Influence of Left Atrium Anatomical Contact Area in Persistent Atrial Fibrillation
– Relationship Between Low-Voltage Area and Fractionated Electrogram –
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**Background:** Atrial low-voltage areas are suggested to be related to maintenance of atrial fibrillation (AF). The influence of the left atrium (LA) contact area (CoA) has not been investigated.

**Methods and Results:** Twenty-two persistent AF patients underwent high-density mapping during AF and sinus rhythm (SR). Three representative CoA regions in the LA (ascending aorta: anterior wall; descending aorta: inferior pulmonary vein [LIPV]; and vertebrae: posterior wall) were identified. Electrogram analysis of both high dominant frequency (high-DF; >8Hz) and complex fractionated atrial electrogram (con-CFAE; <50ms) regions during SR was done. The anatomical relationship between CoA and both the very low-voltage areas (vLVA; <0.2mV) and high-frequency sources was determined. Forty-seven vLVA (194.4 cm²) and 60 CoA (337.0 cm²) were documented, and 32 vLVA directly overlapped CoA. The vLVA were preferentially found in the anterior (45%) and posterior (13%) walls of the LA, and in the LIPV (13%), and corresponded to CoA sites. The mean voltage during SR at high-DF sites was significantly lower than that at con-CFAE sites (0.62 vs. 1.54 mV; P<0.0001). Seventy-two percent of high-DF sites overlapped CoA, while 54% of con-CFAE did. Furthermore, 44% of high-DF surface area directly overlapped CoA, while only 19% of con-CFAE did.

**Conclusions:** Very low-voltage regions had a strong association with CoA. Sites with CoA had a higher incidence of fractionated electrograms both during SR and AF. (Circ J 2014; 78: 1851–1857)

**Key Words:** Atrial fibrillation; Catheter ablation; Fractionated electrogram

**Pulmonary vein (PV) isolation has been proven to be an effective procedure in paroxysmal atrial fibrillation (AF) by blocking the triggers, but still has a low success rate in persistent AF.**

Increasing arrhythmogenic substrates that develop in the atrium are suggested to be 1 of the reasons for this, and a reduction in those substrates such as via complex fractionated atrial electrogram (CFAE), high dominant frequency (high-DF), and focal impulse and rotor modulation ablation methods is considered.

Low-voltage areas, which develop slow conduction and wave collisions, are also suggested to be an important factor in the maintenance of AF. Persistent AF is reported to present more in low-voltage areas than is paroxysmal AF, and that may be an important aspect regarding the difference in the maintenance of those arrhythmias. But, given that AF itself can promote atrial remodeling, low voltage area can be simply a result of the continuous stress from AF.

The progression of low-voltage areas within the human atrium has not been clearly described. We focused on the contact area (CoA) on the left atrium (LA) of external anatomical structures such as the aorta and vertebrae. The aim of this study was to investigate whether CoA were involved in LA remodeling, and to identify an anatomical and electrical relationship between CoA and higher frequency sources within the LA.

**Methods**

**Subjects:** Twenty-two persistent AF patients who were able to be maintained in sinus rhythm (SR) after electrical cardioversion, and
Electrophysiological Study

Every patient underwent high-density 3-D LA mapping during AF and SR, before any radiofrequency application was delivered. All procedures were performed using a 3-D electro-anatomic mapping system (Ensite NavX with CFE software, St. Jude Medical, Minneapolis, MN, USA). Preoperative cardiac computed tomography (CT) was integrated into the electro-anatomic mapping system and the volume of the LA was calculated.

Various catheters were used, as follows: (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, St. Paul, MN, USA) was used for ablation; and (3) a high-density double-loop mapping catheter (20-pole, 20-mm A Focus II, 4-mm bipolar spacing; St. Jude Medical) was used to create the LA geometry, CFAE map and voltage map during SR. After establishing LA access, i.v. heparin was given and activated clotting time in the range of 270–330 s was targeted.

First the LA geometry and high-density CFAE maps were created by using the double-loop multipolar catheter, and then the patients were converted to SR by electrical cardioversion. When the patients failed to return to SR after 2 attempts, they were excluded from the study. After electrical cardioversion was completed, and after waiting 5 min for SR to become stable, a voltage map was then constructed. Every LA map during AF and SR was divided into 11 segments for analysis: anterior; posterior; inferior; roof; septum; lateral; LA appendage; right superior PV (RSPV); right inferior PV (RIPV); left superior PV (LSPV); and left inferior PV (LIPV).

CoA Modeling

Enhanced CT of the LA showed 3 areas that could be expected to be compressed by peripheral structures. The 3 areas were: (1) from the Valsalva (non-coronary cusp) to the ascending aorta where it runs in front of the LA and where a partially compressed area is documented in the anterior wall; (2) the area following along the descending aorta, that runs nearest to the level of the LIPV, of which some patients had a
compressed part at the antrum of the LIPV; and (3) the area where the vertebrae is located behind the LA that is influenced by LA dilatation or distortion of the vertebrae, where some patients exhibit a compressed area in the posterior region. By tracing the compressed areas inside the LA in all 2–3-mm slices on CT, a particular area was created in the 3-D LA maps and those 3 areas were determined to be CoA (Figures 1A, B).

CFAE and DF Mapping During AF
High-density mapping during AF was performed and the automatic “CFE-mean” and “DF” detection algorithm of NavX (St. Jude Medical) was applied to create the CFAE and DF maps. Recording was done for at least 5 s at each LA site, with detection of any electrograms exceeding 0.05 mV. Continuous CFAE (con-CFAE) was defined as CFE-mean <50 ms with a refractory period setting of 40 ms. The high-DF cut-off was set at 8 Hz according to previous studies. The surface area of con-CFAE and high-DF was created by the NavX system and the total surface of those sites and the area of overlap with CoA were calculated and analyzed.

SR Voltage Map
Voltage maps were constructed when SR was judged to be stable. The mean bipolar voltage, deflection and duration were measured for each bipolar electrogram. The borders of the con-

<table>
<thead>
<tr>
<th>Table. Patient Characteristics</th>
<th>Subjects (n=22)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>66±6</td>
</tr>
<tr>
<td>Gender (M/F)</td>
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</tr>
<tr>
<td>BMI</td>
<td>24.1±3.2</td>
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<tr>
<td>Duration of continuous AF (years)</td>
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<td>Longstanding (&gt;1 year)</td>
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<td>Left atrial volume (ml)</td>
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<tr>
<td>Left atrial diameter (mm)</td>
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<td>LVEF (%)</td>
<td>66±8</td>
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<td>Hypertension</td>
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<tr>
<td>Diabetes mellitus</td>
<td>4</td>
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<tr>
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<tr>
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</tr>
<tr>
<td>Posterior</td>
<td>6.7 (n=21)</td>
</tr>
<tr>
<td>LIPV</td>
<td>2.1 (n=17)</td>
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Data given as n (%) or mean±SD.
BMI, body mass index; CoA, contact area; LIPV, left inferior pulmonary vein; LVEF, left ventricular ejection fraction.

Figure 2. Relationship between very low-voltage area (vLVA) and contact area (CoA). (A) Number of vLVA in each segment and the number of vLVA that overlap CoA. The 3 segments (anterior, posterior, and left inferior pulmonary vein [LIPV] regions) where CoA were found, were the 3 most frequent regions of vLVA occurrence. (B) The total number and the 3 representative segments (anterior, LIPV, and posterior regions) of vLVA (cm²) and CoA overlap areas (cm²). LSPV, left superior pulmonary vein; RSPV, right superior pulmonary vein.
CFAE and high-DF sites were outlined on the voltage map during SR and any electrograms inside those sites were analyzed. We defined a very low-voltage area (vLVA) as that with electrogram amplitude <0.2 mV in order to delineate strongly damaged areas in the LA. The surface area of the vLVA (cm²) was measured during the construction of the SR voltage maps, and the areas where vLVA were frequently found such as the anterior and posterior areas and those around the mitral valve, were mapped carefully, ensuring that there was adequate catheter contact.

Anatomical Study of the vLVA and CoA
The anatomical relationship between the vLVA and CoA was analyzed (Figure 1C). The total area of the vLVA, CoA and areas of overlap were calculated by the number of sites in each LA segment. In the 3 segments in which CoA were observed (anterior region, LIPV and posterior wall), the total surface area of the vLVA and their overlap area with the CoA was calculated for each part.

Anatomical Study of CoA and High-Frequency Sites
The total number and surface area of the high-DF (>8-Hz) and con-CFAE (<50-ms) sites was calculated and the percentage of the overlap area with the CoA was calculated. The overlap area was also analyzed in 3 segments (anterior region, LIPV and posterior wall) to consider any further relationship between the CoA and high-frequency sources.

Results
Patient Characteristics
Baseline patient characteristics are listed in Table. The average number of recorded points for each LA was 706±244 during AF, and 667±277 during SR.

Anatomical Characteristics of vLVA and CoA
A total of 47 vLVA (total surface area, 194.4 cm²) and 60 CoA (total surface area, 337.0 cm²) were identified in 22 patients. vLVA were found in the following LA locations: anterior (21/22, 96%), posterior (6/22, 27%), LIPV (6/22, 27%), lateral (4/22, 18%), septal (4/22, 18%), inferior (2/22, 9%), LSPV (2/22, 9%), roof (1/22, 4%), RSPV (1/22, 4%), and RIPV (1/22, 4%; Figure 2A) regions. Additionally, a CoA was found in the anterior (22/22, 100%), posterior (21/22, 95%), and LIPV (17/22, 77%) regions. In terms of overlap area between the vLVA and CoA, a total of 32 vLVA (32/47, 68%) had some areas that overlapped CoA, and 33% of the area of the vLVA (64.0/194.4 cm²) directly overlapped CoA.

Most patients (21/22, 95%) had a vLVA in the anterior LA region, and all of those vLVA overlapped CoA. Furthermore, 3 representative CoA regions (ie, CoA observed in the anterior, LIPV and posterior regions) were also common lodging sites for vLVA (Figure 2A). The total surface area of the vLVA on the anterior wall was 129.9 cm² and occupied 67% (129.9/194.4 cm²) of the total vLVA of the entire LA. In addition, the overlapped area located on the anterior wall was 41.0 cm² and occupied 64% (41.0/64.0 cm²) of the total overlapped area (Figure 2B). Six patients (6/22, 27%) had a vLVA in the LIPV region. Compared to the other 3 PV, there was a trend toward a higher incidence for vLVA in the LIPV region (LIPV/LSPV/RIPV/RSPV, 6/2/1/1; P=0.0533). In terms of the posterior region, 6 patients (6/22, 27%) had a vLVA and in 5 of them (5/6, 83%) it overlapped CoA. The total vLVA area in the posterior region was 15.6 cm², and the percentage of the overlap area with the CoA was 64% (15.6/24.4 cm²), which was higher compared to that of the other 2 regions (Figure 2B). There was 1 case in which the vLVA slightly overlapped the posterior CoA and was mainly located in the inferior region (Figure 2A).

Electrogram Characteristics of Con-CFAE and High-DF
In 22 patients, a total of 127 high-DF and 53 con-CFAE were documented, and the total area of the high-DF was 213.8 cm² and that of the con-CFAE was 108.3 cm². A quantitative analysis of the fractionated electrograms during AF from the SR maps was undertaken. The bipolar voltage at sites with a high DF (>8 Hz) was significantly lower than at sites with a con-CFAE (CFE-mean <50 ms: median, 0.62 mV [IQR 0.32–1.00] vs. 1.54 mV [IQR 0.82–2.67]; P<0.0001; Figure 3A), while the duration (median, 64 ms [IQR 57–71])...
Anatomical CoA and Fractionated Electrogram

A typical example of a DF map and the location of the CoA is shown in Figure 4. A total of 72% (92/127) of the high-DF sites overlapped CoA, while 53% (29/53) of the con-CFAE areas overlapped CoA. (Figure 5A) The percentage of high-DF areas that overlapped CoA in the 3 segments was as follows: anterior, 57% (33.9/59.9 cm²); left inferior pulmonary vein (LIPV), 56% (11.6/20.8 cm²); and posterior, 70% (39.4/56.5 cm²). (D) The con-CFAE areas that overlapped CoA, in the 3 segments, were: anterior, 24% (5.5/22.9 cm²); LIPV, 100% (1.4/1.4 cm²); and posterior, 46% (9.2/19.9 cm²).

Figure 4. Anatomical relationship between the high dominant frequency (high-DF) and contact area (CoA) sites in the DF map. Two of the high-DF sites overlap CoA in the anterior region, 1 in the left inferior pulmonary vein region, and 3 in the posterior region.

Figure 5. (A) Total number of high-frequency sources and those that overlapped contact areas (CoA). A total of 72% of high dominant frequency (high-DF) sites (92/127) overlapped CoA, but only 53% of the continuous complex fractionated atrial electrogram (con-CFAE) areas (29/53) overlapped CoA. (B) A total of 44% of the high-DF areas overlapped CoA (94.9/213.8 cm²), while only 19% (21.3/108.3 cm²) of con-CFAE areas overlapped CoA. (C) The percentage of high-DF areas that overlapped CoA in the 3 segments was as follows: anterior, 57% (33.9/59.9 cm²); left inferior pulmonary vein (LIPV), 56% (11.6/20.8 cm²); and posterior, 70% (39.4/56.5 cm²). (D) The con-CFAE areas that overlapped CoA, in the 3 segments, were: anterior, 24% (5.5/22.9 cm²); LIPV, 100% (1.4/1.4 cm²); and posterior, 46% (9.2/19.9 cm²).

vs. 62 ms [IQR 56–74]; P=0.925) and deflection (median, 6 [IQR 5–6] vs. 6 [IQR 5–7]; P=0.2941) were not significantly different (Figures 3B, C).

Anatomical Relationship of CoA to High-DF and Con-CFAE

A typical example of a DF map and the location of the CoA is shown in Figure 4. A total of 72% (92/127) of the high-DF overlapped CoA, while 53% (29/53) of the con-CFAE were associated with a CoA (Figure 5A). The total overlap area
between the high-DF and CoA was 94.9 cm², which was 44% (94.9/213.8 cm²) of the total high-DF area. In contrast, the overlap area between the con-CFAE and CoA was 21.3 cm², which was only 19% of the total con-CFAE area (Figure 5B). Figures 5C, D shows overlap areas in 3 regions with CoA (anterior, LIPV, and posterior regions). Most of the high-DF overlapped CoA, especially in the 3 representative regions (anterior, 57%, 33.9/59.9 cm²; LIPV, 56%, 11.6/20.8 cm²; and posterior, 70%, 39.4/56.5 cm²; Figure 5C). In terms of con-CFAE, the overlap area on the anterior and posterior LA wall was only 24% (5.5/22.9 cm²) and 46% (9.2/19.9 cm²), respectively. In the LIPV, con-CFAE were documented inside the vLVA (100%; 1.4/1.4 cm²), but the documented area was only 1.4 cm² of the total area (Figure 5D).

Discussion

Major Findings

To the best of our knowledge, this is the first study to investigate the relationship between the anatomical contact with external structures surrounding the LA and arrhythmogenic substrates perpetuating AF in patients with persistent AF. The major findings were that (1) the aorta and vertebrae had CoA in the anterior, posterior, and LIPV regions, which also were frequent sites for vLVA; (2) almost 70% (32/47) of the vLVA had some areas overlapping the CoA, and a total of 33% of the vLVA were inside CoA; (3) high-DF sites during SR had low-voltage fractionated electrograms that developed slow conduction, but the con-CFAE sites had a relatively normal voltage but fractionated electrograms; and (4) most of the high-DF sites were located around CoA, but few of the con-CFAE were. These findings suggest that CoA may have some influence in the low-voltage progression and development of fractionated electrograms.

Influence of CoA on vLVA in Persistent AF

We defined vLVA as an area with an amplitude <0.2 mV in order to delineate the greatly damaged areas in the LA, and the vLVA were located close to a particular area where CoA were present. Persistent AF, which is associated with an enlarged LA volume and a continuous stretching due to frequent movements of the atrium, may be linked to this result. As previously reported, the wall stress from inside and the continuous stretch are suggested to be associated with LA remodeling.16,17 and the present results have indicated another mechanism induced by external involvement that may have some influence on the arrhythmogenic substrates of AF.

In the present study, most of the AF patients had vLVA in the anterior region. Given that anterior CoA are present in every patient, including non-AF patients, this is not a special condition unique to AF patients. Pak et al reported low-voltage areas present in the LA anterior wall that are correlated with the LA-aorta contact region, and those areas are also related to the incidence of atrial tachycardia.18,19 The role of CoA in the remodeling of the LA is unidentified, but the intensity of the contact may be explained by the dilatation of the Valsalva and arteriosclerosis. Age and hypertension are major determinants of the thoracic aortic dimensions: they may stretch the wall and lead to an progression of the anterior wall remodeling.20,21 Given that some risk factors of AF correspond to the suspected progression factors of anterior wall remodeling, anterior CoA may have some involvement in the occurrence of AF.

The relationship of the low-voltage areas around the PV in patients with persistent AF has not been reported. In the present study, LIPV CoA were seen in 17 patients (77%), and the LIPV had a high occurrence of vLVA compared to the other 3 PV. These findings suggest the existence of some progressive factors for the electrical remodeling in this region.

The vertebrae, which form the hardest structure around the LA, can cause external stress, which may lead to a progression of the low-voltage areas. In the present study, 5 patients had overlap areas in the posterior region, and the percentage of the overlap surface areas was higher (64%) there as well, which indicated that there was a strong association with the CoA. Not all vLVA were related to CoA: for example, vLVA were identified in the lateral and septal regions, and they may have occurred due to another mechanism of electrical remodeling.

CoA and High-Frequency Sources

Ablation of con-CFAE sites is associated with a higher likelihood of AF cycle length prolongation,22 but because CFAE ablation does not always have an effect on AF cycle length, not all CFAE are appropriate targets for ablation. High-DF are also considered as a target of AF ablation and are reported to have some influence on the termination of paroxysmal AF.23 In the present study, the sites of high-DF recorded during SR had fractionated electrograms, for example, a low voltage, long duration and high deflection, which may indicate slow conduction and wave collision in the LA. Atrial fibrosis is reported to be the result of LA remodeling and produces fractionated electrograms in the LA.24,25 Many of the high-DF were documented around CoA in the present data, suggesting a tendency for slow conduction around CoA. Although high-DF ablation was not effective in terminating AF or in long-term achievement of a successful ablation in persistent AF,26 it does not exclude any involvement in AF maintenance.

In the present study, sites with con-CFAE had a relatively normal voltage during SR, as previously reported.14-16 Although the bipolar voltage was significantly lower than that at sites with high-DF, the duration and deflection were similar to that for high-DF, which suggests the presence of an atrial abnormality. Jadidi et al noted patchy fibrosis in CFAE areas on magnetic resonance imaging, which was documented in a normal voltage area, and they also identified fractionated electrograms during SR.27 A previous study reported that only 50% of the CFAE sites overlapped high-DF sites.28 In the present study, high-DF sites were located around CoA compared to con-CFAE. Furthermore, both high-DF and con-CFAE were recorded at sites with fractionated electrograms during SR, but high-DF were documented in a significantly low-voltage region during SR. Although little is known with regard to whether high-DF sites and continuous CFE regions have any relationship to each other for AF perpetuation, the present data suggest the possibility of a different role in AF maintenance between con-CFAE and high-DF.

Study Limitations

The present AF patients were a highly selected group referred for ablation. To select higher remodeled LA, persistent AF patients were enrolled. To emphasize the advanced remodeled LA regions, we defined vLVA as that with an amplitude <0.2 mV, but we could not exclude the possibility that a vLVA alternative cut-off of 0.2 mV would have yielded different results. Differences between the CT performed in AF and 3-D electro-anatomic mapping during SR were also suspected. The most important issue is that this study was done using subjective assessment of enhanced CT. Assessment of the contact with the LA was uncertain, but the strong correlation with the vLVA suggested the existence of some influence. Given that CoA were investigated with the NavX system, they were con-
sidered only in the axial view. There might have been some other CoA if we had considered other views.

Conclusions

In patients with persistent AF, vLVA, in particular the LA regions, had a strong association with the regions with CoA, and sites with CoA had a higher incidence of fractionated electrograms during SR and high-frequency sources during AF. A spatial correlation between the CoA and arrhythmogenic substrates was suggested, but whether the damaged myocardium is likely to maintain an arrhythmia remains unclear and needs further investigation.

Disclosures

Conflict of Interest: None.

References