



Adjunctive left anterior line ablation induced left atrial dysfunction and dyssynchrony in atrial fibrillation ablation

Hirosuke Yamaji¹ · Takashi Murakami¹ · Kazuyoshi Hina¹ · Shunichi Higashiya¹ · Hiroshi Kawamura¹ · Masaaki Murakami¹ · Shigeshi Kamikawa¹ · Satoshi Hirohata¹ · Shozo Kusachi^{1,2}

Received: 8 May 2018 / Accepted: 3 August 2018 / Published online: 7 August 2018
© Springer Japan KK, part of Springer Nature 2018

Abstract

We evaluated the effects of adjunctive left anterior line (LAL) ablation on LA dyssynchrony and function using real-time three-dimensional echocardiography (3DE) in connection with thromboembolic complications and tachyarrhythmia recurrence in patients with persistent atrial fibrillation (AF). We randomly and prospectively assigned consecutive persistent AF patients to the LAL ($n = 52$, 65 ± 7 years) and control groups ($n = 50$, 64 ± 10 years). In the LAL group, extensive encircling pulmonary vein isolation (EEPVI), roof line ablation, and LAL ablation regardless of the extent of the low-voltage area (LVA) were performed. The control group underwent EEPVI and roof line ablation. After ablation, 3DE demonstrated LA dyssynchrony in 23 (46%) and 4 patients (8%, $P < 0.001$) of the LAL and control groups, respectively. Baseline LA LVAs were relatively small in most patients and there were no significant differences in extent of LVA between control and LAL groups or between patients with and without dyssynchrony. During the follow-up periods (771 ± 121 days), patients with LA dyssynchrony in the LAL group did not show significant differences in symptomatic thromboembolic events (0%) and atrial tachyarrhythmia recurrence (39%) from patients without LA dyssynchrony in the LAL (0% and 30%) and control groups (0% and 32%, respectively). LA ejection fraction and active emptying fraction were lower by 9% on average in the LAL group than in the control group ($P < 0.0001$). Similarly, in the LAL group, LA ejection fraction, active emptying fraction, and expansion index were significantly lower by approximately 7%, 8%, and 15%, respectively, in LA with dyssynchrony than those in LA without dyssynchrony. In conclusion, LA dyssynchrony and LA hypofunction were induced by LAL ablation in patients with persistent AF and relatively mild LVA. LAL ablation with or without LA dyssynchrony is thought not to affect thromboembolic complications or atrial tachyarrhythmia recurrence.

Keywords Tachyarrhythmia · Catheter ablation · Left atrium · Real-time three-dimensional echocardiography · Complications

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00380-018-1238-x>) contains supplementary material, which is available to authorized users.

✉ Hirosuke Yamaji
yamaji2@mac.com; yamaji@okayama-heart.com

¹ Heart Rhythm Center, Okayama Heart Clinic, Takeda 54-1, Naka-ku, Okayama, Okayama 703-8251, Japan

² Department of Medical Technology, Okayama University Graduate School of Health Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan

Introduction

For treatment of persistent atrial fibrillation (AF), adjunctive substrate modification strategies have been proposed experimentally and introduced clinically [1, 2]. One of the adjunctive substrate modification strategies is the creation of a block line between the anterior/anterolateral mitral annulus and the right superior pulmonary vein, termed the left anterior line (LAL) [3]. The effectiveness of LAL ablation for treatment of persistent AF has been reported [4].

LAL ablation is hypothesized to cause left anterolateral conduction delay and affect LA wall motion. Further, LA dyssynchrony is assumed to associate with thromboembolic complications and atrial tachyarrhythmia recurrence. However, no reports have examined LA functional changes

following LAL ablation. Accordingly, we determined LA dyssynchrony and functions using real-time three-dimensional echocardiography (RT3DE) and investigated the association between LA dyssynchrony after LAL ablation and atrial tachyarrhythmia recurrence and thromboembolic complication.

Patients and methods

Study design and patients

Examination and analysis procedures complied with the guidelines established by the Declaration of Helsinki [5]. The study was approved by the Institutional Ethics Committee for Human Research of Okayama Heart Clinic. Written informed consent for the use of data without personally identifiable information was obtained from all participants. We prospectively and randomly assigned 121 consecutive patients (68 ± 10 years; 79 male) with persistent and long-standing persistent AF who underwent their first ablation therapy at Okayama Heart Clinic to LAL and control groups. In the LAL group ($n = 52$), EEPVI, roof line ablation, and LAL ablation were carried out. The control group ($n = 50$) underwent EEPVI and roof line ablation. Patient flow diagram with exclusion of patients is shown in Fig. 1. Clinical characteristics of these patients are shown in Table 1. Primary endpoints were LA dyssynchrony and function at 1 month after the ablation. Secondary endpoints included atrial tachyarrhythmia recurrence and thromboembolic and bleeding complications.

Anticoagulation

Anticoagulant therapy was performed using non-vitamin K antagonist oral anticoagulants (NOACs) [6]. NOACs were administered at least 3 weeks before and at least 90 days after ablation. NOACs were withheld on the day of AF ablation and were resumed 3 h after the procedure.

Ablation

Activated clotting time (ACT) was maintained within 300–350 s using heparin during the procedure [6]. EEPVI with the double Lasso technique was performed. Methods were described elsewhere in detail [7]. Briefly, ablation was carried out using an open-irrigated ablation catheter (Cool-Flex™; St. Jude Medical, Inc., St. Paul, MN, USA) with an electroanatomical integration mapping system (Ensite-NavX System; St. Jude Medical Inc.). Irrigated RF energy was delivered with a target temperature of 42 °C, a maximal power limit of 35 W (20–30 W for posterior wall ablation and 30–35 W for anterior wall ablation) and an infusion rate of 13 mL/min via the irrigated ablation catheter. RF energy was applied point-by-point for 20 s until the maximal local electrogram amplitude decreased by 70%. After EEPVI, the reconnections (dormant conduction) of PVs were continuously checked using adenosine triphosphate, and reconnection gaps were ablated. Complete EEPVI was performed. Subsequently, LA roof line ablation (between the left superior PV and right superior PV) was carried out point-by-point with RF energy at 30 W for 20 s for controls. LAL ablation with 30–35 W for 20 s was performed point-by-point in the LAL group. The steerable sheath (Agilis™; St. Jude Medical, Inc., St. Paul, MN, USA) was used to

Fig. 1 Patient flow diagram. *AL* anterior line, *EEPVI* extensive encircling pulmonary vein isolation, *AF* atrial fibrillation, *RT3DE* real-time three-dimensional echocardiography

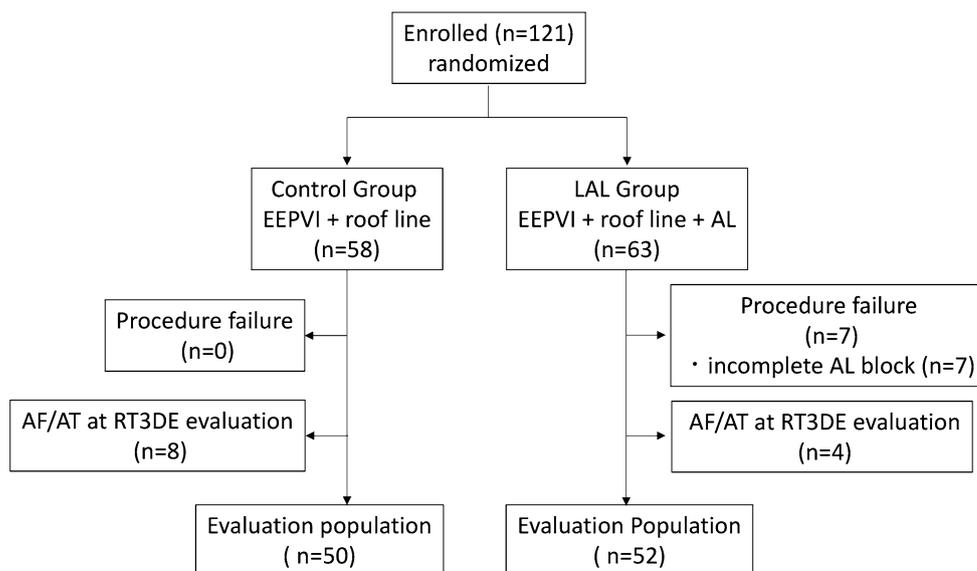


Table 1 Baseline clinical characteristics and AF status

	Control (<i>n</i> =50)	LAL group (<i>n</i> =52)	<i>P</i> value Control vs. LAL	LAL group		<i>P</i> value dyssyn (+) vs dyssyn (-)	<i>P</i> value (3 groups) Control vs. dyssyn (+) vs. dyssyn (-)
				dyssyn (-) (<i>n</i> =28)	dyssyn (+) (<i>n</i> =24)		
Age (yrs)	66±10	70±8	0.175	68±7	71±8	0.104	0.126
Gender (female)	17 (34%)	17 (33%)	0.889	8 (29%)	9 (38%)	0.494	0.784
BW (kg)	67.2±15.6	63.1±10.5	0.274	65.2±10.6	60.6±10.1	0.147	0.191
BMI	24.0±3.5	23.3±3.2	0.264	23.6±3.3	23.0±3.1	0.563	0.443
Cr (mg/dL)	0.82±0.24	0.87±0.21	0.240	0.87±0.23	0.87±0.20	0.797	0.481
CCr (mL/min)	80.9±24.5	72.0±23.6	0.051	75.6±21.9	67.8±25.2	0.155	0.060
CHADS ₂ score	0.9±0.9	1.1±0.9	0.241	0.9±0.7	1.3±1.0	0.106	0.147
Hypertension	20 (40%)	30 (58%)	0.073	16 (57%)	14 (58%)	0.931	0.200
Diabetes	8 (8%)	9 (9%)	0.859	3 (11%)	6 (25%)	0.175	0.389
TIA	2 (2%)	2 (2%)	0.968	1 (4%)	1 (4%)	0.911	0.993
CHA ₂ DS ₂ -VASc score	1.8±1.1	2.0±1.2	0.434	1.7±1.0	2.3±1.4	0.072	0.168
Type of AF							
Persistent	31 (62%)	26 (50%)	0.462	14 (50%)	12 (50%)	0.640	0.589
Long-standing per- sistent	18 (36%)	25 (48%)		13 (46%)	12 (50%)		
AT	1 (2%)	1 (2%)		1 (4%)	0 (0%)		
AF duration (yrs)	3.6±1.9	4.2±1.9	0.107	4.1±1.9	4.4±1.9	0.731	0.249

Values are presented as mean ± SD

AF atrial fibrillation, LAL left anterior line, dyssyn dyssynchrony, BW body weight, BMI body mass index, Cr creatinine, CCr creatinine clearance, AT atrial tachycardia, TIA transient ischemic attack

achieve sufficient and stable catheter contact force during LA ablation in all patients. [8].

For LAL ablation, RF energy delivery was initiated at the anterior part of the mitral annulus (Fig. 2, upper panel). Linear ablation was continued to the anterior segment of the LA appendage and reached the right superior PV. When LAL block was not confirmed in this line ablation, ablation between mitral valve annulus and roof line was additionally performed.

Voltage mapping

In patients with AF after completion of EEPVI, sinus rhythm was restored using direct-current cardioversion. Voltage map was then created under the sinus rhythm. With reference to precise 3D geometry of the LA and PVs, LA voltage map was initially constructed using contact bipolar electrocardiograms obtained from a 20-pole circular mapping catheter (Reflexion HD™, St. Jude Medical). Furthermore, open-irrigation catheter as noted above (CoolFlex™; St. Jude Medical) was used in additional sites where the circular mapping catheter failed to reach appropriately. Low-voltage area (LVA) was defined as an area with bipolar peak-to-peak voltage amplitudes < 0.5 mV

and covering > 5% of the LA body surface area. The PV antrum regions were excluded from the LVA. The LA surface area was defined as the LA body area without the PV antrum regions, LAA orifice, and mitral valve.

Confirmation of LAL block

Bidirectional differential pacing was conducted to confirm complete conduction block across the LAL (Fig. 2, lower panel). The circular mapping catheter was placed in the left atrial appendage (LAA) that is positioned lateral to the line, and the ablation catheter was placed septal to the line. LAA pacing was performed, and the activation sequence on the anterior and septal LA wall was recorded. Activation potential was detected from septal to lateral LA in case of successful block. Activation of LAA and distal CS potentials were recorded during pacing directly septal to the line created by the ablation catheter. When LAA activation was longer than the distal CS activation and the interval to LAA activation was longer, a block was assumed to be established. Widely spaced double potentials along the LAL during pacing from the LAA are further evidence of LAL block.

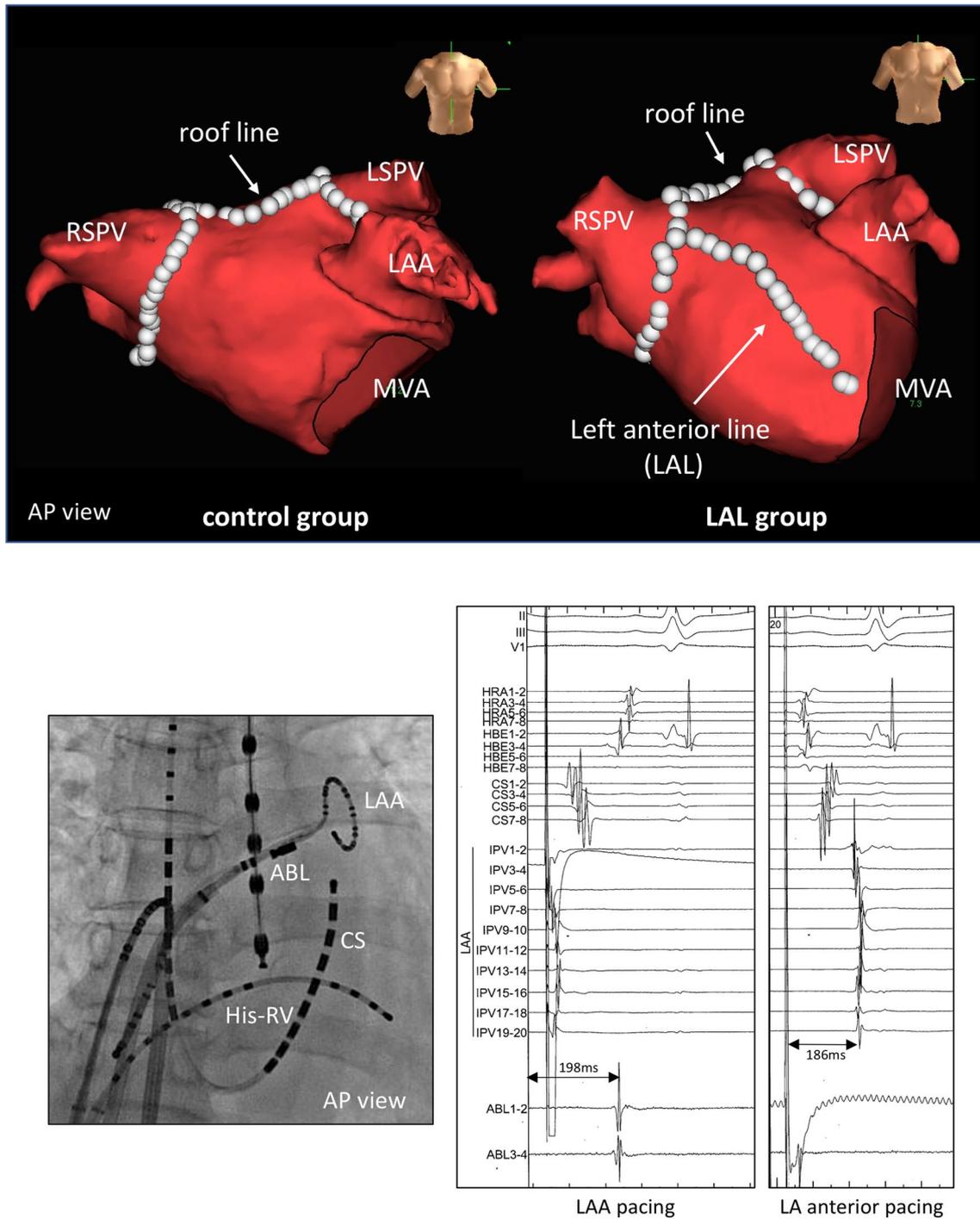


Fig. 2 Upper panel: representative examples of left anterior line ablation and control (no left anterior line ablation). Lower panel: confirmation of bidirectional block of left anterior line ablation by differential pacing from the left atrial appendage (LAA) and right atrial (RA)

septum. *RSPV* right superior pulmonary vein, *LSPV* left superior pulmonary vein, *LAA* left atrial appendage, *MVA* mitral valve annulus, *ABL* ablation catheter, *CS* coronary sinus, *RA* right atrium, *RV* right ventricle, *AP* antero-posterior

Echocardiography

Standard 2DE was performed 24–48 h before and 1 month after AF ablation during AF and sinus rhythm, respectively,

using EPIQ 7 ultrasound system (Philips Medical Systems, Andover, MA, USA). Measurements were performed in accordance with the American Society of Echocardiography guidelines [9].

Three-dimensional echocardiography was performed 1 month after ablation to determine LA volume indices using the same equipment noted above [10–12]. RT3DE images were acquired using a commercial scanner equipped with a fully sampled matrix array transducer (x5-1; Philips Medical Systems) in the harmonic mode. The RT3DE datasets were transferred to a Q-Lab system™ (version 10.5; Philips Medical Systems) for off-line analysis, and RT3DE images were analyzed automatically. The following indexes were measured to assess booster pump function: LA ejection fraction, active and passive emptying fraction, and LA expansion index.

LA segmental volume changes determined using RT3DE

We applied RT3DE systems with software to reconstruct 3D LA image and to determine sequential LA segmental volume changes (Advanced Cardiac 3D quantification™; Philips Medical Systems) [13]. LA cast was automatically

divided into the standard 17 segments using the software (Fig. 3). The center of gravity of each cast can also be calculated, and the volume of each segment relative to the center of gravity was measured. Each of these segmental volumes had a pyramidal shape. The volume of each pyramid was calculated and plotted for each cast/dataset throughout the cardiac cycle. Validity of these analyses has been demonstrated [12, 14].

Definition of LA dyssynchrony

LA dyssynchrony was determined using the following analyses via RT3DE: 1, 3D LA motion image video (Supplemental File 1); 2, reconstructed LA 3D images for maximum and minimum volumes; 3, bull’s eye representing time from maximum to minimum volume and 4, phasic LA segmental volume lines (Fig. 3). When dyssynchrony was observed on video, non-uniform contraction was demonstrated by minimum and maximum volumes in LA 3D reconstructed

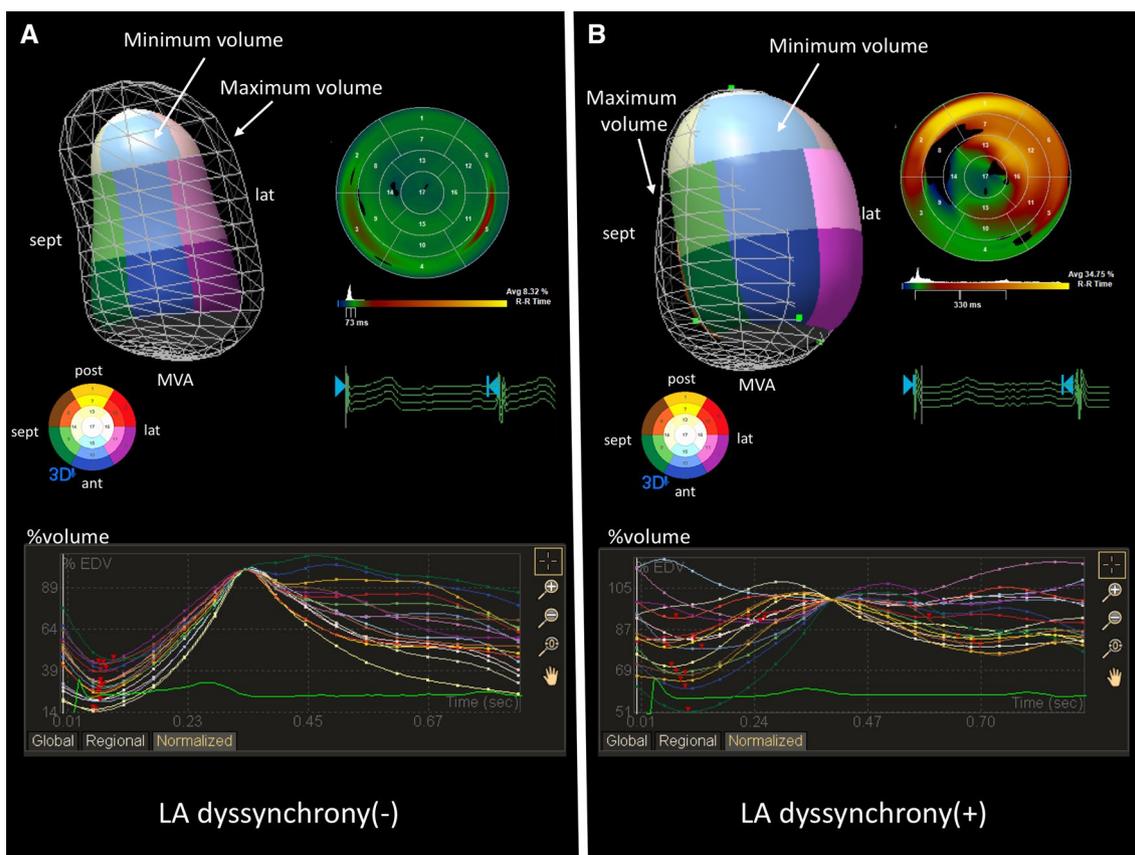


Fig. 3 a Non-dyssynchrony. b Dyssynchrony. Left upper diagram in each panel shows 3D image of the left atrium. Grids indicated maximum LA volume. Colored image showed minimum LA volume. Uniform contraction of LA was observed in dyssynchrony (–) but not in dyssynchrony (+). Right upper diagram in each panel represents colored bull’s eye that directed time from maximum to minimum vol-

ume. Green indicated short time. Bull’s eye demonstrated delayed and non-homogeneous LA volume change in LA dyssynchrony. Lower graph in each panel denotes 17 segment LA phasic volume curve line. Synchronized phasic curve line movements were seen in dyssynchrony (–). In contrast, opposite phasic line movement can be seen in dyssynchrony (+). MVA mitral valve annulus

images, delayed and inhomogeneous phasic volume change was determined by bull's eye analysis, and opposite movement of segmental volume lines was observed, dyssynchrony was defined as present.

Reproducibility of measurements using RT3DE

LA dyssynchrony was determined by a cardiologist and a medical technologist who were unaware of any clinical data. Intra- and inter-observer variability in the measurements of LA volume and function in RT3DE were checked using a randomly selected subgroup of patients ($n = 30$) determined by Bland–Altman analysis.

Complications

Symptomatic cerebrovascular embolism, transient ischemic attacks, pulmonary embolism, and deep venous embolism were defined as thromboembolic complications. Cardiac tamponade, pericardial effusion, and bleeding events were considered bleeding complications. Major bleeding was defined as bleeding requiring blood transfusion, hematomas requiring surgical intervention, and cardiac tamponade requiring drainage. Minor bleeding complications included small hematomas and pericardial effusions not requiring drainage (non-tamponade). The primary safety outcome measured was a composite of bleeding and thromboembolic complications.

Statistical analysis

The t test and Chi-square test were used to compare data between the 2 groups for continuous and categorical variables, respectively. We employed one-way analysis of variance or Kruskal–Wallis test with Bonferroni's post hoc t test for comparison of data from 3 groups when applicable. The sample size of the present study had 80% power at $P = 0.05$ to detect 15% reduction in the AF recurrence rate by LAL ablation from 35%, which was estimated for the control group. Data are expressed as mean \pm standard deviation. Differences at $P < 0.05$ were considered significant.

Results

Reproducibility of RT3D echocardiographic measurements

In the assessment of LA dyssynchrony, no disagreement was observed between the cardiologists and medical technologists. The results of inter- and intra-observer differences in echocardiographic measurements of LA end-diastolic volume measured using RT3DE are shown in upper and lower

panels in Fig. 4. In Bland–Altman plot distribution, differences in two measurements were located between limits of agreement line, confirming acceptable intra- and inter-observer reproducibility. Similar acceptable intra- and inter-observer reproducibility was obtained for LA end-systolic volume, stroke volume, and ejection fraction.

Incidence of LA dyssynchrony, baseline clinical and conventional echocardiographic characteristics

Three-dimensional echocardiography was examined during sinus rhythm after ablation. It could not be examined during AF rhythm before ablation because measurements with

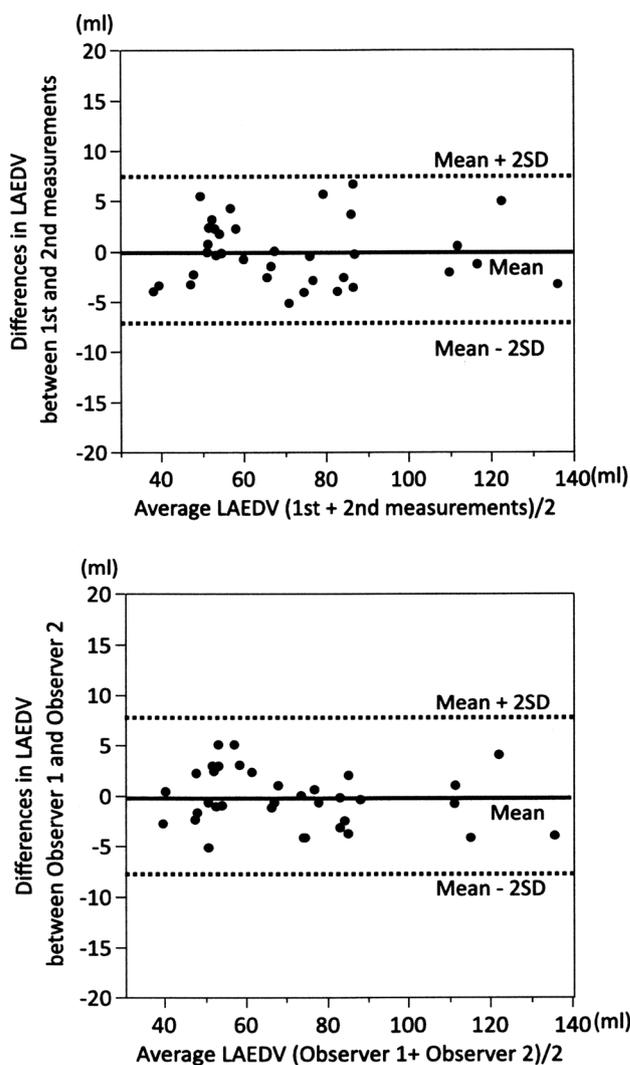


Fig. 4 Intra-observer (upper panel) and inter-observer (lower panel) reproducibility of left atrial end-diastolic volume (LAEDV) measurements using real-time three-dimensional echocardiography. Bland–Altman plots show good intra- and inter-observer reproducibility of LAEDV measurements using real-time three-dimensional echocardiography

p-wave trigger were impossible to perform. RT3DE demonstrated LA dyssynchrony in 23 patients (46%) of the LAL group and in 4 patients of the control group (8%, $P < 0.001$). In contrast, significant differences in conventional echocardiographic measurements including LA indices after ablation were not observed between the control and LAL groups or between LAL group patients with and those without dyssynchrony (Table 2).

No significant differences were found in clinical characteristics, risk of thromboembolism, and AF status between the control and LAL groups or between LAL group patients with and without dyssynchrony (Table 1). Similarly, conventional echocardiographic parameters of left ventricles and atrium were not different between the control and LAL groups or between LAL group patients with and without dyssynchrony recorded during AF before ablation (Table 2).

Table 2 Echocardiographical parameters and voltage mapping results and among control patients and patients with and without dyssynchrony

	Control ($n=50$)	LAL group ($n=52$)	<i>P</i> value Control vs. LAL	LAL group		<i>P</i> value dyssyn (+) vs. dyssyn (-)	<i>P</i> value Control vs. dyssyn (+) vs. dyssyn (-)
				dyssyn (-) ($n=28$)	dyssyn (+) ($n=24$)		
Pre-ablation							
Echocardiography							
Rhythm (AF)	50 (100%)	52 (100%)	1.000	28 (100%)	24 (100%)	1.000	1.000
Left ventricle							
LVEF (%)	65 ± 7	64 ± 10	0.908	65 ± 8	62 ± 12	0.368	0.637
LVEDV (mL)	107 ± 26	109 ± 29	0.997	112 ± 30	104 ± 27	0.263	0.525
LVESV (mL)	38 ± 14	40 ± 23	0.925	40 ± 22	41 ± 26	0.701	0.939
SV (mL)	69 ± 16	67 ± 17	0.703	72 ± 16	63 ± 17	0.061	0.163
Left atrium							
LAD (mm)	41 ± 7	44 ± 6	0.103	43 ± 6	44 ± 7	0.811	0.259
LAV (mL)	60 ± 21	67 ± 26	0.244	69 ± 28	67 ± 24	0.902	0.507
LAVI (mL/m ²)	35 ± 12	40 ± 14	0.215	40 ± 15	40 ± 14	0.880	0.452
LA voltage mapping							
Low-voltage area (<0.5 mV); n (%)	22 (44%)	27 (52%)	0.436	17 (61%)	10 (42%)	0.171	0.284
% Low-voltage area (range)	7 ± 11 (5–51)	11 ± 16 (5–55)	0.934	12 ± 15 (5–55)	5 ± 19 (5–78)	0.235	0.218
% Low-voltage area > 30%; n (%)	3 (6%)	5 (10%)	0.756	3 (11%)	2 (8%)	0.866	0.914
Post-ablation							
Echocardiography							
Rhythm (SR)	50 (100%)	52 (100%)	1.000	28 (100%)	24 (100%)	1.000	1.000
Left ventricle							
LVEF (%)	68 ± 5	67 ± 7	0.965	67 ± 8	67 ± 6	0.167	0.376
LVEDV (mL)	112 ± 17	117 ± 34	0.687	115 ± 38	105 ± 24	0.723	0.867
LVESV (mL)	35 ± 7	38 ± 24	0.644	40 ± 28	34 ± 11	0.812	0.879
SV (mL)	76 ± 15	74 ± 16	0.741	76 ± 16	70 ± 17	0.223	0.460
Left atrium							
LAD (mm)	43.1 ± 6.4	43.1 ± 5.7	0.860	42.4 ± 6.0	44.5 ± 4.8	0.096	0.251
LAV (mL)	61.3 ± 20.0	62.7 ± 20.6	0.930	61.9 ± 22.5	64.1 ± 16.8	0.452	0.749
LAVI (mL/m ²)	36.3 ± 11.8	37.3 ± 11.8	0.775	36.3 ± 12.3	39.3 ± 10.7	0.231	0.483

Values are presented as mean ± SD

LAL left anterior line, dyssyn dyssynchrony, LVEF left ventricular ejection fraction, LVEDV left ventricular end-diastolic volume, LVESV left ventricular end-systolic volume, SV stroke volume, LAD left atrial dimension, LAV left atrial volume, LAVI left atrial volume index, DCT deceleration time

LA echocardiographic indices using RT3DE after ablation

LA ejection fraction and active emptying fraction were significantly lower in patients who received LAL ($32 \pm 9\%$ and $21 \pm 8\%$, respectively) than those in control patients ($41 \pm 10\%$ and $31 \pm 9\%$) (Fig. 5). In the LAL group, patients with dyssynchrony showed lower LA ejection fraction ($28 \pm 10\%$) than those without dyssynchrony ($35 \pm 7\%$). Furthermore, LA active emptying fraction and LA expansion index were lower in patients with dyssynchrony ($17 \pm 7\%$ and $41 \pm 21\%$, respectively) than those in patients without dyssynchrony ($25 \pm 7\%$ and $56 \pm 17\%$). LA dyssynchrony was found in only 4 (8%) patients, which was quite a small number; thus, statistical analysis of the data from these patients could not be performed. LA ejection fraction in 4 patients was $29 \pm 6\%$. LA active and passive emptying fractions were $19 \pm 3\%$ and $12 \pm 6\%$, respectively. LA expansion index in 4 patients was $29 \pm 6\%$. These values were comparable with those in patients with dyssynchrony in the LAL group.

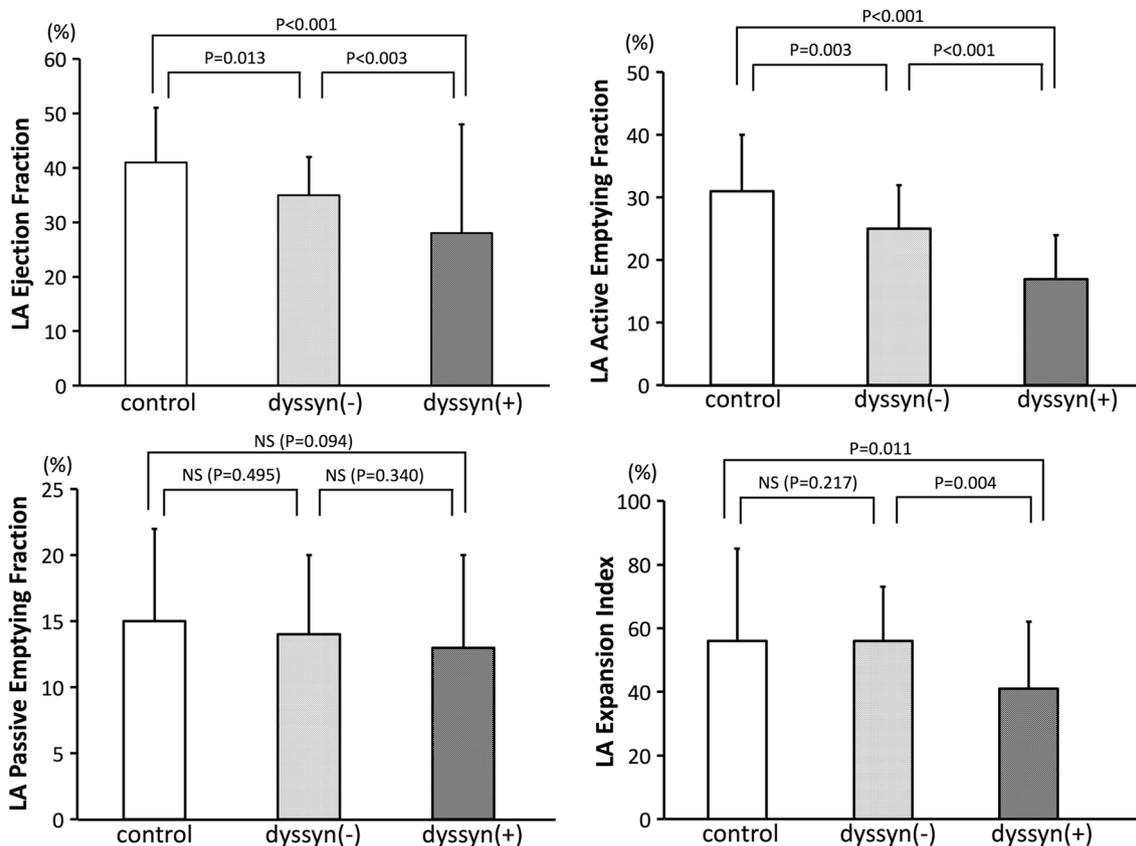


Fig. 5 Comparison of left atrium (LA) function indices among control, left anterior line ablation (LAL) group patients with LA dyssynchrony, and without LA dyssynchrony measured using real-time

LA voltage mapping and procedural parameters and initial ablation success

There were no significant differences in percentage of patients with LVA (+) and (−) between control and LAL groups and between patients with and without dyssynchrony (Table 2). Similarly, there were no significant differences in percentage of patients with large LVA between control and LAL groups and between patient with and without dyssynchrony. No significant differences were observed in procedural parameters, fluoroscopy, and RF energy supply times between patients with and without LA dyssynchrony (Table 3). The PV isolation success rate was 100% in patients with and without LA dyssynchrony.

Complications and atrial tachyarrhythmia recurrence

Neither symptomatic thromboembolic nor bleeding complications occurred in LAL patients with and without LA dyssynchrony or in control patients (Table 4). Thus, no differences in safety outcome were observed between

three-dimensional echocardiography. *dyssyn* dyssynchrony, *LA* left atrium, *NS* not significant, *P* probability value

Table 3 Procedural parameters between patients with and those without LA dyssynchrony in LAL group

	dyssyn (–) (n=28)	dyssyn (+) (n=24)	P value
Procedural variables			
Presenting rhythm			
AF	96% (27/28)	100% (24/24)	0.938
AT	4% (1/28)	0% (0/24)	
Acute success	100% (28/28)	100% (25/24)	1.000
Procedure time (min)	98 ± 26	107 ± 27	0.191
Fluoroscopic time (min)	24 ± 9	28 ± 7	0.043
RF times (min)	26 ± 11	31 ± 10	0.076
Intraprocedural cardioversion	50% (12/24)	63% (15/24)	0.383
PV isolation success	100% (28/28)	100% (24/24)	1.000
LAL success	100% (28/28)	100% (24/24)	1.000

Values are presented as mean ± SD

LAL left anterior line, dyssyn dyssynchrony, AF atrial fibrillation, AT atrial tachycardia, RF radiofrequency, PV pulmonary vein, P probability value

Table 4 Follow-up periods, antiarrhythmic drugs, complications and atrial tachyarrhythmia recurrence

	All patients (n=102)	Control (n=50)	LAL group (n=52)	P value	LAL group		P value
					dyssyn (–) (n=28)	dyssyn (+) (n=24)	
Follow-up and antiarrhythmic drugs							
Follow-up (days)	771 ± 121	792 ± 118	751 ± 121	0.121	743 ± 127	760 ± 117	0.627
Antiarrhythmic drugs	22 (22%)	8 (16%)	14 (27%)	0.231	11 (41%)	3 (13%)	0.063
Thromboembolic complications (n)							
Stroke; transient ischemic attack; deep venous thrombosis; pulmonary embolism							
	0	0	0	1.000	0	0	1.000
Other thromboembolic complication	0	0	0	1.000	0	0	1.000
Bleeding complications	0	0	0	1.000	0	0	1.000
Safety outcome (the composite of thromboembolic and bleeding complications)							
	0	0	0		0	0	1.000
Atrial tachyarrhythmia recurrence							
All	33 (33%)	16 (32%)	17 (33%)	0.940	8 (30%)	9 (39%)	0.494
AF recurrence	20 (20%)	13 (26%)	7 (13%)	0.111	3 (11%)	4 (17%)	0.826
AT recurrence	13 (13%)	3 (6%)	10 (19%)	0.088	5 (18%)	5 (21%)	0.786

Values are presented as mean ± SD

dyssyn left atrial dyssynchrony, AF atrial fibrillation, AT atrial tachycardia, P probability value

LAL group and control group or LAL group patients with and without dyssynchrony.

During the follow-up period (771 ± 121 days), no difference was found in atrial tachyarrhythmia recurrence between LAL group and control group or between LAL group patients with or without LA dyssynchrony (Table 4).

Discussion

This study demonstrated for the first time that LA dyssynchrony appeared after LAL ablation at a considerable rate (about 50%) as shown by RT3DE. LA dyssynchrony was associated with LA hypofunction. Patients with LA

dyssynchrony in the LAL group did not, however, show significant differences in atrial tachyarrhythmia recurrence or thromboembolic complications from patients without LA dyssynchrony in the LAL or control group.

LA dyssynchrony and function were evaluated 1 month after ablation. With regard to the pathological course of LA after ablation, several studies reported that LA pathological changes are almost completed 4 weeks after ablation [15, 16]. Several studies demonstrated that LA swelling and edematous change develop promptly and is resolved within 4 weeks [15, 16]. These pathophysiological courses after ablation correspond with the blanking time [17, 18]. Thus, the time of evaluation of LA function and dyssynchrony in the present study was appropriate. The extent of LVA may be associated with LA function and dyssynchrony. Most of the studied patients showed mild LVA and there were no significant differences in the extent of LVA between control and LAL groups or between patients with and without dyssynchrony. Therefore, patient backgrounds with respect to LVA were not different among groups. These considerations validate comparisons among the groups and open the door for further discussion.

For determination of LA dyssynchrony and dysfunction, we employed the RT3DE system. RT3DE does not require assumptions about cavity shape, and the analytical system can thus be theoretically applied to LA cavity motion analyses. RT3DE approaches have been reported to be characterized by smaller measurement variation due to semi-automated endocardial edge detection [19]. The wall motion tracking process is automated. The software analysis is semi-automatic. Segmental volume sequential changes are not based on regions of interest; instead, RT3DE is performed on the complete LA myocardium using the 3D dataset. Numerous speckles are tracked in this volume. The results of the wall motion tracking are based on thousands of vectors, and these results are presented as averaged values for each segment. RT3DE can thus provide sequential 3D LA motion images as well as sensitive phase differences among the 17 segments in wall motion. We determined LA dyssynchrony by LA 3D motion as well as LA segmental wall movement. Inter-observer differences were not observed in determination of LA dyssynchrony. The present methods to detect LA dyssynchrony as well as dysfunction were thus appropriate and further discussion regarding LAL ablation and LA dyssynchrony and hypofunction can be made.

LA dyssynchrony occurred in approximately half of the patients who received LAL ablation, whereas dyssynchrony was observed only in 4 patients (8%) in the control group. LA functions determined using RT3DE were lower in patients with LAL ablation than those in control patients. Furthermore, LA functions were lower in patients with dyssynchrony than those in patients without dyssynchrony in the LAL group. The present study demonstrated

that LAL ablation caused LA dysfunction and evoked LA dyssynchrony at a considerable rate.

LA dyssynchrony did not show higher incidence of symptomatic thromboembolic complications compared with LA synchrony in the LAL group. The effects of LA dyssynchrony on LA thrombus formation have not been reported, and the present results cannot be discussed with previous reports. LA appendage function and LA size play a key role in LA thrombus formation [20–22]. LA dyssynchrony and LA dysfunction are assumed to cause LA appendage thrombosis. In contrast to these assumptions, thromboembolic complication did not occur in patients with dyssynchrony. Pre-ablation, peri-ablation and post-ablation anticoagulant therapies may at least partly account for the non-association of LA dyssynchrony with thromboembolic complications.

The present results showed that patients with LA dyssynchrony did not present lower tachyarrhythmia recurrence compared with patients without LA dyssynchrony or control patients. Furthermore, tachyarrhythmia recurrence was not different between the LAL and control groups. The follow-up period of the present study was based on the findings of a long-term follow-up study that most AF recurrences occur over the first 6–12 months [23]. The durations of the follow-up in the present study were thus satisfactorily long. It can be assumed that LA dyssynchrony may reflect more LA histological damage and thus might result in more intensive electrophysiological substrate modification than LA without dyssynchrony. In contrast to this assumption, tachyarrhythmia recurrence was not different between patients with LA dyssynchrony and those without LA dyssynchrony. In addition, atrial tachyarrhythmia recurrence was not different between patients with LA dyssynchrony and control group. Several studies reported the efficacy of adjunctive LAL creation on tachyarrhythmia recurrence, and controversial results have been reported [24, 25]. The present results suggest that LAL creation may not be an effective method to decrease incidence of atrial tachyarrhythmia recurrences.

Further research

Low-voltage area-based ablation is a novel method for substrate modification. Several studies have suggested that LVA-based ablation is thought to improve ablation outcomes, though these studies included a relatively small number of patients and efficacy is thus not completely established [26–28]. When RF energy is supplied to the low-voltage zone located in the anterior LA, LA dyssynchrony is hypothesized to be induced, as in LAL ablation. Future research is warranted to further examine whether LVA ablation-induced dyssynchrony is functionally similar to LAL ablation-induced dyssynchrony.

Limitations

This study has several limitations. First, LA dyssynchrony was evaluated 1 month after the ablation. The time course of LA dyssynchrony was not examined. Second, asymptomatic thromboembolic complications were not examined using magnetic resonance imaging. Third, this study included a small number of patients. Fourth, long-term follow-up of more than several years was not performed. Although it appears that an increase in the number of patients and/or expansion of follow-up period would most likely not produce significant changes in results, it is not certain; however, the present results can provide useful data for meta-analysis.

Conclusions

The present study demonstrated first that LA dyssynchrony and hypofunction were induced by LAL ablation. However, significant association of LA dyssynchrony with increase in thromboembolic complications or decrease in atrial tachyarrhythmia recurrence was not found. Adjunctive LAL ablation is indicated not to show beneficial effects of AF ablation outcomes.

Compliance with ethical standards

Conflict of interest All authors declare that they have no competing interests.

References

- Jiang Z, Yin H, He Y, Ma N, Tang M, Liu H, Ding F, Mei J (2015) Efficacy and safety of novel epicardial circumferential left atrial ablation with pulmonary vein isolation in sustained atrial fibrillation. *Heart Vessels* 30:675–681
- Haissaguerre M, Hocini M, Sanders P, Sacher F, Rotter M, Takahashi Y, Rostock T, Hsu LF, Bordachar P, Reuter S, Roudaut R, Clementy J, Jais P (2005) Catheter ablation of long-lasting persistent atrial fibrillation: clinical outcome and mechanisms of subsequent arrhythmias. *J Cardiovasc Electrophysiol* 16:1138–1147
- Tzeis S, Luik A, Jilek C, Schmitt C, Estner HL, Wu J, Reents T, Fichtner S, Kolb C, Karch MR, Hessling G, Deisenhofer I (2010) The modified anterior line: an alternative linear lesion in perimitral flutter. *J Cardiovasc Electrophysiol* 21:665–670
- Ammar S, Luik A, Hessling G, Bruhm A, Reents T, Semmler V, Buiatti A, Kathan S, Hofmann M, Kolb C, Schmitt C, Deisenhofer I (2015) Ablation of perimitral flutter: acute and long-term success of the modified anterior line. *Europace* 17:447–452
- (2000) World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 284:3043–3045
- Yamaji H, Murakami T, Hina K, Higashiya S, Kawamura H, Murakami M, Kamikawa S, Komtasubara I, Kusachi S (2016) Adequate initial heparin dosage for atrial fibrillation ablation in patients receiving non-vitamin K antagonist oral anticoagulants. *Clin Drug Investig* 36:837–848
- Yamaji H, Murakami T, Hina K, Higashiya S, Kawamura H, Murakami M, Kamikawa S, Hirohata S, Kusachi S (2013) Usefulness of dabigatran etexilate as periprocedural anticoagulation therapy for atrial fibrillation ablation. *Clin Drug Investig* 33:409–418
- Piorowski C, Eitel C, Rolf S, Bode K, Sommer P, Gaspar T, Kircher S, Wetzel U, Parwani AS, Boldt LH, Mende M, Bollmann A, Husser D, Dages N, Esato M, Arya A, Haverkamp W, Hindricks G (2011) Steerable versus nonsteerable sheath technology in atrial fibrillation ablation: a prospective, randomized study. *Circ Arrhythm Electrophysiol* 4:157–165
- Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ (2005) Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 18:1440–1463
- Marsan NA, Tops LF, Holman ER, Van de Veire NR, Zeppenfeld K, Boersma E, van der Wall EE, Schalij MJ, Bax JJ (2008) Comparison of left atrial volumes and function by real-time three-dimensional echocardiography in patients having catheter ablation for atrial fibrillation with persistence of sinus rhythm versus recurrent atrial fibrillation three months later. *Am J Cardiol* 102:847–853
- Murata M, Iwanaga S, Tamura Y, Kondo M, Kouyama K, Ogawa S (2008) A real-time three-dimensional echocardiographic quantitative analysis of left atrial function in left ventricular diastolic dysfunction. *Am J Cardiol* 102:1097–1102
- Aune E, Baekkevar M, Roislien J, Rodevand O, Otterstad JE (2009) Normal reference ranges for left and right atrial volume indexes and ejection fractions obtained with real-time three-dimensional echocardiography. *Eur J Echocardiogr* 10:738–744
- Lang RM, Badano LP, Mor-Avi V, Afalalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU (2015) Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 16:233–270
- Anwar AM, Soliman OI, Geleijnse ML, Nemes A, Vletter WB, ten Cate FJ (2008) Assessment of left atrial volume and function by real-time three-dimensional echocardiography. *Int J Cardiol* 123:155–161
- Schwartzman D, Ren JF, Devine WA, Callans DJ (2001) Cardiac swelling associated with linear radiofrequency ablation in the atrium. *J Interv Card Electrophysiol* 5:159–166
- Okada T, Yamada T, Murakami Y, Yoshida N, Ninomiya Y, Shimizu T, Toyama J, Yoshida Y, Ito T, Tsuboi N, Kondo T, Inden Y, Hirai M, Murohara T (2007) Prevalence and severity of left atrial edema detected by electron beam tomography early after pulmonary vein ablation. *J Am Coll Cardiol* 49:1436–1442
- Verma N, Knight BP (2017) What happens during the blanking period does not stay in the blanking period. *J Cardiovasc Electrophysiol* 28:634–635
- Alipour P, Azizi Z, Pirbaglou M, Ritvo P, Pantano A, Verma A, Khaykin Y (2017) Defining blanking period post pulmonary vein antrum isolation. *JACC Clin Electrophysiol* 3:568–576
- Jenkins C, Bricknell K, Chan J, Hanekom L, Marwick TH (2007) Comparison of two- and three-dimensional echocardiography with sequential magnetic resonance imaging for evaluating left

- ventricular volume and ejection fraction over time in patients with healed myocardial infarction. *Am J Cardiol* 99:300–306
20. Grimm RA, Stewart WJ, Arheart K, Thomas JD, Klein AL (1997) Left atrial appendage “stunning” after electrical cardioversion of atrial flutter: an attenuated response compared with atrial fibrillation as the mechanism for lower susceptibility to thromboembolic events. *J Am Coll Cardiol* 29:582–589
 21. Ellis K, Ziada KM, Vivekananthan D, Latif AA, Shaaraoui M, Martin D, Grimm RA (2006) Transthoracic echocardiographic predictors of left atrial appendage thrombus. *Am J Cardiol* 97:421–425
 22. Santiago D, Warshofsky M, Li Mandri G, Di Tullio M, Coromilas J, Reiffel J, Homma S (1994) Left atrial appendage function and thrombus formation in atrial fibrillation-flutter: a transesophageal echocardiographic study. *J Am Coll Cardiol* 24:159–164
 23. Weerasooriya R, Khairy P, Litalien J, Macle L, Hocini M, Sacher F, Lellouche N, Knecht S, Wright M, Nault I, Miyazaki S, Scavee C, Clementy J, Haissaguerre M, Jais P (2011) Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up? *J Am Coll Cardiol* 57:160–166
 24. Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, Macle L, Morillo CA, Haverkamp W, Weerasooriya R, Albenque JP, Nardi S, Menardi E, Novak P, Sanders P (2015) Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med* 372:1812–1822
 25. Wong KC, Paisey JR, Sopher M, Balasubramaniam R, Jones M, Qureshi N, Hayes CR, Ginks MR, Rajappan K, Bashir Y, Betts TR (2015) No benefit of complex fractionated atrial electrogram ablation in addition to circumferential pulmonary vein ablation and linear ablation: benefit of complex ablation study. *Circ Arrhythm Electrophysiol* 8:1316–1324
 26. Rolf S, Kircher S, Arya A, Eitel C, Sommer P, Richter S, Gaspar T, Bollmann A, Altmann D, Piedra C, Hindricks G, Piorowski C (2014) Tailored atrial substrate modification based on low-voltage areas in catheter ablation of atrial fibrillation. *Circ Arrhythm Electrophysiol* 7:825–833
 27. Jadidi AS, Lehrmann H, Keyl C, Sorrel J, Markstein V, Minners J, Park CI, Denis A, Jais P, Hocini M, Potocnik C, Allgeier J, Hochholzer W, Herrera-Sidloky C, Kim S, Omri YE, Neumann FJ, Weber R, Haissaguerre M, Arentz T (2016) Ablation of persistent atrial fibrillation targeting low-voltage areas with selective activation characteristics. *Circ Arrhythm Electrophysiol* 9:e002962
 28. Yagishita A, Gimbel JR, De Oliveira S, Manyam H, Sparano D, Cakulev I, Mackall J, Arruda M (2017) Long-term outcome of left atrial voltage-guided substrate ablation during atrial fibrillation: a novel adjunctive ablation strategy. *J Cardiovasc Electrophysiol* 28:147–155