Circulation Reports
Circ Rep 2023; 5: 371–380
doi:10.1253/circrep.CR-23-0073

ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Chronic Effect of HotBalloon-Based Wide Planar Ablation on Epicardial Adipose Tissue in Persistent Atrial Fibrillation

Shiro Nakahara, MD, PhD; Yuichi Hori, MD, PhD; Reiko Fukuda, MD, PhD; Hirotsugu Sato, MD; Hideyuki Aoki, MD; Tetsuya Ishikawa, MD, PhD; Yuji Itabashi, MD, PhD; Sayuki Kobayashi, MD, PhD; Isao Taguchi, MD, PhD; Yasuo Okumura, MD, PhD

Background: Adverse atrial remodeling, including epicardial adipose tissue (EAT) deposition in the left atrium (LA), is implicated in atrial fibrillation (AF). Radiofrequency hotballoon (RHB) ablation can produce wide planar lesions because the balloon is highly compliant; however, chronic effects of RHB ablation on structural remodeling remain unknown. This clinical-experimental investigation characterized chronic effects of RHB ablation on EAT in persistent AF (PsAF).

Methods and Results: The clinical study involved 91 patients (obese, n=30; non-obese, n=61) undergoing RHB ablation for PsAF. LA-EAT was assessed from computed tomography images obtained before ablation and 6 months later. Tissue effects of RHB ablation were explored in a chronic swine model. RHB ablation significantly reduced LA volume (mean [±SD] 177.7±29.7 vs. 138.4±29.6 mL; P<0.001) and LA-EAT volume (median [interquartile range] 22.0 [12.4–33.3] vs. 16.5 [7.9–25.8] mL; P<0.001). The reduction in EAT was significantly greater in the pulmonary vein (PV) antrum than in other LA regions (37.9% vs. 15.8%; P<0.001). The percentage reduction in PV antrum EAT was equivalent between obese and non-obese patients, as was the postablation success rate (73% vs. 70%; P=0.77). RHB ablation produced transmural lesions reaching the pigs' epicardial fat region.

Conclusions: RHB-based planar-transmural lesions altered the structurally remodeled LA, including EAT. Further studies are needed to determine whether factors other than PV isolation contribute to the clinical success of RHB ablation.

Key Words: Atrial fibrillation; Epicardial adipose tissue; Radiofrequency hotballoon

Atrial fibrillation (AF), the most common arrhythmia, is associated with significant morbidity and mortality.[1] Despite technical advances in ablation therapy, persistent AF (PsAF) recurs at a high rate, with effective treatment remaining elusive.

Structural remodeling has been shown to contribute to the persistence and recurrence of AF.[2] Some studies have focused on the proarrhythmic effects of epicardial adipose tissue (EAT), now recognized as an AF biomarker.[3,4] Other studies have shown a causal link between left atrial (LA) EAT and the occurrence of AF.[5,6] Further, a direct association between EAT and adverse atrial remodeling has been proposed, attributed to complex cross-talk between EAT and the neighboring myocardium.[7] Conversely, in terms of the patient characteristics, obesity is associated with an increased LA-EAT volume and electroanatomical remodeling, resulting in an increased incidence of PsAF or long-lasting PsAF.[8] Furthermore, an increased body mass index (BMI) is associated with increased procedural complications during ablation and adversely affects postoperative outcomes.[8,9]

Radiofrequency hotballoon (RHB) ablation has been used to treat paroxysmal AF (PAF) and is now covered by Japan's national insurance system not only for treating PAF, but also PsAF.[10] The latest registry-based study of RHB ablation of AF in Japan has shown good clinical results in treating PsAF.[11] However, the specific mechanisms underlying the therapeutic effect of RHB ablation, including effects on associated anatomical and pathological changes, remain unknown. The RHB catheter is a

Received August 30, 2023; accepted August 30, 2023; J-STAGE Advance Publication released online September 16, 2023 Time for primary review: 1 day
Department of Cardiology, Dokkyo Medical University Saitama Medical Center, Koshigaya (S.N., Y.H., R.F., H.S., H.A., T.I., Y.I., S.K., I.T.); Division of Cardiology, Department of Medicine, Nihon University School of Medicine, Tokyo (Y.O.), Japan
I.T. is a member of *Circulation Reports*' Editorial Team.
Mailing address: Shiro Nakahara, MD, PhD, Department of Cardiology, Dokkyo Medical University Saitama Medical Center, 2-1-50 Minami Koshigaya, Koshigaya, Saitama 343-8555, Japan. email: nshiro@dokkyomed.ac.jp

ISSN-2434-0790

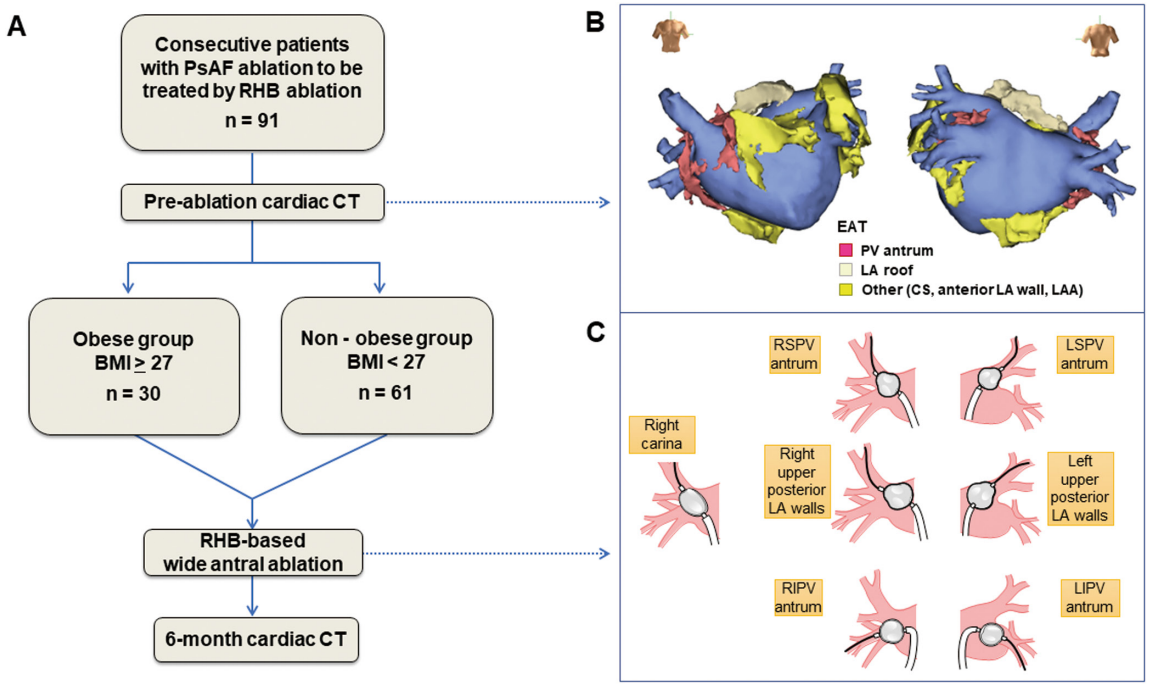

Figure 1. Study protocol and epicardial adipose tissue (EAT) distribution. (**A**) Study flow diagram. BMI (kg/m^2), body mass index; CT, computed tomography; PsAF, persistent atrial fibrillation; RHB, radiofrequency hotballoon. (**B**) Representative images of EAT distribution around the left atrium (LA), including the pulmonary vein (PV) antral region (both PV antra), LA roof, and other areas (LA anterior wall, LA appendage [LAA], and coronary sinus [CS]). (**C**) Details of the procedural technique. The hotballoon is positioned including each of the 4 PV antra and PV–LA junctions. In addition, the RHB is applied bilaterally to the upper posterior LA wall and right carina region. LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein.

device that can produce wide planar ablation lesions around the pulmonary vein (PV) antrum, especially due to the conductive heating properties of the highly compliant balloon.[12] Thus, we hypothesized that RHB ablation may have some effect on the structurally remodeled atrium, including the EAT, over the longer term. We also examined whether obese patients with abundant EAT would have a favorable clinical outcome after RHB ablation.

We conducted a clinical-experimental investigation in which we first compared routine pre- and postprocedure cardiac computed tomography (CT) images obtained from PsAF patients treated by RHB ablation to investigate the postprocedural effects on structurally remodeled atria, including the EAT. We further compared the effects of RHB ablation in obese patients with abundant EAT with those in non-obese patients to determine any differences in outcomes. Given the lack of previous reports investigating chronic pathological changes after RHB, we evaluated the chronic effect of RHB ablation by pathological examination in a porcine model from which PV antral tissue could be excised and examined.

Methods

The investigation's clinical component included a prospective observational single-center study of a consecutive series of 91 patients undergoing RHB ablation procedures for either PsAF (n=66) or longstanding PsAF (n=25). All patients were treated at Dokkyo Medical University Saitama Medical Center between October 2018 and December 2020. PsAF was defined as AF lasting >7 days but <12 months, whereas longstanding PsAF was defined as AF lasting >12 months. Excluded from the series were patients who had previously undergone an ablation procedure. Patients provided written informed consent for the procedure and inclusion in the study, the protocol of which was approved by the Bioethics Committee of Dokkyo Medical University Saitama Medical Center (Approval no. 21106).

The 91 patients were classified by BMI into 2 groups, namely an obese group (BMI >27 kg/m^2; n=30) and a non-obese (reference) group (BMI <27 kg/m^2; n=61), as in a previously reported trial.[13] All antiarrhythmic drugs (AADs) except amiodarone were discontinued for at least 5 half-lives before ablation. **Figure 1A** shows a flow diagram of the clinical study.

The experimental component included an animal study with 6 Yorkshire pigs in which RHB ablation was performed under general anesthesia. The experimental protocol was approved by the Institutional Animal Care and Use Committee of IVTeC Co., Ltd.

CT Acquisition and Assessment of Atrial EAT

Contrast-enhanced multidetector 192-slice CT (Somatom Definition; Siemens Medical Solutions) was performed before the procedure and 6 months later in all 91 clinical

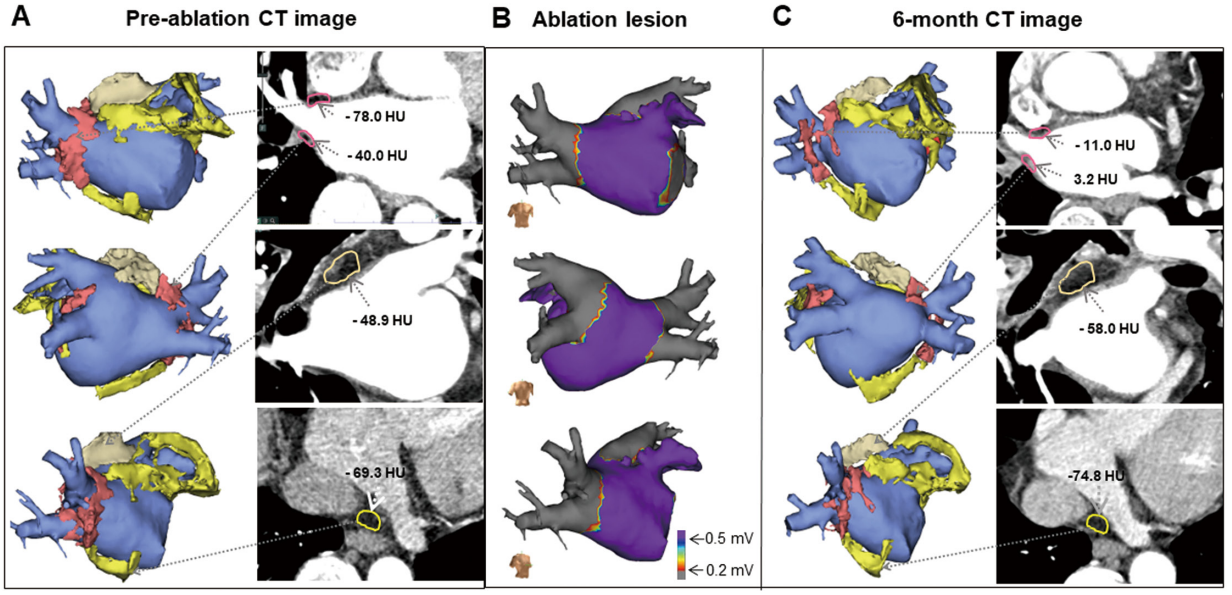

Figure 2. Local epicardial adipose tissue (EAT) reduction after radiofrequency hotballoon (RHB) ablation. (**A**) 3-Dimensional computed tomography (CT) images of the left atrium (LA) and local EAT (images obtained before ablation) and EAT quantification (Hounsfield unit [HU]) on the anterior and posterior walls of the right superior pulmonary vein (PV) in the axial plane, LA roof EAT in the coronal plane, and EAT around the coronary sinus (CS) in the axial plane (**Upper**, **Middle**, and **Lower** images, respectively). (**B**) Voltage maps obtained immediately after RHB ablation show planar lesion formation over the entire PV antrum. (**C**) CT images from the same patients obtained 6 months after ablation. Compared to what is seen in (**A**), the PV antrum EAT (red) along the planar ablation lesion is decreased, as is the entire LA's EAT, including the PV antrum. HU values in the same areas are increased. The quality and quantity of EAT in other areas have not changed significantly.

patients.

EAT was assessed on both pre- and postablation CT images using Synapse Vincent (Fujifilm) on the basis of Hounsfield unit (HU) values from −30 to −190.[14] Total EAT was defined as EAT within the pericardial sac from the level of the pulmonary artery bifurcation to the level of the diaphragm. EAT on the ventricular side of both annuli was manually deleted. LA-EAT was then identified by deleting the EAT right of the interatrial septal line. The CT data were transferred to the EnSite system.

For a quantitative analysis of LA-EAT, the EAT was reconstructed and segmented using the image integration software included in EnSite Verismo (Abbott Medical). Further, the LA-EAT was divided between the PV antral region (both PV antra), LA roof, and other areas (LA anterior wall, LA appendage [LAA], and coronary sinus [CS]), and the volume of each was calculated (**Figure 1B**). Interobserver variability was assessed for structural atrial and EAT volumetric measurements on the basis of images obtained in 20 randomly selected data.

For a qualitative analysis of LA-EAT, each EAT-containing region was manually traced with reference to the local EAT images described above, and average HU values were calculated using Synapse Vincent. The EAT of the PV antrum, LA anterior wall, and CS was traced and analyzed from axial plane images, whereas the EAT in the LA roof region was traced from coronal plane images (**Figure 2**).

These quantitative and qualitative analyses were repeated on CT images obtained at 6 months to calculate the volumes and qualitative changes in EAT over the longer term. To ensure uniform CT contrast effects when comparing both pre- and postablation images, a region of interest (ROI) was set up in the aorta near the tracheal bifurcation, and imaging was performed when the specified CT value (150 HU) was reached after injecting contrast medium.

Classification of PV Anatomical Changes

As in the EAT analysis, the diameter of each PV was measured from CT images obtained before ablation and then 6 months later. The diameter of both the superoinferior (SI) and anteroposterior (AP) PV was measured at the level of the ostium and common trunks. The diameter of each PV was measured at the maximum distance between 2 ostial points before and after the ablation procedure. The PV ostium was defined as the inflexion point between the left atrium and PV wall. The PV diameter was assessed ostially and at the narrowest point of stenosis if this point was away from the ostium. At the 6-months, the PV diameters were measured in the same views and identical locations using the same software as in the initial scan. In the consensus statement on catheter and surgical ablation of AF, PV stenosis is defined as a reduction in PV diameter and classified as mild (<50% diameter reduction), moderate (50–70% diameter reduction), and severe (>70% diameter reduction).[15] We classified mild stenosis as a diameter reduction of 30–50% and moderate and severe stenosis according to the consensus statement.

RHB Ablation

RHB ablation was performed with the HotBalloon ablation catheter (Toray Industries, Inc.) during sinus rhythm

Table 1. Clinical Characteristics of All Study Patients and per Study Group

	All patients (n=91)	Obese patients (n=30)	Non-obese patients (n=61)	P value
Age (years)	63.7±10.2	58.9±11.0	66.1±9.0	0.001
Male sex	68 (75)	21 (70)	47 (77)	0.0554
BMI (kg/m^2)	26.1±4.7	30.9±4.9	23.7±2.1	<0.001
Type of AF				
Persistent	66 (73)	19 (63)	47 (77)	0.171
Longstanding	25 (27)	11 (37)	14 (25)	0.157
Comorbidities/risk factors				
Hypertension	51 (55)	20 (67)	31 (50)	0.138
Diabetes	13 (14)	7 (23)	6 (10)	0.08
Prior cerebral ischemia	8 (9)	1 (3)	7 (11)	0.207
Heart failure	14 (15)	6 (20)	8 (13)	0.395
Age >75 years	15 (13)	3 (10)	9 (15)	0.531
$CHADS_2$ score	1.0 (0.3, 2.0)	1.0 (0, 2.0)	1.0 (0.8, 2.0)	0.804
CHA_2DS_2-VASc score	2.0 (1.0, 3.0)	1.0 (1.0, 2.0)	2.0 (1.0, 3.0)	0.18
Echocardiographic variables				
LA diameter (mm)	43.4±6.8	45.2±6.8	42.4±6.7	0.07
LVEF	62.6±13.0	65.1±14.0	61.3±12.4	0.20
EAT as quantified on CT images (mL)				
Total EAT	22.0 [12.4–33.3]	36.1 [26.0–54.5]	17.3 [8.5–24.1]	<0.001
PV antral EAT	5.5 [2.2–8.2]	7.7 [6.2–15.5]	4.3 [1.9–6.7]	<0.001
Left side	1.4 [0.2–2.4]	2.0 [1.0–3.8]	0.9 [0.0–2.2]	0.019
Right side	4.2 [2.0–6.2]	6.2 [4.4–13.3]	2.8 [0.8–4.8]	<0.001
LA roof EAT	2.5 [1.5–4.6]	4.6 [2.3–6.6]	2.1 [1.2–3.3]	<0.001
Other EAT (LA anterior wall, CS)	13.6 [6.7–20.8]	21.9 [16.4–29.5]	9.5 [5.1–15.2]	<0.001

Data are presented as the mean±SD, median [interquartile range], or n (%), unless indicated otherwise. AF, atrial fibrillation; BMI, body mass index; CS, coronary sinus; EAT, epicardial adipose tissue; LA, left atrium; LVEF, left ventricular ejection fraction; PV, pulmonary vein.

Table 2. Epicardial Adipose Tissue Volume Before and 6 Months After Ablation in All Patients and per Study Group

	All patients (n=91)			Obese patients (n=30)			Non-obese patients (n=61)		
	Before	6 months	P value	Before	6 months	P value	Before	6 months	P value
LA volume (mL)	177.7±29.7	138.4±29.6	<0.001	181.6±24.7	140.5±23.4	<0.0001	173.2±36.3	137.4±34.0	<0.0001
EAT volume (mL)									
Total LA-EAT	22.0 (12.4–33.3)	16.5 (7.9–25.8)	<0.001	36.1 (26.0–54.5)	26.3 (19.5–40.0)	<0.001	17.3 (8.5–24.1)	11.8 (5.7–19.5)	<0.001
PV antral EAT	5.5 (2.2–8.2)	3.2 (1.1–5.6)	<0.001	7.7 (6.2–15.5)	5.5 (2.8–10.3)	<0.001	4.3 (1.9–6.7)	2.2 (1.1–4.4)	<0.001
Left side	1.4 (0.2–2.4)	0.5 (0–1.4)	<0.001	2.0 (1.0–3.8)	1.3 (0.2–2.0)	<0.001	0.9 (0–2.2)	0.3 (0–1.2)	<0.001
Right side	4.2 (2.0–6.2)	2.2 (0.9–4.0)	<0.001	6.2 (4.4–13.3)	3.7 (2.5–7.7)	<0.001	3.0 (1.1–5.0)	2.0 (0.6–3.4)	<0.001
LA roof EAT	2.5 (1.4–4.6)	1.8 (1.0–3.0)	<0.001	4.6 (2.3–6.6)	3.0 (1.8–5.2)	<0.001	2.1 (1.2–3.3)	1.5 (0.8–2.4)	<0.001
Other EAT (LA anterior wall, CS)	13.6 (6.7–20.8)	10.8 (5.3–17.4)	<0.001	21.9 (16.4–29.5)	19.9 (12.6–27.0)	<0.001	9.5 (5.1–15.2)	7.4 (3.8–13.3)	<0.001

Unless indicated otherwise, data are given as the mean±SD or median (interquartile range). CS, coronary sinus; EAT, epicardial adipose tissue; LA, left atrium; PV, pulmonary vein.

after cardioversion. The balloon was positioned at each PV ostium by adjusting the injection volume (8–12 mL) so that the balloon completely apposed the antrum and occluded the PV. Subsequently, thermal energy was delivered with a single shot to the right PV carina region (**Figure 1C**). For a wide planar antral ablation, an upper posterior wall-targeted RHB ablation was performed bilaterally (for additional details, see **Supplementary Methods**). Electroanatomical voltage mapping was performed in every case before and just after ablation with the EnSite system. Bipolar signals were acquired with a 20-pole circular catheter (A Focus-II; Abbott). If necessary, coronary pacing was used to determine the local electrocardiogram. Exit block was confirmed by sequential pacing from the circular catheter. If and where residual PV potentials (manifesting as spontaneous PV reconnections) were seen, touch-up radiofre-

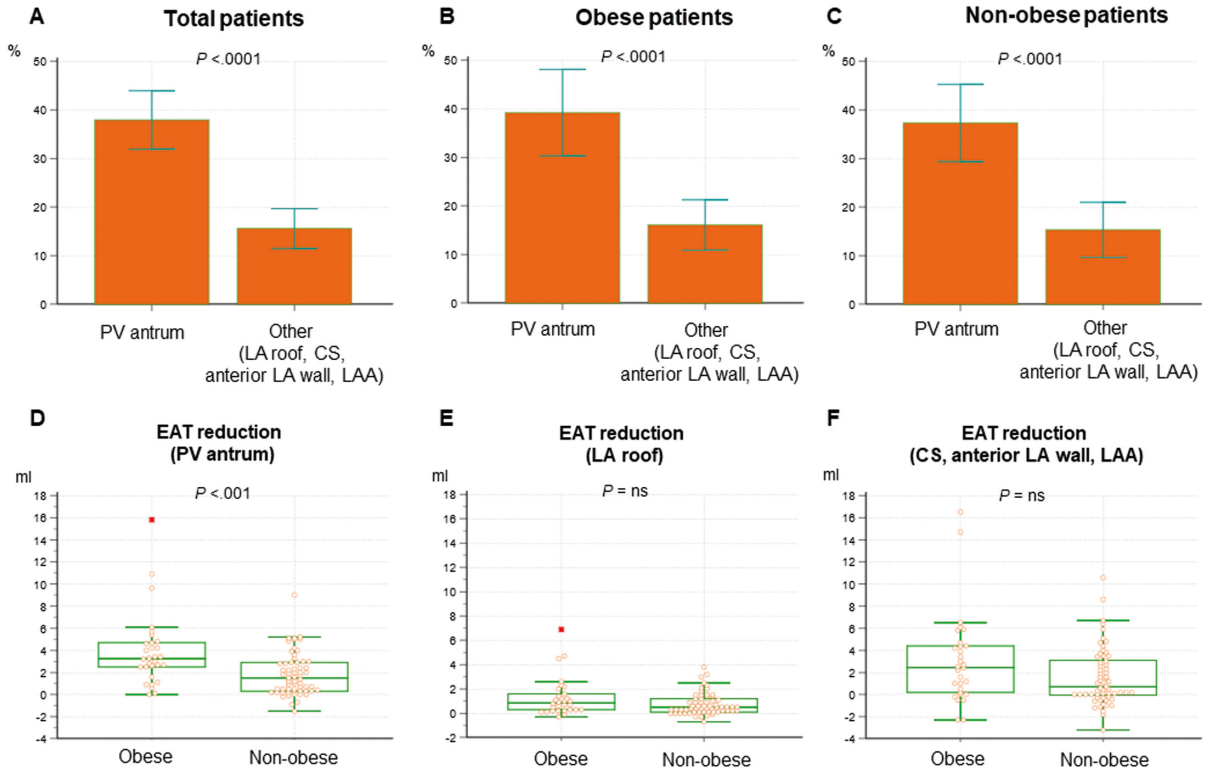

Figure 3. Percentage and volume reductions in local epicardial adipose tissue (EAT). (**A**–**C**) Percentage reductions in pulmonary vein (PV) antrum EAT and EAT in other regions after hotballoon ablation in the total patient cohort (**A**) and in obese (**B**) and non-obese (**C**) patients separately. Data are the mean [95% CI]. CS, coronary sinus LA, left atrium; LAA, left atrial appendage. (**D**–**F**) Box plots showing absolute reductions (mL) in the PV antrum EAT, LA roof EAT, and CS, LA anterior wall, and LAA EAT after hotballoon ablation in obese and non-obese patients. The boxes show the interquartile range, with the median value indicated by the horizontal line; whiskers show the range.

quency (RF) ablation was performed at those sites with a 4-mm-tip irrigation catheter (FlexAbility; Abbott). RF energy was applied point by point with a maximum power output of 25–35 W, and the temperature was set to a maximum of 43°C.

Postablation Management and Follow-up

AADs previously prescribed were resumed after the procedure at the operators' discretion. The patients' first outpatient clinic visit was 4 weeks after the procedure. Subsequent follow-up was performed every 3 months by our cardiology clinic staff and consisted of clinical interviews, echocardiographic examinations, and 24-h Holter monitoring. Further, 14-day monitoring with an external loop recorder (SpiderFlash; Sorin Group) or 7-day Holter monitoring (RAC-5000; Nihon Kohden) was undertaken at least once every 6 months after ablation in all patients, with patients being followed up for approximately 24 months. Recurrence was defined as any atrial tachyarrhythmia lasting longer than 30s, and early recurrence of AF was defined as recurrence within a 3-month blanking period, according to the latest guidelines.[15]

Animal Study

The purpose of the study's second component was to supplement the clinical findings with distinct features of targeted tissues around the PV antrum presumably resulting from RHB ablation. A single RHB ablation of the right superior PV (RSPV) antrum was performed in 6 pigs via a transseptal puncture, in accordance with the clinical protocol (70°C, 180 s at each ostium). After the procedure, 2 of the 6 pigs were immediately killed, and tissue was excised for pathological evaluation of the ablation area. Another 2 pigs were housed and fed for 2 weeks, and the remaining 2 pigs were housed and fed for 6 weeks, before being killed to evaluate the ablation area. The heart of a pig used for experiments on other organs was used as a non-RHB reference (details regarding the preparation and study of the animal model are provided in the **Supplementary Methods**).

Statistical Analysis

Continuous variables are presented as the mean±SD or median (interquartile range). The significance of differences in clinical characteristics between the obese and non-obese groups was analyzed by unpaired Student's t-test or the Wilcoxon test. The significance of differences in categorical variables was analyzed by Fisher's exact test. Interobserver agreement was assessed on the basis of linear correlations and intraclass correlation coefficients (ICCs); 95% confidence intervals (CI) were also calculated. Kaplan-Meier curves were generated for the freedom from

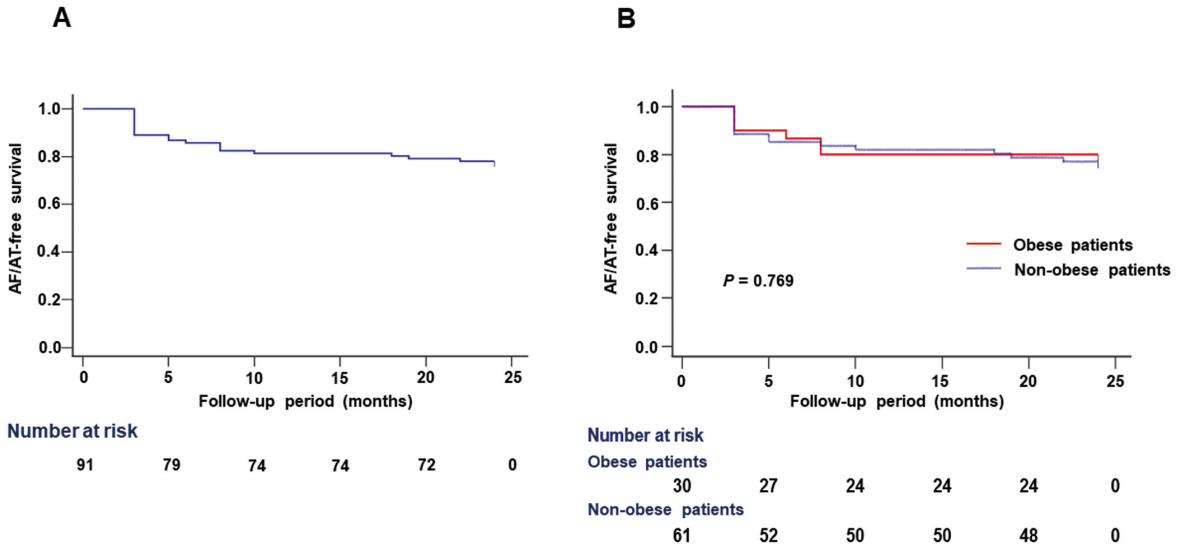

Figure 4. Kaplan-Meier curves of the atrial fibrillation (AF)/atrial tachycardia (AT)-free survival in (**A**) in the total patient cohort and (**B**) obese and non-obese patients.

AF/atrial tachycardia (AT), and between-group differences were analyzed by a log-rank test. SPSS software (version 25.0; IBM Corp.) was used for all statistical analyses, and two-tailed P<0.05 was considered significant.

Results

Patient Characteristics and CT-Based Analysis

Patient clinical characteristics, including baseline EAT volumes, are presented in **Table 1**. Patients in the obese group were significantly younger than those in the non-obese group, but the types of AF and comorbidities were similar between the 2 groups. Ten (11%) patients had common left PV ostia. The LA-EAT volume was significantly greater in the obese than non-obese group, and a similar trend was observed at each site examined within the LA. Overall, BMI was significantly correlated with LA-EAT volume (r=0.640; P<0.001). The interobserver variability tests had excellent agreement for semiautomated measurements, including EAT volume (r=0.989; ICC 0.987 [95% CI 0.962–0.995]; P<0.001) and for manual measurements, including the PV diameter (r=0.988; ICC 0.987 [95% CI 0.981–0.992]; P<0.001).

RHB Ablation

Our RHB protocol was applied in all 91 clinical cases. The procedural details, including the ablation time and balloon injection volume, are provided in the **Supplementary Table**. Acute isolation was achieved by RHB ablation in 332 (94%) of 354 PVs in 74 (81%) of the 91 patients in total. Adjunct point-by-point RF energy deliveries resulted in complete PV isolations in the remaining patients. No additional touch-up ablation was performed in extra-antral regions. Wide planar antral ablation was achieved in all patients. Representative voltage maps displaying the isolated planar surface area achieved using the RHB are shown in **Figure 2B**.

Effect of RHB Ablation on EAT

Measurements obtained before the procedure and 6 months later are presented in **Table 2**. A typical example of an LA-EAT reduction is shown in **Figure 2**. The EAT volume before and after the procedure is presented in **Table 2**. In all cases, the total EAT volume decreased significantly by the time of the 6-month assessment, and the decrease was similar between the obese and non-obese groups. In addition, the PV antral EAT, peri-LA roof EAT, and EAT at other sites (LA anterior wall, CS) volumes decreased significantly at the 6-months follow-up in the total study cohort and in both the obese and non-obese groups separately. The reduction in the LA-EAT volume was significantly greater in the PV antral area (37.9%; 95% CI 31.9–43.9) than in the other regions (LA roof, CS, LAA, LA anterior wall; 15.8%; 95% CI 11.5–19.7; P<0.001; **Figure 3A**), and the same trend was observed in the obese (39.2% [95% CI 30.3–48.0] vs. 16.1% [95% CI 10.9–21.2]; P<0.001) and non-obese (37.3% [95% CI 29.4–45.2] vs. 15.3% [95% CI 9.7–21.0]; P<0.001) groups (**Figure 3B**,**C**). The absolute change in EAT volume in the PV antral region was significantly greater in the obese than non-obese group (median [IQR] 3.3 [2.5–4.7] vs. 1.5 [0.3–2.9] mL; P=0.004; **Figure 3D**), but no significant changes were confirmed on the LA roof (0.9 [0.3–1.6] vs. 0.5 [0.1–1.2] mL; P=0.100) or other regions (LA anterior wall, LAA, and CS; 2.5 [0.2–4.4] vs. 0.7 [0–3.1] mL; P=0.071; **Figure 3E**,**F**). There was no difference in the amount of local change in EAT volume from baseline to 6 months between patients who remained in sinus rhythm (n=65) and those who had recurrent atrial arrhythmias (n=26; PV antrum: 36.8% [95% CI 31.1–42.5] vs. 46.4% [95% CI 35.5–57.3], P=0.09; other regions: 15.4% [95% CI 11.6–19.3] vs. 16.5%; [95% CI 8.5–24.6], P=0.77).

A typical example of the qualitative differences in LA-EAT at 6 months is shown in **Figure 2**. At 6 months after RHB ablation, the EAT attenuation values around the PV

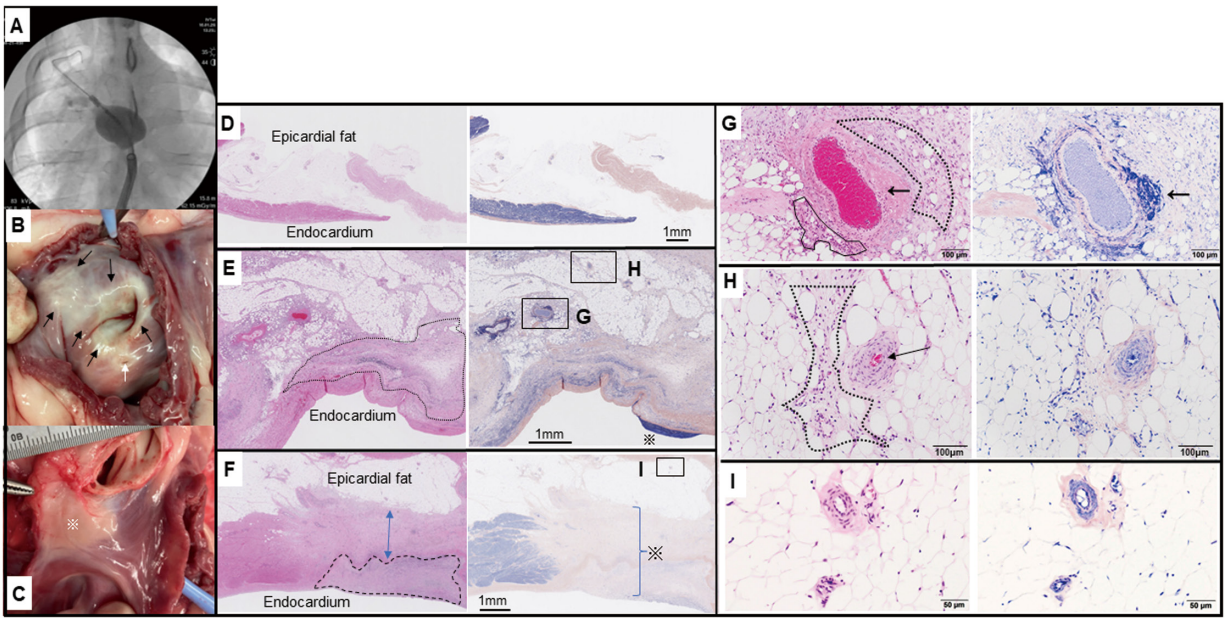

Figure 5. (**A**) A cine image of right superior pulmonary vein (RSPV) ablation in a swine model. (**B**) Representative RSPV antral lesion observed 6 weeks after radiofrequency hotballoon (RHB) ablation. The black arrows indicate balloon contact and thermal ablation of tissue areas. The white arrow indicates the transseptal puncture site. (**C**) The opposite side (i.e., the epicardial side) of the lesion in panel (**A**). Asterisks indicate epicardial fat. (**D**–**I**) Hematoxylin and eosin-stained (**Left**) and phosphotungstic acid–hematoxylin (PTAH)-stained (**Right**) lesion sections. (**D**–**F**) Longitudinal RSPV ostial sections. (**G**–**I**) Higher-magnification views of (**E**) and (**F**). (**D**) Section from the animal for which RHB ablation was not performed. The atrial myocardium appears normal, as does the epicardial fat around the RSPV ostial region. (**E**) Histopathologic sections of tissue obtained in the subacute phase (at 2 weeks). Granulation tissue extends into the adjacent epicardial fat (shaded area; **Left panel**). Asterisks indicate fibrin deposition (**Right panel**). (**F**) Histopathologic sections of tissue obtained in the chronic phase (at 6 weeks). Fibrosis (shaded area; **Left panel**) and overlying granulation tissue (blue arrow) appear on the endocardial side of the ablated surface. A transmural lesion (asterisk) reaching into the epicardial fat is shown. (**G**) Vessels encased in epicardial fat, with fibrinoid degeneration throughout the vessel wall (arrows). Around the vessels, cellular infiltration (solid line) and granulation tissue formation due to fibroblast proliferation (shaded area) are evident. (**H**) Thickening of the arterial tunica media in the epicardial fat (arrow) is evident, as well as fibrosis and inflammatory cell infiltration in the epicardial fat around the vessels (shaded area). (**I**) In the vessels encased in epicardial fat, endothelial cells have increased in number, the tunica media is thickened, and the inflammatory cell infiltration within the epicardial fat has subsided compared with that seen in the subacute phase (at 2 weeks).

antral region were significantly reduced (median [IQR] +41.0 [20.0, 64.8] HU; P<0.001), whereas the LA roof and other areas exhibited no significant change (−5.5 [−12, 8.5] HU; P=0.339).

Effect of RHB Ablation on LA Volume and PV Antrum

In all cases, the LA volume decreased significantly by the time of the 6-month evaluation (**Table 2**). On average, all PVs decreased significantly in size, with no difference in the diameter reduction between the SI and AP diameters (median [IQR] 22% [11–33%] vs. 23% [7–35%]; P=0.918). In total 124 (35.0%) PVs had mild stenosis (42 left superior [LS] PVs, 3 left common [LC] PVs, 17 left inferior [LI] PVs, 35 right superior [RS] PVs, and 27 right inferior [RI] PVs) and 23 (6.4%) had moderate stenosis (6LSPV, 6 LIPVs, 8 RSPVs, and 3 RIPVs). No patients were symptomatic with severe stenosis or required angioplasty.

Postablation Outcomes

Eight (27%) obese and 11 (18%) non-obese patients were prescribed ≥1 AAD even after the 3-month blanking period, with no significant difference in AAD use between the 2 groups (P=0.34). During a 20.3±7.6-month follow-up period, 26 (29%) patients (8 [27%] in the obese group and 18 [30%] in the non-obese group) experienced recurrences, either of AF or AT. Only 3 non-obese patients experienced ATs. Kaplan-Meier curves are shown in **Figure 4**; the freedom from AF/AT recurrence was similar between the obese and non-obese groups (P=0.77).

Effect of RHB Ablation on EAT (per Pathological Examination)

All 6 pigs underwent ablation procedures without any complications. The 2 subacute phase (2 weeks) and 2 chronic phase (6 weeks) model pigs survived without any change in their behavior, and none displayed signs of distress. Macroscopically, immediately after ablation and at 2 and 6 weeks, all RHB ablation lesions were clearly distinguishable, and there was no gross thrombus or charring (**Figure 5B**). Regardless of the phase, whitish atrial tissue, possibly EAT, was visible on the surface of the anterior wall of the RSPV antrum (epicardial side; **Figure 5C**). A histologic examination of the RSPV antrum in the pig's heart that did not undergo RHB revealed epicardial fat regions in the superficial layer of the myocardium (**Figure 5D**). The median thickness of the RSPV was

2.1 mm (IQR 1.7–2.2 mm), and that of the epicardial fat region 2.0 mm (IQR 1.5–2.9 mm). Histopathology sections obtained from the subacute-phase (2-week) model are shown in **Figure 5E**. Fibrin deposition on the endocardium and granulation tissue extended into the adjacent EAT. Sections from the chronic-phase (6-week) model are shown in **Figure 5F**. Fibrosis and overlying granulation tissue were identified on the endocardial side of the ablated surface. Further, transmural lesions reaching into the epicardial fat regions were also identified. Magnified views of blood vessels and surrounding structures encased within the epicardial fat regions are shown in **Figure 5G–I**. The subacute phase (**Figure 5G,H**) was characterized by perivascular inflammatory cell infiltration, granulation, and thickening of the vessel tunica media. In the chronic phase (**Figure 5I**), tunica media thickening was observed, but the inflammatory cell infiltration had subsided.

Discussion

To the best of our knowledge, our investigation included the first prospective observational study conducted to assess the effects of RHB ablation on structural atrial remodeling associated with PsAF. Our main findings were as follows: (1) RHB ablation resulted in negative LA remodeling and a significant reduction in EAT in the area corresponding to the planar ablation zone; (2) in the swine model, RHB ablation produced transmural lesions that reached into the epicardial fat region; and (3) RHB ablation produced similar decreases in the PV antral EAT in obese and non-obese patients, and the ablation success rate was similar in the obese (i.e., with abundant EAT) and non-obese groups.

Increased LA wall thickness and LA and EAT deposition are recognized as structural remodeling and serve as biomarkers in AF patients.[3–5] Further, some reports support a connection between successful AF ablation and reverse LA remodeling.[16,17] Our patient cohort included a fairly substantial proportion of patients with an enlarged PV antrum. The RHB, which is size adjustable and maintains compliance even during energy deliveries, may have contributed to a proper fit with the enlarged PV antral surface area. The ablation lesions, which were planar and transmural, may have led to subsequent negative remodeling effects. However, to the best of our knowledge, a pathological evaluation of RHB ablation has only been performed in acute-phase animal models,[12,18] with no reports of chronic-phase models. Confirming transmural lesions in our chronic-phase swine model subjected to the RHB ablation protocol we used clinically supported the above hypothesis. Those changes were localized and probably due to a loss of myocytes, contributing not only to local ablation effects, but also to reverse remodeling due to restoration of sinus rhythm.

Peri-atrial EAT is thought to be involved in AF substrate formation through adipocyte infiltration, profibrotic effects, proinflammatory effects, and oxidative stress.[6] Further, EAT depots are thought to initiate and maintain AF through various forms of cross-talk with the atrial myocardium. EAT is significantly thicker in PsAF patients than in PAF patients, and an increased EAT thickness is a significant predictor of the AF burden.[3] There have been reports of reductions in overall cardiac EAT with diet, bariatric surgery, pharmaceutical intervention, and rhythm control obtained by AF ablation.[17,19,20] However, to the best of our knowledge, there have been no reports of a localized reduction in EAT confined to the vicinity of the PV antrum.

Several mechanisms can be postulated for reducing the local EAT volume after RHB ablation. The region is highly suspect for involvement of EAT in the AF substrate via the cardiac plexus,[6] and the reduction in PV antral EAT is likely to have resulted from using the RHB. Our previous animal experiments verified the effect of conduction heating created by RHB ablation and confirmed that sufficient lethal temperatures were reached on the epicardial side.[12] EAT is a metabolically active tissue, the myocardium and EAT are fed by the coronary arteries, and they are thought to share a common blood supply.[21] Although direct microcirculatory interconnections between the 2 tissues have not yet been demonstrated, there is robust evidence of microcirculatory connections between the EAT of the atrioventricular groove and coronary artery wall via the vasa vasorum.[21,22] EAT has also been found to inhibit RF energy deliveries to the targeted myocardium due to its insulating nature and significant resistance.[23] The following is a pathological consideration of the EAT reduction induced by RHB in our animal studies. First, granulation tissue hyperplasia and fibrosis extending into the EAT indicate the formation of a transmural lesion with a high durability of the RHB. The absence of an anatomical separation between the fat and myocardium is unique to EAT. Therefore, it is possible that paracrine or vasocrine cross-talk is involved in the increase in EAT.[22] The thermal effect of RHB may have influenced the cross-talk during the remote period. Second, the persistent granulation of blood vessels within the EAT and the transient inflammatory cell infiltrate findings suggested that conductive heating may have reached deep enough into the EAT. Those findings may be an indication that inflammatory changes in the encased vessels may have had an effect on the microcirculation between the EAT and myocardium. Further studies are necessary to evaluate the tissue changes in our experiments and to demonstrate the mechanism by which the RHB reduces EAT. Another factor at play may be the reduction in systemic and/or local inflammation that is achieved once sinus rhythm is maintained after RHB ablation. AF is common in obese patients due to atrial enlargement and obesity-associated local and systemic inflammatory factors.[6,24] Sinus rhythm maintenance after ablation decreases systemic inflammatory markers, such as high-sensitivity C-reactive protein and interleukin-6, in the remote phase.[25] Those factors may have also contributed to the reduction in EAT in regions other than the PV antrum.

Obese patients have a greater EAT deposition and substrate complexity, contributing to resistance to current AF treatments.[9,13] In the present study, the AF recurrence rate did not differ between the obese and non-obese groups. Although our cohort included some patients needing AADs even after the blanking period, our results were somewhat better than the general success rates reported from previous studies (e.g., the earlier HARVEST study [a national registry-based study including patients needing AADs]).[11] Therefore, the possibility that a mechanism other than PV isolation by RHB is involved cannot be ruled out. In our cohort, the EAT volume around the PV antrum decreased equally by approximately 40% in both obese and non-obese patients. Further, the absolute EAT volume reduction was more significant in obese patients, in line with the increased baseline EAT volumes.

Changes in the EAT's HU values also may indicate a weakening of EAT attenuation. Thus, we suggest that postablation sinus rhythm maintenance and/or planar ablation lesions may temporarily modulate both the complex interactions between the EAT and neighboring atrial myocardium and local inflammation, especially in obese patients. Further investigations are needed to determine whether such effects are reliable and durable. Furthermore, our study showed no significant difference in the degree of EAT reduction between the recurrent and non-recurrent groups. This suggests that thermal denaturation of the EAT around the PV antrum by RHB ablation alone is not a preventive factor for recurrence. Further validation of the causal relationship between the clinical outcomes and degree of EAT degeneration after RHB is needed.

The risk of PV stenosis (PVS) after AF ablation has been reported in recent years and the observed risk is similar for RHB.[10] Our finding of a localized reduction in EAT in the present study is probably due to the extensive transmural planar ablation. In the present cohort, 6.4% of patients were also found to have moderate PVS, although fortunately it was asymptomatic. However, the reason why most cases were less than mild is probably due to the 40% reduction in energy delivery time compared with the trial protocol (see **Supplementary Table**). Furthermore, the recent clinical use of balloons with an estimated surface temperature function and the introduction of cooler protocols may further reduce the risk of PVS in the future.

Study Limitations

This investigation was limited first by the fact that it was conducted, in part, as a single-center study and thus included a small number of patients. Second, the use of swine models has inherent limitations because of potential differences between pigs and humans in terms of the response of atrial tissue to ablation. However, this model provided an assessment of the direct effects of RHB ablation on epicardial fat regions, which would not be possible in humans.

Third, the effect of RHB planar ablation on reducing EAT needs to be compared with a group of patients who received cryoballoon or conventional RF ablation. Finally, because of the retrospective nature of the study, we do not have complete data on weight changes after ablation. However, there were no weight interventions, such as exercise or diet, during the follow-up period, so this effect may have been small.

Conclusions

RHB-based planar and transmural lesions resulted in localized alterations in the structurally remodeled LA, including the EAT, in PsAF patients. Those changes were observed in obese and non-obese patients, and further studies are needed to determine whether factors other than PV isolation contribute to the clinical success of RHB ablation.

Sources of Funding

None.

Disclosures

S.N. has received speaker honoraria/consulting fees from Toray Industries, Inc. Y.O. has received speaker honoraria from Toray Industries, Inc. I.T. is a member of *Circulation Reports*' Editorial Team.

IRB Information

This study was conducted in strict adherence to the principles of the Declaration of Helsinki and was approved by the Bioethics Committee of Dokkyo Medical University Saitama Medical Center (Approval no. 21106).

Data Availability

The data associated with this study will not be shared.

References

1. Andersson T, Magnuson A, Bryngelsson IL, Frobert O, Henriksson KM, Edvardsson N, et al. All-cause mortality in 272,186 patients hospitalized with incident atrial fibrillation 1995–2008: A Swedish nationwide long-term case-control study. *Eur Heart J* 2013; **34:** 1061–1067, doi:10.1093/eurheartj/ehs469.
2. Nattel S, Harada M. Atrial remodeling and atrial fibrillation: Recent advances and translational perspectives. *J Am Coll Cardiol* 2014; **63:** 2335–2345, doi:10.1016/j.jacc.2014.02.555.
3. Batal O, Schoenhagen P, Shao M, Ayyad AE, Van Wagoner DR, Halliburton SS, et al. Left atrial epicardial adiposity and atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010; **3:** 230–236, doi:10.1161/CIRCEP.110.957241.
4. Beyer C, Tokarska L, Stuhlinger M, Feuchtner G, Hintringer F, Honold S, et al. Structural cardiac remodeling in atrial fibrillation. *JACC Cardiovasc Imaging* 2021; **14:** 2199–2208, doi:10.1016/j.jcmg.2021.04.027.
5. Hatem SN, Redheuil A, Gandjbakhch E. Cardiac adipose tissue and atrial fibrillation: The perils of adiposity. *Cardiovasc Res* 2016; **109:** 502–509, doi:10.1093/cvr/cvw001.
6. Poggi AL, Gaborit B, Schindler TH, Liberale L, Montecucco F, Carbone F. Epicardial fat and atrial fibrillation: The perils of atrial failure. *Europace* 2022; **24:** 1201–1212, doi:10.1093/europace/euac015.
7. Mancio J, Azevedo D, Fragao-Marques M, Falcao-Pires I, Leite-Moreira A, Lunet N, et al. Meta-analysis of relation of epicardial adipose tissue volume to left atrial dilation and to left ventricular hypertrophy and functions. *Am J Cardiol* 2019; **123:** 523–531, doi:10.1016/j.amjcard.2018.10.020.
8. Winkle RA, Mead RH, Engel G, Kong MH, Fleming W, Salcedo J, et al. Impact of obesity on atrial fibrillation ablation: Patient characteristics, long-term outcomes, and complications. *Heart Rhythm* 2017; **14:** 819–827, doi:10.1016/j.hrthm.2017.02.023.
9. Wong CX, Abed HS, Molaee P, Nelson AJ, Brooks AG, Sharma G, et al. Pericardial fat is associated with atrial fibrillation severity and ablation outcome. *J Am Coll Cardiol* 2011; **57:** 1745–1751, doi:10.1016/j.jacc.2010.11.045.
10. Sohara H, Ohe T, Okumura K, Naito S, Hirao K, Shoda M, et al. HotBalloon ablation of the pulmonary veins for paroxysmal AF: A multicenter randomized trial in Japan. *J Am Coll Cardiol* 2016; **68:** 2747–2757, doi:10.1016/j.jacc.2016.10.037.
11. Yamasaki H, Nakahara S, Sohara H, Yoshida Y, Kohno T, Shimane A, et al. HotBalloon pulmonary vein isolation registry study: Real-world efficacy and safety of HotBalloon ablation. *Circ J* 2023; **87:** 65–73, doi:10.1253/circj.CJ-21-0994.
12. Nakahara S, Wakamatsu Y, Sato H, Otsuka N, Fukuda R, Watanabe R, et al. A porcine study of the area of heated tissue during hot-balloon ablation: Implications for the clinical efficacy and safety. *J Cardiovasc Electrophysiol* 2021; **32:** 260–269, doi:10.1111/jce.14861.
13. Mahajan R, Nelson A, Pathak RK, Middeldorp ME, Wong CX, Twomey DJ, et al. Electroanatomical remodeling of the atria in obesity: Impact of adjacent epicardial fat. *JACC Clin Electrophysiol* 2018; **4:** 1529–1540, doi:10.1016/j.jacep.2018.08.014.
14. Oikonomou EK, Marwan M, Desai MY, Mancio J, Alashi A, Hutt Centeno E, et al. Non-invasive detection of coronary inflammation using computed tomography and prediction of residual cardiovascular risk (the CRISP CT study): A post-hoc analysis of prospective outcome data. *Lancet* 2018; **392:** 929–939, doi:10.1016/S0140-6736(18)31114-0.
15. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: Executive summary. *J Arrhythm* 2017; **33:** 369–409, doi:10.1016/j.joa.2017.08.001.
16. Ausma J, van der Velden HM, Lenders MH, van Ankeren EP, Jongsma HJ, Ramaekers FC, et al. Reverse structural and gap-junctional remodeling after prolonged atrial fibrillation in the

goat. *Circulation* 2003; **107:** 2051–2058, doi:10.1161/01.CIR.0000062689.04037.3F.
17. Monno K, Okumura Y, Saito Y, Aizawa Y, Nagashima K, Arai M, et al. Effect of epicardial fat and metabolic syndrome on reverse atrial remodeling after ablation for atrial fibrillation. *J Arrhythm* 2018; **34:** 607–616, doi:10.1002/joa3.12124.
18. Evonich RF, Nori DM, Haines DE. Efficacy of pulmonary vein isolation with a novel hot balloon ablation catheter. *J Interv Card Electrophysiol* 2012; **34:** 29–36, doi:10.1007/s10840-011-9646-1.
19. Requena-Ibanez JA, Santos-Gallego CG, Rodriguez-Cordero A, Vargas-Delgado AP, Mancini D, Sartori S, et al. Mechanistic insights of empagliflozin in nondiabetic patients with HFrEF: From the EMPA-TROPISM Study. *JACC Heart Fail* 2021; **9:** 578–589, doi:10.1016/j.jchf.2021.04.014.
20. Liang KW, Tsai IC, Lee WJ, Lin SY, Lee WL, Lee IT, et al. Correlation between reduction of superior interventricular groove epicardial fat thickness and improvement of insulin resistance after weight loss in obese men. *Diabetol Metab Syndr* 2014; **6:** 115, doi:10.1186/1758-5996-6-115.
21. Marchington JM, Mattacks CA, Pond CM. Adipose tissue in the mammalian heart and pericardium: Structure, foetal development and biochemical properties. *Comp Biochem Physiol B* 1989; **94:** 225–232, doi:10.1016/0305-0491(89)90337-4.
22. Iacobellis G, Corradi D, Sharma AM. Epicardial adipose tissue: Anatomic, biomolecular and clinical relationships with the heart. *Nat Clin Pract Cardiovasc Med* 2005; **2:** 536–543, doi:10.1038/ncpcardio0319.
23. Zipse MM, Edward JA, Zheng L, Tzou WS, Borne RT, Sauer WH, et al. Impact of epicardial adipose tissue and catheter ablation strategy on biophysical parameters and ablation lesion characteristics. *J Cardiovasc Electrophysiol* 2020; **31:** 1114–1124, doi:10.1111/jce.14383.
24. Javed S, Gupta D, Lip GYH. Obesity and atrial fibrillation: Making inroads through fat. *Eur Heart J Cardiovasc Pharmacother* 2021; **7:** 59–67, doi:10.1093/ehjcvp/pvaa013.
25. Okumura Y, Watanabe I, Nakai T, Ohkubo K, Kofune T, Kofune M, et al. Impact of biomarkers of inflammation and extracellular matrix turnover on the outcome of atrial fibrillation ablation: Importance of matrix metalloproteinase-2 as a predictor of atrial fibrillation recurrence. *J Cardiovasc Electrophysiol* 2011; **22:** 987–993, doi:10.1111/j.1540-8167.2011.02059.x.

Supplementary Files

Please find supplementary file(s);
https://doi.org/10.1253/circrep.CR-23-0073