1.01	0.97–1.05	0.731	–	–	–
ACEi/ARB	0.75	0.27–2.09	0.581	–	–	–
Aldosterone receptor antagonist	0.85	0.32–2.25	0.747	–	–	–
P-wave duration	1.01	0.99–1.02	0.500	–	–	–
LA bipolar voltage	0.78	0.46–1.34	0.370	–	–	–
Presence of LVZ	0.82	0.19–3.56	0.794	–	–	–
Only PVI	0.74	0.30–1.82	0.506	–	–	–
Linear ablation	1.50	0.58–3.84	0.400	–	–	–

Data are presented as a HRs with 95% CIs. Two-tailed P<0.05 was considered significant. ^ATime to treatment is the time from the first clinical diagnosis of AF to the ablation procedure. ATs, atrial tachyarrhythmias; HR, hazard ratio; LVZ, low-voltage zone; PVI, pulmonary vein isolation. Other abbreviations as in Table 1.

Table 6. Univariate and Multivariate Cox Regression Analysis for Prediction of ATs Recurrence During 3-Year Follow-up After Catheter Ablation in the Whole Cohort

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Female gender	0.69	0.33–1.43	0.321	–	–	–
Age	1.00	0.96–1.03	0.837	–	–	–
AF duration >6 months	1.99	0.70–5.70	0.198	2.36	0.69–8.03	0.169
Time to treatment	1.00	1.00–1.00	0.748	–	–	–
BMI	0.94	0.89–1.01	0.073	0.97	0.89–1.06	0.512
Dyslipidemia	1.03	0.53–1.99	0.926	–	–	–
Hypertension	0.75	0.39–1.45	0.396	–	–	–
OSA	1.26	0.66–2.43	0.487	–	–	–
Paroxysmal AF history	1.05	0.55–2.02	0.881	–	–	–
Sinus node dysfunction	2.45	1.02–5.87	0.045	1.64	0.61–4.45	0.330
CHA ₂ DS ₂ -VASc score ≥3	0.84	0.44–1.61	0.603	–	–	–
eGFR	1.01	0.99–1.03	0.336	–	–	–
LAIV	1.01	1.00–1.02	0.170	1.01	1.00–1.02	0.267
LAIVI	1.01	0.98–1.03	0.540	–	–	–
ACEi/ARB	0.70	0.37–1.33	0.273	–	–	–
Aldosterone receptor antagonist	0.83	0.36–1.89	0.658	–	–	–
P-wave duration	1.01	0.99–1.02	0.373	–	–	–
LA bipolar voltage	1.05	0.74–1.48	0.802	–	–	–
Presence of LVZ	0.97	0.48–1.95	0.930	–	–	–
Only PVI	1.03	0.54–1.96	0.937	–	–	–
Linear ablation	1.25	0.63–2.47	0.524	–	–	–

Data are presented as a HRs with 95% CIs. Two-tailed P<0.05 was considered significant. ^ATime to treatment is the time from the first clinical diagnosis of AF to the ablation procedure. LVZ, low-voltage zone. Other abbreviations as in Tables 1,5.

At 36 months, 67±9% of TIC patients and 56±8% of non-TIC patients were free of ATs. In the whole cohort, AADs were discontinued in 73% (101/139) patients. Among patients without AT recurrence at 12 months, AADs were discontinued in 75% (94/126) of the cohort (70% (39/56) of TIC patients and 79% (55/70) of non-TIC patients; $P=0.37$).

Factors Predictive of Atrial Arrhythmia Recurrence

For the TIC cohort, multivariate analysis could not be performed because AF duration >6 months was the sole parameter that had $P<0.2$ in univariate analysis (Table 5).

In the univariate analysis regarding the whole cohort, AF duration >6 months, BMI, ACEi/ARB use, and LA volume were chosen as variables ($P<0.1$) for multivariate analysis, but none of them was found to be a significant predictor of AF recurrence after CA (Table 6).

Discussion

In the present study, we report that TIC patients exhibit less LA electrophysiological substrate remodeling with a smaller LA volume, higher bipolar voltage, and fewer LVZs compared with non-TIC patients. TIC patients also have similar and favorable outcomes after a single voltage-guided ablation procedure compared with non-TIC patients. AF ablation consisted only of PVI in 87% of TIC patients, compared with 61% of non-TIC patients.

AF and heart failure often coexist, and the presence of AF in heart failure patients increases the risk of stroke, hospitalization for heart failure, and death.¹⁵ The CASTLE-AF study reported that AF catheter ablation significantly reduces hospitalizations for heart failure and deaths from any cause compared with medical therapy, thereby decreasing the burden of AF and improving LVEF. The CAMERA-MRI study demonstrated that restoration and maintenance of SR with CA significantly improve LVEF in patients with AF and LVSD despite adequate ventricular rate control. Normalization of LVEF was more frequent in the absence of ventricular fibrosis detected on cardiac magnetic resonance imaging, identifying “super responders”. Thus, a significant proportion of patients with persistent AF and otherwise unexplained LVSD may have an arrhythmia-mediated cardiomyopathy called TIC.¹⁶

AF rarely causes severe, reversible LVSD in patients without pre-existing structural heart disease, a condition known as TIC. More commonly, AF induces mild to moderate LVSD. The mechanisms responsible for TIC are not yet fully understood.¹⁷ LVSD appears to be mediated through 3 mechanisms: tachycardia, irregular rhythm and dyssynchrony.¹ In experimental animal models, chronic tachycardia invariably results in LV dilation and LVSD. Mechanisms such as subclinical ischemia, myocardial energy depletion with resultant disruption of energy storage with ATP depletion, abnormal calcium handling, and extracellular matrix remodeling could contribute to the exacerbation of LV dysfunction.¹⁷ In animal models, 3 distinct phases have been described: a compensatory phase lasting up to 7 days, an LV dysfunction phase extending up to 3 weeks, and a third LV failure phase characterized by pump failure after 3 weeks. The clinical entities of AF-induced mild LV dysfunction and TIC likely share common cellular mechanisms but differ in the severity of their clinical presentations. Whether additional mechanisms, cellular pathways, or genetic background are involved in

TIC remains unknown.

Data on LA substrate remodeling and volume in TIC are limited. Previous studies in AF ablation have highlighted a correlation between LA enlargement and the presence of LVZs on voltage maps.¹⁸ Both enlarged LA volume and continuous atrial stretch are known to favor atrial substrate remodeling.¹⁹ Sanders et al. demonstrated right atrial substrate remodeling, characterized by reduced atrial bipolar voltage and increased LVZs in patients with ischemic and idiopathic chronic heart failure.²⁰ Similarly, Prabhu et al. reported an association between HF and reduced biatrial bipolar voltage, along with the presence of LVZs in patients with idiopathic chronic heart failure.²¹

Our findings revealed smaller LA volumes and fewer LVZs in TIC compared with non-TIC patients. TIC, characterized by reversible cardiomyopathy and impaired LVEF at the time of diagnosis, typically presents with severe clinical manifestations of heart failure.

Previously, there was a lack of data on atrial bipolar voltage and LVZs in TIC. Our study represents the first examination of LA voltage maps in TIC patients, revealing higher bipolar voltage in both the LA and each atrial region compared with non-TIC patients. Interestingly, Sugumar et al. observed reverse structural and electrical right atrial remodeling in SR in TIC patients following recovery of LV function and CA; right atrial bipolar voltage amplitude increased significantly from 1.6 to 1.9 mV.²²

We found important differences in the baseline characteristics between the 2 groups. Specifically, patients with TIC tended to be younger, more likely to be obese, and were less likely to have a history of paroxysmal AF. In addition, TIC patients had smaller LA volumes. The time from first clinical diagnosis of AF to the ablation procedure was significantly shorter in the TIC group because of both a serious clinical presentation at the time of diagnosis leading to a faster AF ablation and the less likely history of paroxysmal AF. Some authors have previously reported an association between LVZ and age.¹³ A longer history of AF is known to cause increased LA remodeling, potentially explaining the larger LA volume, LA voltage reduction, and LVZs observed in non-TIC patients. Both enlarged LA volume and continuous atrial stretch are recognized as key factors in atrial remodeling. Takahashi et al. showed that histological factors such as fibrosis, increased intercellular space, myofibrillar loss, decreased myocardial nuclear density, and reduced wall thickness were significantly associated with voltage reduction.²³ These histological changes lead to a decrease in the amount of viable myocardium, which is likely the main cause of voltage reduction. Both wall thickness and the amount of viable myocardium influence bipolar voltage, and an increase in fibrosis leads to decreased voltage. Aging may also influence the number of myocardial cells, which decreases over time. This histological study revealed that patients with AF in the early stages of progression exhibit an increase in the intercellular space and only initial interstitial changes, while their voltage remains preserved.

However, the exact mechanisms underlying TIC are not fully understood and are likely multifactorial. Even after PS matching, we still observed less LA remodeling ($P=0.048$) in patients with TIC, which remains an intriguing phenomenon.

It is worth noting that 70.5% of patients in our cohort were in SR at the time of CA following previous cardioversion and optimized medical treatment. This comprehensive

strategy likely contributes to mitigating LA remodeling.

In our cohort, a significantly higher proportion of TIC patients received treatment with β -blockers, ACEi/ARB, and ARA than non-TIC patients prior to CA owing to the initial impairment in LVEF. TIC is associated with neuro-hormonal activation characterized by elevated levels of epinephrine, norepinephrine, renin-aldosterone activity, and plasma atrial natriuretic peptide.¹ Interestingly, these same mechanisms are observed in Takotsubo cardiomyopathy, a stress-related and transient reversible cardiomyopathy frequently associated with AF.²⁴

Activation of the renin-angiotensin-aldosterone system induces structural atrial remodeling, primarily through its profibrotic effects.²⁵ Numerous studies have evidenced the preventive effects of ACEi/ARB on AF recurrence.²⁶ In the context of TIC, we can speculate that ACEi/ARB and ARA may exert an early protective effect against LA remodeling.

Moreover, in our cohort, the smaller extent of LVZ in TIC patients may have contributed to the favorable outcomes observed after CA. The presence of LVZ is a well-established predictor of AF recurrence following PVI alone and no modification of LA substrate.⁷ Calvo et al. reported similar CA outcomes in terms of AF recurrence between TIC patients and those without structural heart disease, with 60% of TIC patients free from AT recurrence at 12 months.⁵ Similarly, Yamashita et al. observed that 85% of TIC patients remained free from AT recurrence 1 year after CA.⁶ In our study, 93% and 67% of TIC patients were free from AT recurrence at 12 and 36 months, respectively, with 70% of patients discontinuing AADs and no significant difference observed compared with non-TIC patients.

Interestingly, our study is among the first to assess the results of LVZ-guided ablation in persistent AF patients with TIC. Notably, PVI alone was performed in 87% of TIC patients, thereby limiting substrate ablation and LA scar formation. In their studies, Calvo et al. performed linear ablation after PVI,⁵ and Yamashita et al. performed complex fractionated atrial electrograms with or without linear ablation after PVI.⁶ Nevertheless, the results of a voltage-guided ablation strategy in addition to PVI appear promising in both AF TIC and non-TIC patients. Other studies of persistent AF ablation have demonstrated similar 12-month outcomes with this same ablation strategy.^{27,28} Yamaguchi et al. reported a 72% success rate at 18 months after a single procedure;²⁷ Wang et al. reported a 65.5% AF-free success rate at 12 months after a single procedure.²⁸ Finally, a recent multicenter randomized trial demonstrated that LVZ-guided ablation in addition PVI was superior to PVI alone for patients with persistent AF.²⁹ Nonetheless, further randomized studies are warranted to validate these findings.

In our analysis of predictive factors for arrhythmia recurrence after a single AF ablation procedure in the entire cohort, we did not identify any significant predictors of AF recurrence after CA. This lack of significant findings may be attributed to the small size and the homogeneity of the cohort, which could have limited the statistical power to detect meaningful associations.

Study Limitations

This was a retrospective single-center study with a limited number of patients. In addition, data on the discontinuation of AADs could not be obtained for the whole cohort

because the follow-up was performed by patients' individual cardiologists. Further studies are essential to assess the long-term follow-up after AF ablation in TIC patients.

Conclusions

Persistent AF patients with TIC exhibit less LA substrate remodeling characterized by smaller LA volume, higher bipolar voltage, and fewer LVZs compared with patients with structurally normal hearts. TIC emerged as a protective factor against LVZ in the entire cohort. Despite their severe initial clinical presentation, TIC patients demonstrated comparable and favorable outcomes following a single voltage-guided ablation procedure, confirming CA as a first-line strategy.

Sources of Funding

This work was supported by GERCA (Groupe pour l'Enseignement, la Prévention et la Recherche Cardiologique en Alsace).

Sources of Support (Financial, Equipment, Drugs)

None.

Disclosures

The authors declare that they have no conflicts of interest. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

IRB Information

The study protocol was approved by the Institutional Review Board of Strasbourg University (CE-2023-113).

References

1. Sugumar H, Prabhu S, Voskoboinik A, Kistler PM. Arrhythmia induced cardiomyopathy. *J Arrhythm* 2018; **34**: 376–383.
2. Sairaku A, Nakano Y, Oda N, Uchimura Y, Tokuyama T, Kawazoe H, et al. Incomplete cure of tachycardia-induced cardiomyopathy secondary to rapid atrial fibrillation by heart rate control without sinus conversion. *J Cardiovasc Electrophysiol* 2014; **25**: 1037–1043.
3. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2021; **42**: 373–498.
4. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, et al. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med* 2018; **378**: 417–427.
5. Calvo N, Bisbal F, Guiu E, Ramos P, Nadal M, Tolosana JM, et al. Impact of atrial fibrillation-induced tachycardiomyopathy in patients undergoing pulmonary vein isolation. *Int J Cardiol* 2013; **168**: 4093–4097.
6. Yamashita S, Tokuda M, Matsuo S, Mahida S, Hachisuka EO, Sato H, et al. Comparison of atrial arrhythmia recurrence after persistent atrial fibrillation ablation between patients with or without tachycardia-induced cardiomyopathy. *J Cardiovasc Electrophysiol* 2019; **30**: 2310–2318.
7. Yamaguchi T, Tsuchiya T, Nagamoto Y, Miyamoto K, Murotani K, Okishige K, et al. Long-term results of pulmonary vein antrum isolation in patients with atrial fibrillation: An analysis in regards to substrates and pulmonary vein reconnections. *Europace* 2014; **16**: 511–520.
8. Yamaguchi T, Otsubo T, Takahashi Y, Nakashima K, Fukui A, Hirota K, et al. Atrial structural remodeling in patients with atrial fibrillation is a diffuse fibrotic process: Evidence from high-density voltage mapping and atrial biopsy. *J Am Heart Assoc* 2022; **11**: e024521.
9. Masuda M, Asai M, Iida O, Okamoto S, Ishihara T, Nanto K, et al. Low-voltage-area ablation in paroxysmal atrial fibrillation: Extended follow-up results of the VOLCANO trial. *Circ J* 2022; **86**: 245–252.

10. Kircher S, Arya A, Altmann D, Rolf S, Bollmann A, Sommer P, et al. Individually tailored vs. standardized substrate modification during radiofrequency catheter ablation for atrial fibrillation: A randomized study. *Europace* 2018; **20**: 1766–1775.
11. Brugada J, Katritsis DG, Arbelo E, Arribas F, Bax JJ, Blomström-Lundqvist C, et al. 2019 ESC guidelines for the management of patients with supraventricular tachycardia. The Task Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC). *Eur Heart J* 2020; **41**: 655–720.
12. Huo Y, Gaspar T, Pohl M, Sitzy J, Richter U, Neudeck S, et al. Prevalence and predictors of low voltage zones in the left atrium in patients with atrial fibrillation. *Europace* 2018; **20**: 956–962.
13. Teh AW, Kistler PM, Lee G, Medi C, Heck PM, Spence SJ, et al. Long-term effects of catheter ablation for lone atrial fibrillation: Progressive atrial electroanatomic substrate remodeling despite successful ablation. *Heart Rhythm* 2012; **9**: 473–480.
14. Mahnkopf C, Badger TJ, Burgon NS, Daccarett M, Haslam TS, Badger CT, et al. Evaluation of the left atrial substrate in patients with lone atrial fibrillation using delayed-enhanced MRI: Implications for disease progression and response to catheter ablation. *Heart Rhythm* 2010; **7**: 1475–1481.
15. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, et al; CASTLE-AF Investigators. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med* 2018; **378**: 417–427.
16. Sugumar H, Prabhu S, Costello B, Chieng D, Azzopardi S, Voskoboinik A, et al. Catheter ablation versus medication in atrial fibrillation and systolic dysfunction: Late outcomes of CAMERA-MRI study. *JACC Clin Electrophysiol* 2020; **6**: 1721–1731, doi:10.1016/j.jacep.2020.08.019.
17. Cha YM, Redfield MM, Shen WK, Gersh BJ. Atrial fibrillation and ventricular dysfunction a vicious electromechanical cycle. *Circulation* 2004; **109**: 2839–2843, doi:10.1161/01.CIR.0000132470.78896.A8.
18. Ammar-Busch S, Buiatti A, Tatzber A, Reents T, Bourier F, Semmler V, et al. Predictors of low voltage areas in persistent atrial fibrillation: Is it really a matter of time? *J Interv Card Electrophysiol* 2020; **57**: 345–352.
19. Wang XH, Li Z, Mao JL, Zang MH, Pu J. Low voltage areas in paroxysmal atrial fibrillation: The prevalence, risk factors and impact on the effectiveness of catheter ablation. *Int J Cardiol* 2018; **269**: 139–144.
20. Sanders P, Morton JB, Davidson NC, Spence SJ, Vohra JK, Sparks PB, et al. Electrical remodeling of the atria in congestive heart failure: Electrophysiological and electroanatomic mapping in humans. *Circulation* 2003; **108**: 1461–1468.
21. Prabhu S, Voskoboinik A, McLellan AJA, Peck KY, Pathik B, Nalliah CJ, et al. Batrial electrical and structural atrial changes in heart failure: Electroanatomic mapping in persistent atrial fibrillation in humans. *JACC Clin Electrophysiol* 2018; **4**: 87–96.
22. Sugumar H, Prabhu S, Voskoboinik A, Young S, Gutman SJ, Wong GR, et al. Atrial remodeling following catheter ablation for atrial fibrillation-mediated cardiomyopathy: Long-term follow-up of CAMERA-MRI study. *JACC Clin Electrophysiol* 2019; **5**: 681–688.
23. Takahashi Y, Yamaguchi T, Otsubo T, Nakashima K, Shinzato K, Osako R, et al. Histological validation of atrial structural remodelling in patients with atrial fibrillation. *Eur Heart J* 2023; **44**: 3339–3353.
24. Jesel L, Berthon C, Messas N, Lim HS, Girardey M, Marzak H, et al. Atrial arrhythmias in Takotsubo cardiomyopathy: Incidence, predictive factors, and prognosis. *Europace* 2019; **21**: 298–305.
25. Goette A, Staack T, Röcken C, Arndt M, Geller JC, Huth C, et al. Increased expression of extracellular signal-regulated kinase and angiotensin-converting enzyme in human atria during atrial fibrillation. *J Am Coll Cardiol* 2000; **35**: 1669–1677.
26. Zhang Y, Zhang P, Mu Y, Gao M, Wang JR, Wang Y, et al. The role of renin-angiotensin system blockade therapy in the prevention of atrial fibrillation: A meta-analysis of randomized controlled trials. *Clin Pharmacol Ther* 2010; **88**: 521–531.
27. Yamaguchi T, Tsuchiya T, Nakahara S, Fukui A, Nagamoto Y, Murotani K, et al. Efficacy of left atrial voltage-based catheter ablation of persistent atrial fibrillation. *J Cardiovasc Electrophysiol* 2016; **27**: 1055–1063.
28. Wang XH, Li Z, Mao JL, He B. A novel individualized substrate modification approach for the treatment of long-standing persistent atrial fibrillation: Preliminary results. *Int J Cardiol* 2014; **175**: 162–168.
29. Huo Y, Gaspar T, Schönbauer R, Wójcik M, Fiedler L, Roithinger FX, et al. Low-voltage myocardium-guided ablation trial of persistent atrial fibrillation. *NEJM Evid* 2022; **1**: EVIDoa2200141, doi:10.1056/EVIDoa2200141.

Supplementary Files

Please find supplementary file(s);
<https://doi.org/10.1253/circj.CJ-24-0079>