

The influence of the external structures in atrial fibrillation patients: Relationship to focal low voltage areas in the left atrium



Yuichi Hori, Shiro Nakahara^{*}, Naofumi Tsukada, Ayako Nakagawa, Akiko Hayashi, Takaaki Komatsu, Sayuki Kobayashi, Yoshihiko Sakai, Isao Taguchi

Department of Cardiology, Dokkyo Medical University Koshigaya Hospital, Saitama, Japan

ARTICLE INFO

Article history:

Received 4 September 2014

Received in revised form 8 November 2014

Accepted 10 December 2014

Available online 11 December 2014

Keywords:

Atrial fibrillation

Catheter ablation

Electroanatomic mapping

Remodeling

Voltage mapping

ABSTRACT

Introduction: Left atrial (LA) low voltage areas (LVAs) are suggested as an important factor for maintaining atrial fibrillation (AF). The relationship between focal LVAs and anatomical contact is still unclear.

Methods: Thirty paroxysmal AF (PAF) and 30 persistent AF (PsAF) patients underwent high density voltage mapping during sinus rhythm before any radiofrequency applications were performed. The relationship between the LVA (<0.5 mV) and contact area (CoA) demonstrated by enhanced CT and the distance to near external structures were investigated.

Results: The anterior region, posterior wall and left pulmonary vein (LPV) antrum were the three most frequent LVA sites that corresponded to CoA sites, and LVAs mostly overlapped with CoAs (PAF 47/61: 77%, PsAF 63/74: 85%). In the PAF group, patients with posterior-LVAs had a shorter distance to the vertebrae than those without (2.8 ± 1.1 vs. 4.4 ± 1.9 mm; $P = 0.0086$). The distance to the vertebrae was the only predictive factor of the existence of a posterior-LVA and the cut-off value was ≤ 2.9 mm ($P < 0.0001$). Similarly, an LPV-LVA also had the same results (2.0 ± 0.5 vs. 2.7 ± 0.8 mm, $P = 0.0127$) and the cut-off value was ≤ 2.6 mm ($P = 0.0391$). In contrast, the PsAF patients had no difference in the distance when compared to the existence of an LVA.

Conclusions: Anatomical CoAs demonstrated a spatial relationship to the LVAs in AF patients. In PAF patients, the distance to near external structures in the posterior region was a predictive factor for the existence of an LVA and may have had some influence on maintaining AF, while in PsAF patients no relationship was suggested.

© 2014 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Pulmonary vein isolation has been proven to be an effective procedure for maintaining sinus rhythm in atrial fibrillation (AF) patients, while not all patients achieve a successful result [1–3]. The influence of the arrhythmogenic substrates and left atrium (LA) remodeling is suggested to be one of the answers for these outcomes [4–8]. Low voltage areas (LVAs) appear in the LA, which is the result of the progression of remodeling, and are suggested to be one of the important factors for the maintenance of AF by their development of slow conduction and wave collisions [4–6,9–11]. LA remodeling in AF patients is suggested to be associated with continuous stretch and wall stress from the inside, and LVAs are reported to increase in persistent AF (PsAF) patients compared to paroxysmal AF (PAF) patients [5,6,12]. However, as AF itself can promote atrial remodeling, it may just be the result of the continuous stress from AF.

As reported previously, LVAs in the LA are the outcome of LA fibrosis, and the total area of an LVA differs in each patient [13–15], and also does

not exist equally in each region. The wall stress from the inside demonstrated by the shapes of the LA was reported by Hunter et al. and is suggestive of focal remodeling [12].

In enhanced computed tomography (CT) performed in the supine position, some AF patients demonstrated areas of compression in the anterior region, posterior wall of the LA, and left pulmonary vein (LPV) antrum. These anatomical contact areas (CoAs) demonstrated by CT can also be represented as advanced stretched areas due to contact with external structures. The aim of this study was to investigate the distribution of the LVAs in the LA and consider the influence of the near external structures on the CoA, and determine the distance to those structures.

2. Methods

2.1. Patient population

Thirty PAF patients and 30 PsAF patients, who were able to maintain sinus rhythm (SR) after electrical cardioversion, and before ablation, were enrolled. Patients with a prior history of an AF ablation procedure, ischemic heart disease, or those who were not able to maintain SR during the LA mapping, were excluded. Antiarrhythmic drugs were stopped at least 5 half-lives before the procedure. All patients received oral anticoagulation for at least 1 month and underwent trans-esophageal echocardiography to exclude the presence of any thrombi. All patients provided written informed consent before the procedure.

^{*} Corresponding author at: Department of Cardiology, Dokkyo Medical University Koshigaya Hospital, 2-1-50 Minami Koshigaya, Koshigaya, Saitama 343-8555, Japan.
E-mail address: nshiro@dokkyomed.ac.jp (S. Nakahara).

2.2. Electrophysiological study

Every patient underwent high-density 3D LA mapping during SR, before any radiofrequency applications were delivered. PsAF patients were converted to SR by electrical cardioversion and when the patients failed to return to SR within two tries, they were excluded from the study. All procedures were performed with the assistance of a 3D electro-anatomic mapping system (Ensite NavX, St. Jude Medical, Minneapolis, USA). Pre-operative cardiac CT images taken before the procedure were integrated into the electro-anatomic mapping system and the volume of the LA was calculated. Enhanced CT was performed in sinus rhythm in the PAF patients and AF rhythm in the PsAF patients. Every LA was divided into 9 segments for the analysis: Anterior, posterior, inferior, roof, septum, lateral, left atrial appendage (LAA), right pulmonary vein antrum (RPV) and LPV.

The following catheters were introduced: (1) a duodecapolar catheter was placed in the coronary sinus and was also used for a positional reference; (2) a 4 mm tip externally irrigated-tip catheter (Safire Blu, St. Jude Medical) was used for ablation; and (3) a high-density double-loop mapping catheter (20 poles, 20 mm A Focus II, 4 mm bipolar spacing; St. Jude Medical) was used to create the LA geometry and voltage map during SR. After establishing an LA access, intravenous heparin was administered and an activated clotting time in the range of 270 to 330 s was targeted.

2.3. Analysis of the low voltage areas

LVAs were demonstrated by a voltage of <0.5 mV [16–18] by the assistance of the Ensite NavX system and the analysis was performed in both the PAF ($n = 30$) and PsAF ($n = 30$) patients. In each segment, the total number of LVAs and surface area of the LVAs (cm^2) was documented to compare the distribution of the LVAs in the LA. The areas where LVAs were frequently found, such as the anterior and posterior areas and around the mitral valve, were mapped carefully making sure of an adequate catheter contact.

2.4. Relationship between the contact areas and low voltage areas

All preoperative cardiac enhanced CT scans were performed in the systolic phase in both the PAF and PsAF patients. In the axial view of the enhanced CT, the LA demonstrated three compressed parts which were (1) from the sinus of Valsalva (non-coronary cusp) to the ascending aorta, which was documented on the anterior region of the LA, (2) the area following along the descending aorta, that runs nearest to the level of the LPV, of which

some patients demonstrated a compressed part at the antrum of the LPV, and (3) the area where the vertebrae was located behind the LA, and some patients exhibited a compressed area in the posterior region (Fig. 1A). When those compressed areas were observed on the enhanced CT, they were traced inside the LA in 2–3 mm slices and particular areas were created on the 3D LA maps (Fig. 1B). Those areas were observed on the enhanced CT, but as they had no evidence of compression and could disappear in different positions, those areas were determined as contact areas (CoAs). The esophagus is also located in the posterior region, but since it did not create a compressed area in the LA, the anatomical relationship was hard to examine, thus it was not included in this study. The total number and area (cm^2) of the CoAs in the three regions were documented, and the overlapping area with the LVAs was also analyzed (Fig. 2).

2.5. Low voltage area and the distance to the near external structures

A comparison of the existence of LVAs and the distance to the near external structures was made between both the PAF and PsAF patients. In the anterior region there were frequent LVA and CoA sites, which mostly overlapped with each other but because most of the anterior wall in the AF patients bordered the aorta [19] and demonstrated a CoA, the distance to the external structures was considered for the posterior-LVA and LPV-LVA only. The distance to the external structures was measured in the axial view of the enhanced CT and the nearest point between (1) the vertebrae–posterior and (2) descending aorta–LPV, was documented (Fig. 1C). The existence of a posterior-LVA and LPV-LVA was considered according to the following factors: (1) weight (2) hypertension, (3) diabetes mellitus, (4) age, (5) AF duration, (6) left atrial diameter, (7) LA volume index (LA volume/body surface area; mL/m^2), and (8) distance to the near external structures.

2.6. Statistical analysis

All continuous variables are expressed as the mean \pm SD. For comparing continuous variables, an unpaired Student's *t*-test was used and a $P < 0.05$ was considered statistically significant. To confirm the independent predictive factors of the existence of an LVA, the factors selected to be tested in the multivariate analysis were those with a *P* value of less than 0.2 in the univariate models. A receiver operating characteristic (ROC) analysis was used to assess whether the distance to the near external structures was associated with the existence of an LVA.

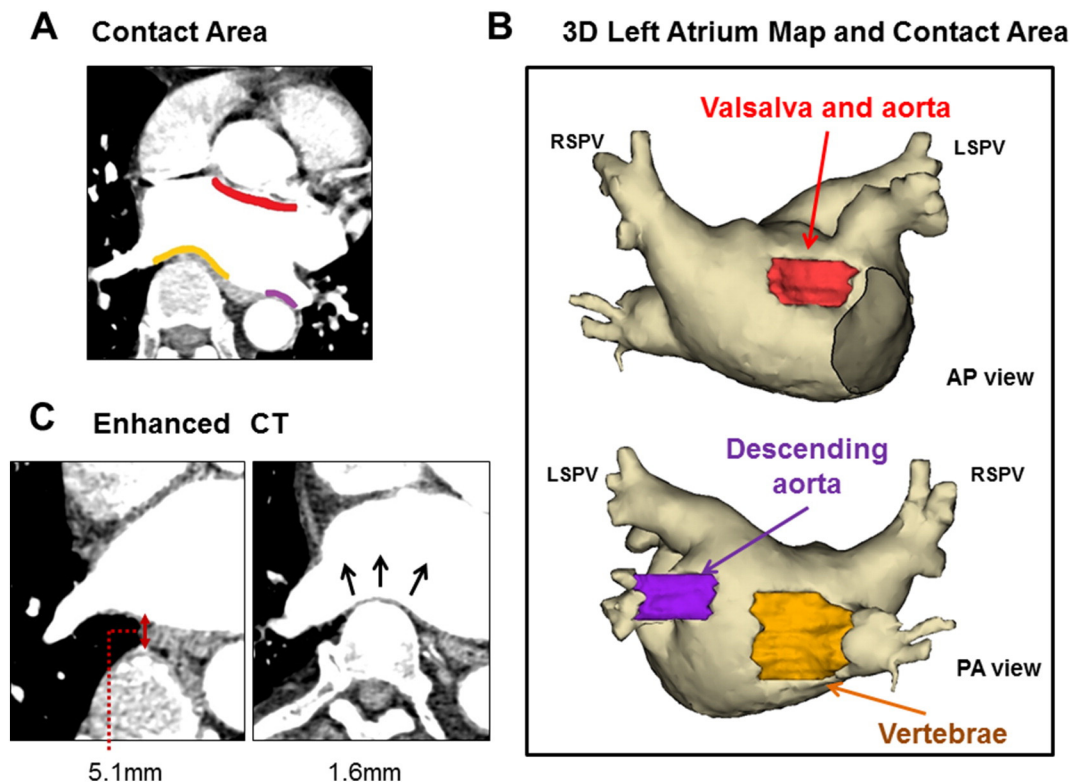


Fig. 1. Contact area modeling. A: The contact area (CoA) was traced inside the LA. Anterior-CoA: red, posterior-CoA: yellow, and left pulmonary vein (LPV)-CoA: purple. B: A CoA created in the 3D left atrium (LA) map. C: The distance between the near external structures was measured in the enhanced CT. The distance in the case the left panel is 5.1 mm and in the case the right panel 1.6 mm. The right panel shows the CoA as an additional stretched area of the posterior wall of the LA (LSPV = left superior pulmonary vein; RSPV = right superior pulmonary vein).

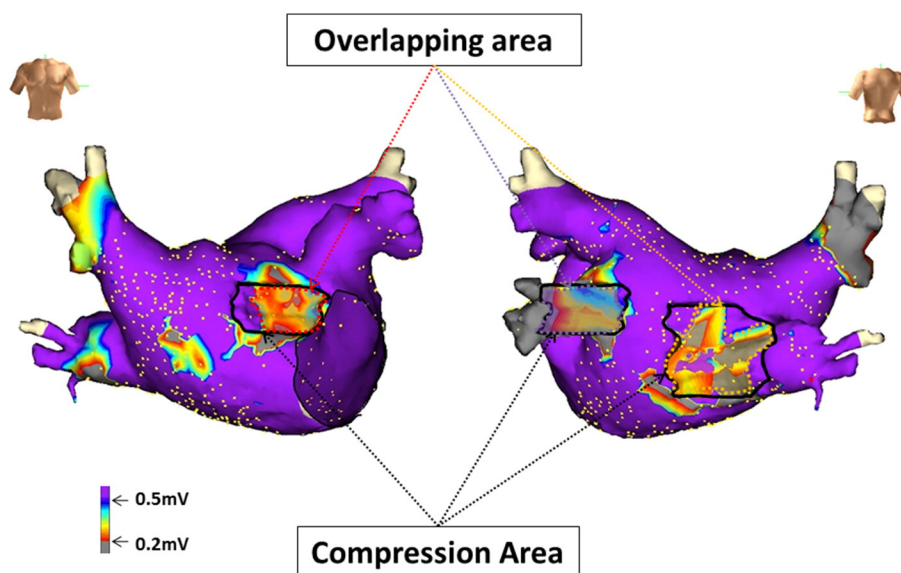


Fig. 2. Relationship between the CoA and the low voltage area (LVA) (<math><0.5\text{ mV}</math>) in the 3D LA map (same patient as in Fig. 1).

3. Results

3.1. Patient characteristics

The baseline patient characteristics are shown in Table 1. The average number of recorded points for each LA was 670 ± 376 points in the PAF patients and 696 ± 256 points in the PsAF patients.

3.2. Comparison of the anatomical characteristics between the LVAs and CoAs

A total of 105 LVAs (total surface area: 203.3 cm^2) and 62 CoAs (total surface area: 234.4 cm^2) were documented in 30 PAF patients, and 121 LVAs (total surface area: 566.6 cm^2) and 82 CoAs (total surface area: 438.1 cm^2) in 30 PsAF patients. The area of the LVAs in the PsAF patients was significantly greater than that in the PAF patients (17.5 ± 10.4 vs. $10.0 \pm 6.3\text{ cm}^2$, $P = 0.0035$).

Both the PAF and PsAF patients demonstrated LVAs frequently in the anterior (PAF; 75.7 cm^2 in 27 pt, PsAF; 295.2 cm^2 in 30 pt), posterior (PAF; 24.9 cm^2 in 15 pt, PsAF; 83.8 cm^2 in 22 pt), and LPV (PAF; 31.6 cm^2 in 19 pt, PsAF; 57.0 cm^2 in 22 pt) regions, which corresponded to CoA sites (Fig. 3). The CoAs documented in the cardiac enhanced CT were the anterior (PAF; 100.5 cm^2 in 27 pt, PsAF; 167.1 cm^2 in 30 pt), posterior (PAF 88.5 cm^2 in 19 pt, PsAF 201.8 cm^2 in 28 pt), and LPV

Table 1
Patient characteristics.

	Paroxysmal AF (n = 30)	Persistent AF (n = 30)	P
Age (years)	65 ± 9	66 ± 10	0.1139
Gender (male/female)	16/14	20/10	0.4292
Weight (kg)	61 ± 12	62 ± 14	0.2457
Hypertension (%)	11 (37%)	19 (63%)	0.0707
Diabetes mellitus (%)	3 (10%)	4 (13%)	1.0000
BNP (pg/mL)	37 ± 46	176 ± 90	<0.001
LA volume index (mL/m ²)	80 ± 15	106 ± 21	<0.001
Left atrial diameter (mm)	40 ± 6	45 ± 6	<0.001
Left ventricular ejection fraction	0.72 ± 0.06	0.65 ± 0.09	0.002
Distance to vertebrae (mm)	3.6 ± 1.7	2.2 ± 1.2	0.0036
Distance to descending aorta (mm)	2.3 ± 0.7	2.0 ± 0.9	0.4495
Duration of continuous AF (months)	–	2.4 (1.0, 3.0)	–

Values are expressed as the mean \pm SD, or median (quartiles).

(PAF; 35.4 cm^2 in 16 pt, PsAF; 69.2 cm^2 in 24 pt) regions (Fig. 4, green-bar).

In the PAF patients (n = 30), a total of 47 overlapping areas were documented, which was 45% (47/105) of the total number of LVAs and 27% ($55/203.3\text{ cm}^2$) of the total surface area of the LVAs. In the PsAF patients (n = 30), a total of 63 overlapping areas were documented, which was 52% (63/121) of the total number of the LVAs and 27% ($155.7/566.6\text{ cm}^2$) of the total surface area of the LVAs. In the 3 regions (anterior, posterior, LPV) 77% (47/61) of the LVAs overlapped with CoAs in the PAF patients and 85% (63/74) overlapped in the PsAF patients.

The anterior wall was the most frequent region for LVAs to occur in both the PAF and PsAF patients. In the PAF patients, a total of 37% ($75.7/203.3\text{ cm}^2$) of the LVAs was documented in the anterior region and in the PsAF patients it was 52% ($295.2/566.6\text{ cm}^2$). In the PAF patients, 24 patients demonstrated an overlapping area with an anterior-CoA and the total area was 35.5 cm^2 , which was 47% ($35.5/75.7\text{ cm}^2$) of the total LVAs in the anterior region (Fig. 4A and C; blue & red bar). In the PsAF patients, every patient demonstrated an overlapping area with the anterior-CoA and the total overlapping area was 95.0 cm^2 , which was 32% ($95.0/295.2\text{ cm}^2$) of the total LVAs in the anterior wall (Fig. 4B and D, blue & red bars). The total LVA in the posterior region was 24.9 cm^2 (n = 15) in the PAF and 83.8 cm^2 (n = 22) in the PsAF patients (Fig. 4, blue bar). In the PAF patients the total overlapping area between the posterior-CoA was 9.8 cm^2 (n = 11), which was 39% ($9.8/24.9\text{ cm}^2$) of the total posterior-LVA (Fig. 4A and C, blue & red bars), and in the PsAF patients, the overlapping area was 23.3 cm^2 (n = 19), which was 45% ($37.4/83.8\text{ cm}^2$) of the total LVAs in the posterior region (Fig. 4B and D, blue & red bars). The total LVA in the LPV was 31.6 cm^2 (n = 19) in the PAF and 57.0 cm^2 (n = 22) in the PsAF patients (Fig. 4, blue bar). The overlapping area between the LPV-CoAs was 9.7 cm^2 (n = 12) in the PAF (Fig. 3A and C, red bar) and 23.3 cm^2 (n = 19) in the PsAF patients (Fig. 4B and D, red bar). The percentage of the total LPV-LVA was 31% ($9.7/31.6\text{ cm}^2$) in the PAF and 41% ($23.3/57.0\text{ cm}^2$) in the PsAF patients (Fig. 4C and D, red & blue bars).

3.3. LVAs in the posterior region and the distance to the vertebrae

In this study 15 PAF patients demonstrated an LVA on the posterior wall of the LA. The group with a posterior-LVA had a significantly shorter distance from the vertebrae to the posterior wall compared to the group without a posterior-LVA (posterior-LVA(+) vs. posterior-LVA(–) = 2.8 ± 1.1 vs. $4.4 \pm 1.9\text{ mm}$; $P = 0.0086$). Additionally, a

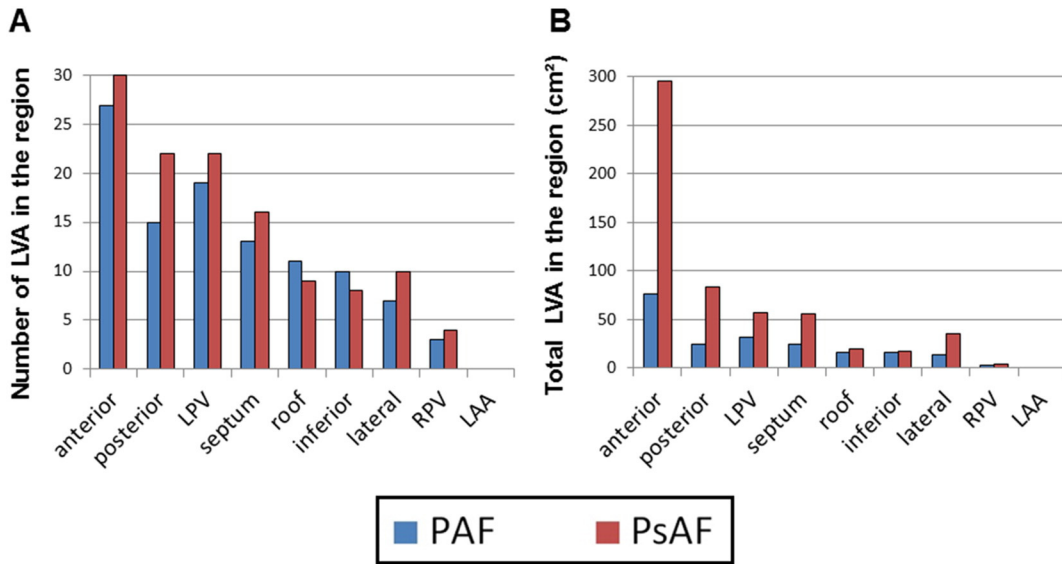


Fig. 3. Anatomical distribution of the LVAs. A: Number of LVAs in each LA region. B: Total LVA in each LA region.

multivariate analysis was performed between the factors that had a $P \leq 0.02$, and the distance to the vertebrae was the only predictive factor for the existence of a posterior-LVA ($P = 0.0491$; Table 2). In the PAF patients, an ROC analysis demonstrated that the distance to a vertebrae of ≤ 2.9 mm had a sensitivity of 76.5%, and specificity of

92.3% for predicting the presence of an LVA in the posterior wall (area under the curve = 0.844; $P < 0.0001$).

In the PsAF patients, the distance to the vertebrae was significantly shorter than the distance measured in the PAF patients (PsAF vs. PAF = 2.2 ± 1.2 vs. 3.1 ± 1.7 mm $P = 0.003$, Table 1). As the

Total numbers of areas in the 3 region

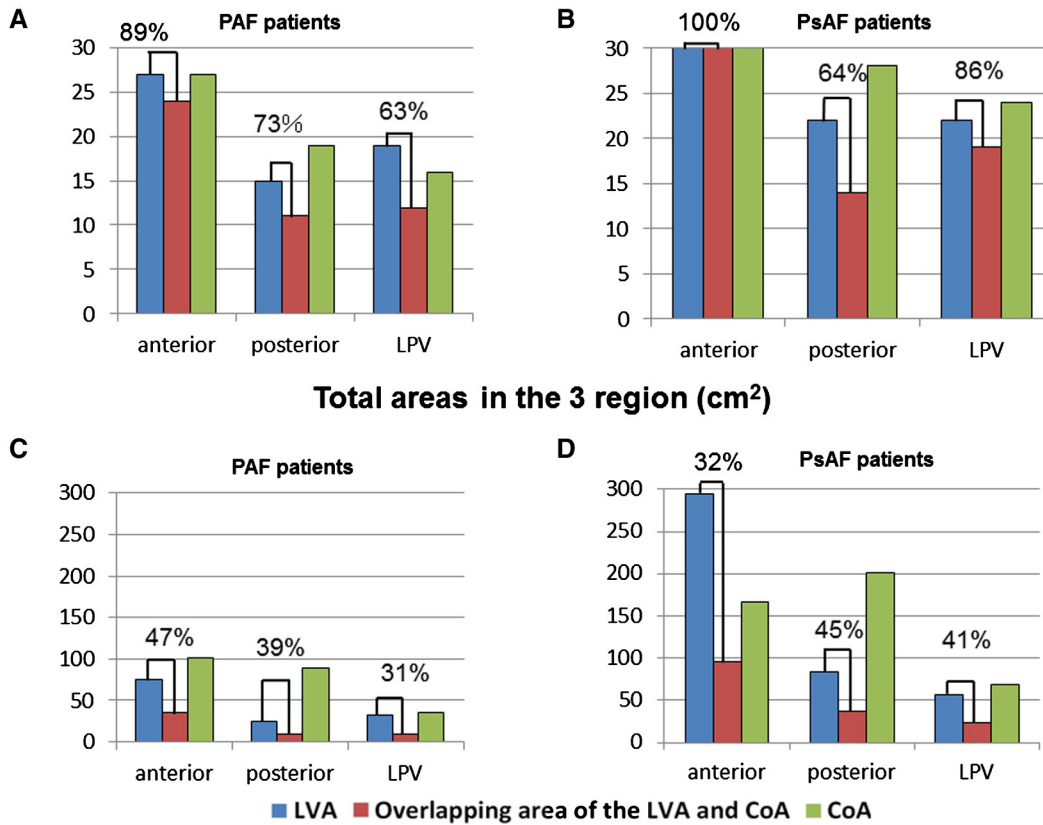


Fig. 4. Relationship between the LVA, CoA and overlapping area between the LVAs and CoAs. A: Total number in each region in the PAF patients and the percentage of the overlapping area of the LVAs. B: Total number in each region in the PsAF patients and the percentage of the overlapping area of the LVAs. C: Total area in each region in the PAF patients and the percentage of the overlapping area of the LVAs. D: Total area in each region in the PsAF patients and the percentage of the overlapping area of the LVAs.

Table 2
Multivariate analysis of the predictors of the existence of a posterior LVA.

Posterior-LVA	Paroxysmal AF (n = 30)				Persistent AF (n = 30)			
	LVA(+)	LVA(-)	Univariate P value	Multivariate P value	LVA(+)	LVA(-)	Univariate P value	Multivariate P value
n	15	15			22	8		
Weight (kg)	60 ± 12	63 ± 11	0.2178	–	62 ± 16	65 ± 9	0.8993	–
Hypertension (%)	5 (33%)	6 (40%)	0.7046	–	14 (67%)	5 (63%)	0.9545	–
Diabetes mellitus (%)	1 (7%)	2 (13%)	0.5393	–	1 (5%)	3 (37%)	0.9351	–
Age (y)	65 ± 7	62 ± 10	0.1275	0.8838	65 ± 7	67 ± 8	0.9028	–
AF duration (year)	–	–	–	–	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	0.6382	–
Left atrial diameter (mm)	39 ± 6	41 ± 5	0.3744	–	43 ± 6	48 ± 5	0.8958	–
LA volume index (mL/m ²)	79 ± 14	82 ± 15	0.8733	–	97 ± 21	116 ± 13	0.0954	–
Distance to vertebrae (mm)	2.8 ± 1.1	4.4 ± 1.9	0.0033	0.0491	2.2 ± 1.2	1.9 ± 1.3	0.4424	–

Values are expressed as the mean ± SD, or median (quartiles).

documented distance to the vertebrae was shorter in the PsAF patients, no difference in the distance was shown when compared for the existence of a posterior-LVA (posterior-LVA(+) vs. posterior-LVA(-) = 2.2 ± 1.2 vs. 1.9 ± 1.3 mm P = 0.302).

3.4. LVAs in the LPV and the distance to the descending aorta

The patients with an LPV-LVA also had a significantly shorter distance from the descending aorta to the LPV compared to those without (LPV-LVA(+) vs. LPV-LVA(-) = 2.0 ± 0.5 mm vs. 2.7 ± 0.8 mm, P = 0.0127). A multivariate analysis showed that the distance to the descending aorta was the only predictive factor for the existence of an LPV-LVA (P = 0.0405; Table 3). An ROC analysis demonstrated that a distance to the descending aorta of ≤2.6 mm had a sensitivity of 95.0%, and specificity of 70.0% for predicting the presence of an LPV-LVA (area under the curve = 0.793; P = 0.01). In the PsAF patients, 22 (73%) demonstrated an LVA in the LPV. The groups with an LPV-LVA had no significant difference in the distance of the descending aorta to the LPV (1.9 ± 0.9 vs. 2.3 ± 1.1 mm, P = 0.0728).

4. Discussion

In our study, the influence of the near external structures on focal low voltage regions in patients with AF was examined by both the CoA demonstrated in the enhanced CT and the distance from the LA to the surrounding structures. The major findings were that (1) in both the PAF and PsAF patients, the anterior, posterior and LPV regions were the three most frequent regions that had an LVA, (2) most of the LVAs in the anterior, posterior wall and LPV regions overlapped with the CoAs, and (3) in the PAF patients, the existence of a focal LVA located on both the posterior wall and LPV antrum was associated with the distance to the near external structures, while in the PsAF patients, those LVA areas had no relationship with the distance to the external structures.

These findings suggest that dilatation of the LA shortens the distance to particular external structures, and these anatomical factors may have

an influence on the existence of some progressive factors for the electrical remodeling in particular LA regions.

4.1. Relationship between the low voltage areas and CoAs

We defined an LVA as an area with an amplitude <0.5 mV in order to delineate the greatly damaged areas in the LA [16,18]. The anterior, posterior and LPV regions were the 3 most frequent regions where an LVA was documented and corresponded to the segments of the CoAs. In the three regions, most of the LVAs overlapped with CoAs in both the PAF (63–89%) and PsAF (64–100%) patients (Fig. 3). In this study, the CoAs were demonstrated by enhanced CT, which was performed in the supine position. These areas may change or disappear in some different positions or a CT taken in a different phase, but as the three most frequent LVA sites corresponded to the CoA sites, the relationship between the two is suggestive.

4.2. Low voltage area in the posterior region and the distance to the vertebrae

By comparing the PAF patients with the existence of an LVA in the posterior wall, the group with a posterior-LVA demonstrated a significantly shorter distance to the vertebrae. The influence of the anatomical contact was suggested by the relationship to the CoAs, and additionally, the distance to the vertebrae was a predictive factor for the existence of a posterior-LVA. As indicated from the ROC analysis (a cut off of ≤2.9 mm), the distance to the near external structures may have some influence on the existence of a posterior-LVA. On the other hand, in the PsAF patient group, there was no significant difference in the distance to the vertebrae when compared to the existence of a posterior-LVA. The dilatation of the LA may shorten the distance to the vertebrae, however, the small number of patients in this study may also have influenced the results.

When comparing the PAF and PsAF patients, the documented distance was shorter in the PsAF patients. As all the CTs in the PsAF patients were performed during an AF rhythm, the direct comparison between

Table 3
Multivariate analysis of the predictors of the existence of a left PV antrum LVA.

LPV-LVA	Paroxysmal AF (n = 30)				Persistent AF (n = 30)			
	LVA(+)	LVA(-)	Univariate P value	Multivariate P value	LVA(+)	LVA(-)	Univariate P value	Multivariate P value
n	19	11			22	8		
Weight (kg)	63 ± 11	60 ± 10	0.0928	0.3038	64 ± 16	59 ± 9	0.3467	–
Hypertension (%)	7 (37%)	4 (36%)	0.9791	–	13 (59%)	6 (75%)	0.4148	–
Diabetes mellitus (%)	3 (16%)	0 (0%)	0.0869	0.9935	3 (14%)	1 (13%)	0.9351	–
Age (y)	60 ± 9	68 ± 8	0.1275	0.9839	66 ± 7	66 ± 5	0.3225	–
AF duration (year)	–	–	–	–	2.0 (1.0, 3.0)	1.5 (1.0, 2.5)	0.3071	–
Left atrial diameter (mm)	42 ± 7	38 ± 3	0.3744	–	43 ± 6	47 ± 4	0.2465	–
LA volume index (mL/m ²)	75 ± 15	84 ± 13	0.2772	–	105 ± 23	106 ± 17	0.6935	–
Distance to LPV (mm)	2.0 ± 0.5	2.7 ± 0.8	0.0053	0.0402	1.9 ± 0.7	2.3 ± 1.1	0.0728	–

Values are expressed as the mean ± SD, or median (quartiles).

the two groups may have no importance. However as the total posterior-LVAs were higher in the PsAF patients, the closer distance of the posterior wall to the vertebrae due to LA dilatation and continuous AF may have had some influence on the progression of the posterior-LVA.

4.3. Low voltage area in the LPV and the distance to the descending aorta

In the PAF patients, similar to the posterior-LPV, the distance to the descending aorta was a predictive factor for an LPV-LVA, while no relationship was documented in the PsAF patients. When comparing the PAF and PsAF patients, no significant difference was shown for the distance to the descending aorta (PAF vs. PsAF = 2.3 ± 0.7 mm vs. 2.0 ± 0.9 mm $P = 0.4495$). Continuous AF and LA dilatation may have had a smaller influence on the distance to the descending aorta.

4.4. Relationship between the LA volume index and posterior-LVA and LPV-LVA

When the LA volume index was compared for the existence of a focal LVA in the posterior and LPV regions, there were no significant differences in either the PAF or PsAF patients. The relationship between an LVA and the LA volume has been reported [8,17], but as our results were focused only on the focal LVAs in posterior wall and LPV region, the results may have differed from the previous data. Our data suggests that focal LVAs in the posterior and LPV regions are influenced by contact with the external structures. In the patients with a focal LVA, the LA was anatomically close to the external structures in the posterior region, thus the limited space between the ascending aorta and external structures in posterior region may have influenced the progress of the LA dilatation. However as the study was performed in a small number of patients, further study is needed with a larger number of patients.

4.5. Atrium stretch and AF maintenance

Suspected from the CT, the CoAs could also be represented as an advanced stretched area due to a contact from the external structures (Fig. 1C). Atrial stretch is suggested to be a progressive factor of LA remodeling and also is reported to be an important factor in AF maintenance [20–22]. Myocardial stretch is suggested to be one of the causes of the changes in the electrophysiological properties of the heart, which are represented as electrical remodeling and cell death. The existence of stretch-activated ion channels (SACS) has been documented in cardiac cells and these SACS are reported to explain the observations of the electrophysiological changes, such as the changes in the action potential duration (APD) [15]. In the human heart, atrial dilatation and stretch suggest a predisposition to AF by the relationship to the LA pressure and the changes in the dominant frequency values [20,23]. Pak H.N. et al. reported that low voltage areas presented in the LA anterior wall correlate with the LA-aorta contact region, and those areas are also related to the incidence of atrial tachycardia [19]. Similarly in a sheep model, stretch-induced AF (SAF) was demonstrated by high-frequency focal discharges that generate fibrillatory conduction and wavebreaks, which may play a major role in the maintenance of the arrhythmia [21,22]. In our study we suggested the influence of CoAs in the LA, and the CoAs were also suspected to be in some of the additionally stretched areas. In this study no arrhythmogenic factors were suggested, but by considering the influence from the external structures, there is the possibility that they played a role in the AF maintenance by an electrophysiological change due to SACS, or the development of slow conduction and wave collisions induced by atrial fibrosis. However the relationship between the external structures and arrhythmogenic substrates still remains unclear and needs further investigation.

5. Limitations

Firstly, the CTs in the PsAF patients were performed during an AF rhythm and the voltage map was documented in SR, which may have led to a slight difference in the anatomical analysis. As PsAF patients demonstrated an LVA more frequently than the PAF patients, the group without an LVA was comparatively small in the PsAF patients, which may have led to an insufficient consideration. In this study, the CoA was documented in the axial view of the enhanced CT, which was performed in the supine position. Those CoA sites demonstrated by the CT may have changed or disappeared when the patients changed their position, and the actual intensity of the stretch was also unknown.

6. Conclusions

The LVAs documented in AF patients had a relationship to the CoAs demonstrated in the enhanced CT. In the PAF patients the distance from the near external structures in the posterior region of the LA was a predictive factor for the existence of an LVA for both the posterior wall and left PV antrum. As the LVAs in the LA had an unequal distribution, some factors were suspected to cause the progression of the low voltage. Contact from the external structures may be one of the factors that had an influence on the existence of an LVA in particular regions such as the anterior, posterior wall and left PV antrum regions.

Conflict of interest

None.

References

- [1] M. Haissaguerre, P. Jais, D.C. Shah, et al., Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins, *N. Engl. J. Med.* 339 (1998) 659–666.
- [2] M.A. Allesie, P.A. Boyden, A.J. Camm, et al., Pathophysiology and prevention of atrial fibrillation, *Circulation* 103 (2001) 769–777.
- [3] R. Latchamsetty, F. Morady, Long-term benefits following catheter ablation of atrial fibrillation, *Circ. J.* 77 (2013) 1091–1096.
- [4] B. Ghorraani, R. Dalvi, S. Gizurason, et al., Localized rotational activation in the left atrium during human atrial fibrillation: relationship to complex fractionated atrial electrograms and low-voltage zones, *Heart Rhythm* 10 (2013) 1830–1838.
- [5] A.W. Teh, P.M. Kistler, G. Lee, et al., Electroanatomic remodeling of the left atrium in paroxysmal and persistent atrial fibrillation patients without structural heart disease, *J. Cardiovasc. Electrophysiol.* 23 (2012) 232–238.
- [6] A.S. Jadidi, E. Duncan, S. Miyazaki, et al., Functional nature of electrogram fractionation demonstrated by left atrial high-density mapping, *Circ. Arrhythm. Electrophysiol.* 5 (2012) 32–42.
- [7] M.K. Stiles, B. John, C.X. Wong, et al., Paroxysmal lone atrial fibrillation is associated with an abnormal atrial substrate: characterizing the “second factor”, *J. Am. Coll. Cardiol.* 53 (2009) 1182–1191.
- [8] J.H. Park, H.N. Pak, E.J. Choi, et al., The relationship between endocardial voltage and regional volume in electroanatomical remodeled left atria in patients with atrial fibrillation: comparison of three-dimensional computed tomographic images and voltage mapping, *J. Cardiovasc. Electrophysiol.* 20 (2009) 1349–1356.
- [9] N. Lellouche, E. Buch, A. Celigoj, et al., Functional characterization of atrial electrograms in sinus rhythm delineates sites of parasympathetic innervation in patients with paroxysmal atrial fibrillation, *J. Am. Coll. Cardiol.* 50 (2007) 1324–1331.
- [10] K.C. Roberts-Thomson, P.M. Kistler, P. Sanders, et al., Fractionated atrial electrograms during sinus rhythm: relationship to age, voltage, and conduction velocity, *Heart Rhythm* 6 (2009) 587–591.
- [11] K. Miyamoto, T. Tsuchiya, S. Narita, et al., Bipolar electrogram amplitudes in the left atrium are related to local conduction velocity in patients with atrial fibrillation, *Europace* 11 (2009) 1597–1605.
- [12] R.J. Hunter, Y. Liu, Y. Lu, W. Wang, R.J. Schilling, Left atrial wall stress distribution and its relationship to electrophysiological remodeling in persistent atrial fibrillation, *Circ. Arrhythm. Electrophysiol.* 5 (2012) 351–360.
- [13] A.S. Jadidi, H. Cochet, A.J. Shah, et al., Inverse relationship between fractionated electrograms and atrial fibrosis in persistent atrial fibrillation: combined magnetic resonance imaging and high-density mapping, *J. Am. Coll. Cardiol.* 62 (2013) 802–812.
- [14] A. Boldt, U. Wetzel, J. Lauschke, et al., Fibrosis in left atrial tissue of patients with atrial fibrillation with and without underlying mitral valve disease, *Heart* 90 (2004) 400–405.
- [15] A.M. De Jong, A.H. Maass, S.U. Oberdorf-Maass, R.A. De Boer, W.H. Van Gilst, I.C. Van Gelder, Cyclical stretch induces structural changes in atrial myocytes, *J. Cell. Mol. Med.* 17 (2013) 743–753.

- [16] A.W. Teh, P.M. Kistler, G. Lee, et al., Long-term effects of catheter ablation for lone atrial fibrillation: progressive atrial electroanatomic substrate remodeling despite successful ablation, *Heart Rhythm*. 9 (2012) 473–480.
- [17] A. Verma, O.M. Wazni, N.F. Marrouche, et al., Pre-existent left atrial scarring in patients undergoing pulmonary vein antrum isolation: an independent predictor of procedural failure, *J. Am. Coll. Cardiol.* 45 (2005) 285–292.
- [18] M. Fiala, D. Wichterle, J. Chovancik, et al., Left atrial voltage during atrial fibrillation in paroxysmal and persistent atrial fibrillation patients, *Pacing Clin. Electrophysiol.* 33 (2010) 541–548.
- [19] H.N. Pak, Y.S. Oh, H.E. Lim, Y.H. Kim, C. Hwang, Comparison of voltage map-guided left atrial anterior wall ablation versus left lateral mitral isthmus ablation in patients with persistent atrial fibrillation, *Heart Rhythm*. 8 (2011) 199–206.
- [20] K. Yoshida, M. Ulfarsson, H. Oral, et al., Left atrial pressure and dominant frequency of atrial fibrillation in humans, *Heart Rhythm*. 8 (2011) 181–187.
- [21] J. Kalifa, J. Jalife, A.V. Zaitsev, et al., Intra-atrial pressure increases rate and organization of waves emanating from the superior pulmonary veins during atrial fibrillation, *Circulation* 108 (2003) 668–671.
- [22] M. Yamazaki, L.M. Vaquero, L. Hou, et al., Mechanisms of stretch-induced atrial fibrillation in the presence and the absence of adrenergic stimulation: interplay between rotors and focal discharges, *Heart Rhythm*. 6 (2009) 1009–1017.
- [23] Y. Hori, S. Nakahara, T. Kamijima, et al., Influence of left atrium anatomical contact area in persistent atrial fibrillation, *Circ. J.* 78 (2014) 1851–1857.