Complete title: Low Voltage Zones as the Atrial Fibrillation Substrates: Relationship with Atrial Fibrillation Initiation, Perpetuation, and Termination.

Short title: Low voltage as AF substrates

Authorship: Zheng Liu, MD [1]; Yuan-Feng Gao, MD [1]; Xian-dong Yin, MD [1]; Yu Xia, MD [2]; Chang-yan Guo, MD [3]; Yuxin Wang, MD[1]; Xiaoqin Liu, MD [1]; Xingpeng Liu, MD[1]; Xinchun Yang, MD [1];

Department and Institute:

1 Heart Center, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China

2 Cardiac Arrhythmia Center, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China.

3 Department of cardiology, Xilin gol league central hospital, Inner Mongolia, China

Correspondence:

Xinchun Yang: Heart Center, Beijing Chao-yang Hospital, No. 8 gongti south road, Chaoyang District, Beijing, China. 100020. Email: Yangxc6229@126.com; Telephone: +8613581804133; Fax: +8601085231462

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Doctors Liu Z, Gao YF and Yin XD contributed equally to this article.

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Abstract

Background: Low voltage Zones (LVZ) were usually targeted for ablation in atrial fibrillation (AF). But its relationship with AF initiation, maintenance, and termination remains to be studied. We tried to explore the relationships.

Methods and Results: Consecutive AF patients were enrolled for assessment AF inducibility, AF duration or AF termination before ablation. Inducible AF was defined if induced AF last over 30 seconds. Sustainable AF was defined if it last over 300 seconds. Terminable AF was defined if it could be cardioverted into sinus rhythm within 1-hour after ibutilide administration. Voltage mapping was performed in sinus rhythm for all patients before stimulation or after cardioversion. LVZ was quantified as the percentage of LVZ area（LVZ%）to left atrium (LA) body surface. A total of 86 patients enrolled for AF induction and 36 for AF termination. 32 (37.2%) patients had inducible AF, 24 (27.9%) were sustainable, and 12 (33.3%) were terminable. Inducible AF patients had higher LVZ% in anterior wall (18.6±24.6 vs. 7.0±12.1, P=0.014). Global LVZ% was not different between inducible and uninducible AF patients. Global LVZ% was higher in patients with sustainable AF or interminable AF (LVZ%: sustainable vs unsustainable AF: 10.6±12.1 vs. 0.8±0.8, p=0.001; terminable vs. interminable: 17.1±13.5vs.40.6±24.5, p<0.001). Sustainable AF had larger LVZ% in roof, anterior wall, septum, floor. Interminable AF patients had higher LVZ% in anterior wall, septum, posterior wall and floor. Higher LVZ% was independent risk factor of recurrence (OR=1.015, P=0.042).

Conclusion: The association between LVZ with AF initiation, perpetuation and termination were different.

Key words: atrial fibrillation; electroanatomic mapping; low voltage; inducibility; sustainability；termination.

Introduction:

The initiation and perpetuation of atrial fibrillation (AF) involve a complex relationship between triggers and substrate. Previous study found that atrial fibrosis played an important role in atrial remolding in AF patients[1]. The extent of atrial fibrosis reflecting the severity of atrial remolding, affected long-term outcome in AF patients underwent catheter ablation[2]. Low voltage Zones (LVZ) harboring complex electrogram or colocalizing spatio-temporal dispersion were considered as surrogate for atrial fibrosis[3, 4]. Ablation targeting LVZ can help to improve long-term outcome for patients underwent AF ablation[5, 6]. However, the specific relationship between LVZ with AF initiation, AF perpetuation, and AF termination have not been studied systematically. In this study, we tried to explore these specified relationships.

Methods:

1. Study population:

Between November 2017 and November 2018, A consecutive cohort of non-valvular AF patients were enrolled from the AF ablation database of our hospital. Patients were divided into two groups: (1) Patients in sinus rhythm were assessed with AF inducibility and sustainability by introducing atrial pacing. And (2) patients in spontaneous AF were administered with ibutilide to assess AF termination. Study protocol was shown in Figure 1.

All symptomatic AF patients must meet all following criteria. (1) patients aged must be above 18-years-old; (2) before ablation, voltage mapping of the left atria (LA) during sinus rhythm was conducted. (3) All antiarrhythmic drugs (AAD) were withheld at least 5 half-lives before the procedure. Besides, patients with amiodarone taking history within 6 months that may affect the AF inducibility were excluded. Other exclusion criteria were (1) previous catheter ablation procedure, previous surgical procedure performed in heart, lungs, esophagus and previous radiotherapy or chemotherapy that might cause scar in the LA. (2) known cardiac

thrombi, pregnancy, LA diameter >60 mm. and contraindication to anticoagulation. (3) ibutilide could not be administered in case of QTc longer than 450ms, or LVEF<30%. All enrolled patients were anticoagulated for 4 weeks before procedure. Demographic factors, clinical mobilities and ultrasonographic heart structural parameters were collected and the CHA2DS2-VASc score were calculated[7]. Classification of paroxysmal AF and persistent AF was based on the diagnostic criteria from the guideline[7].

The study was approved and reviewed by the institutional ethics review board. All patients provided written informed consent before the clinical procedure.

2. Electrophysiological study

The procedure was performed with sedation utilizing fentanyl. LA access was achieved after a transseptal puncture, with two long sheaths introduced into the LA. Intravenous heparin was given with 100 unit/kg, adjusted with ACT at 250-350 seconds before LA transseptal puncture. Catheters were positioned as follows: (1) a 10-pole catheter with interelectrode space of 2-5-2-mm was positioned in the coronary sinus (CS) with the proximal electrode pair near the ostium of the CS; (2) A steerable mapping catheter with 20-pole arranged in 5 soft radiating spines covering a diameter of 3.5 cm (PentaRay, Biosense Webster; interelectrode spacing 2-6-2 mm) was advanced into the LA through the long sheath for mapping; (3) finally, a 3.5-mm tip, open irrigated, contact force sensing (CFS) catheter (ThermoCool SmartTouch, Biosense Webster, USA) was placed in the LA via the long sheath for mapping and ablation. Also, intracardiac echocardiographic (ICE) catheter (SoundStar 3D, Biosense Webster, USA) were placed in the right atrium for continuously monitoring.

3. Atrial effective refractory period measurement

In patients with sinus rhythm, atrial effective refractory period (ERP) was evaluated at fixed pacing output of 10mA and 2 ms pulse width. Atrial pacing was delivered in three sites

including the anterior wall of left and right pulmonary vein (PV) ostium, and ostium of CS vein by using the CFS catheter. A 5 to 10 grams electrode-tissue contact force was required to initiate pacing in order to ensure enough but not excessive contact. Pacing protocol was the same to that described by Sanders et al [8]. In brief, it contains an extrastimulus introduced following an 8-beat drive with cycle length of 500 ms, starting with a start extrastimulus coupling interval of 150 ms and increasing in 10 ms increments. Local ERP was defined as the shortest coupling interval that was able to capture the LA at the pacing site. At each site, the ERP was measured 3 times and the total averaged. ERP mean was defined as the mean value of the local ERP three pacing sites. ERP dispersion was defined as the difference between the longest and the shortest local ERP of the three sites[9, 10].

4. Inducibility and Sustainability of Atrial Fibrillation

The inducibility of AF by single extrastimulus was counted during ERP determination. AF was defined as any rapid atrial activity (rate >350 beats/min) with irregular cycle length, polarity, configuration, and amplitude on atrial electrograms lasting over 5 cycles[10]. The duration of induced AF was documented. We reported the incidence of induced AF of any duration, $\geqslant$30 seconds, $\geqslant$5 minutes as previously used definition[8, 10]. Inducible AF was defined only when AF last over 30 seconds. Sustainable AF was defined when it last over 300 seconds as previously described[8]. If induced AF could not terminate after 300 seconds simultaneously, electrical cardioversion was performed to restore sinus rhythm. And after awaiting period of 10 minutes, ERP measurement continued.

5. Response of Spontaneous AF to Ibutilide.

The ability to terminate spontaneous AF was assessed with ibutilide 1mg administered intravenously in 10 minutes with continuous ECG monitoring during whole procedure. If paired PVC or PVC with R-on-T phenomenon was observed, Ibutilide administration was stopped

immediately. If Torsade de points occurred, ibutilide administration was stopped immediately. Magnesium sulphate 1.25g and lidocaine 100mg administration was performed to prevent it from recurring. If hemodynamically unstable, or Torsade de points sustained over 30 seconds, electrical cardioversion was performed immediately to restore sinus rhythm. Observation time was started from the beginning of ibutilide administration until 1 hour. If AF could not be stopped, electrical cardioversion was performed to restore sinus rhythm in order to perform voltage mapping. Cardioversion from AF to sinus rhythm in 1 hour was documented. If AF could be terminated within 1-hour, terminable AF was defined, otherwise interminable AF was defined. In patients with ibutilide termination protocol we did not test ERP.

6. Voltage electroanatomic mapping

Electroanatomic map of the LA and PVs were constructed. LA voltage was all collected in sinus rhythm before ablation. Mapping was performed with the PentaRay catheter and the CFS ablation catheter. To ensure detailed and uniform mapping of the entire chamber, we set the mapping filling threshold of 3 mm as a requirement for a complete map. Mapping LA with minimum 500 points was required and equally distributed in the LA.

Besides, to ensure adequate catheter tissue contact with the LA body, at least 3 out 4 of the following criteria that need to be fulfilled: (1) ICE confirmed catheter and LA wall contact; (2) Proximity to the tissue is indicated by highlighting the electrodes with a white frame, when "Tissue proximity indication" was switched on; (3) The catheter movement was consistent with the cardiac silhouettes under fluoroscopy; (4) In LA septum where reliable contact cannot be achieved with PentaRay catheter, the CFS ablation catheter was used and a minimum contact force of 5g was required. Anatomic annotation of the mitral annulus was tagged in the LA electroanatomic map where the A/V amplitude ratio of 1:1 as Jais et al previously described[11]. To avoid perforation of the LA appendage (LAA), catheters were prohibited from going deep

into the LAA. Thus surface area of the LAA was not counted for analysis. Measurement of the LA surface area were performed with the tool inside the system with exclusion of the mitral annulus, LA appendage, and pulmonary veins. Volume of the LA was manually assessed with tool included in the mapping system after exclusion of PV branches extending 1cm over PV ostium. All bipolar electrograms were filtered between 30 and 500Hz. Local voltage was defined as the amplitude of the peak positive to the peak negative deflections. Low voltage cut-off was < 0.5mV in sinus rhythm as commonly used. Low voltage zone (LVZ) was defined if it possessed at least 3 neighboring sampled points with voltage <0.5mV as previously described[12]. LVZ area was measured with the same tool for LA surface measurement. The size of LVZ was presented as a percentage of the entire LA surface (LVZ%). To describe LVZ's regional distribution, LA was manually separated into 6 regions as previously described [6] (Figure 2) .

7. Catheter Ablation and Follow-up:

Ablation strategy was briefly stated as following: Complete circumferential pulmonary vein antrum isolation (PVI) was performed in all patients. Additional ablations include lines that connecting PVs and anatomical barriers were created to eliminate LA macro-reentry tachycardias or lines that transecting scarred areas. Besides, mappable extra-PV sources were ablated. Tricuspid valvular isthmus (TVI) was ablated in patients with clinical typical atrial flutter. The endpoints were bilateral PVI, bidirectional conduction block of the linear ablation lesion, and elimination of all identified extra-PV foci.

All patients were anticoagulated for at least 3 months after index procedure. Antiarrhythmic medication was administered for 2 months. Patients was followed-up with a 7-day holter monitoring (SmartPatch, Ensense Biomedical Technologies, Shanghai, China) every 3 months. Documentation of any atrial tachycardia, atrial flutter or AF lasting over 30 seconds

after a blanking period of 3 months was defined as recurrence. Antiarrhythmic drug treatment or redo-ablation was performed in patients with recurrence.

8. Statistical analysis:

Continuous variables were expressed as the mean values. Grouped variants were expressed as count and ratio. The independent samples t-test or Mann-Whitney U-test was used for continuous variables, according to their distributions. The Chi-square test and Fisher's exact test were used for the categorical and dichotomous variables. Univariate and multivariate logistic regression analyses or Cox proportional hazard models were used to determine the factors that were associated with the inducibility, Sustainability, termination of AF before ablation and recurrence after ablation. P value <0.05 was considered statistically significant. The SPSS statistical package (version 22.0 for Windows; SPSS Inc, Chicago, IL, USA) was used.

Results:

1. Patients characteristics, ablation, and follow-up:

A total of 122 AF patients (age=65.8±10.2 years-old, female=46, persistent AF=50) were enrolled. The duration of diagnosed AF before procedure was 19.5±47 months. CHA2DS2-VASC, LA volume, LA diameters and LVZ% were significantly higher in persistent AF patients (in table 1). 86 patients were in sinus rhythm underwent induction protocol while the remaining 36 in AF underwent ibutilide termination protocol. Patients underwent ibutilide termination protocol prone to have larger LA and higher global LVZ% (table 1) and larger LVZ% in all LA segments (P<0.05).

60 patients were given additional ablation after PVI, including TVI ablation in 30, supra vena cava (SVC) isolation in 8, LA linear ablation in 34 patients. All procedures were

performed uneventfully. During 12.6 ± 4.0 months follow-up, Recurrence happened in 36 patients (29.5%). Factors including age, gender, AF type, BMI, CHA2DS2-VASC score, LA diameters, LA volumes, ERP mean, ERP dispersion, and LVZ% were analyzed for the risk factors of recurrence. Only LVZ%, and LA volume were remained as the risk factors (Odds Ratio:1.015, P=0.042) (Table 2).

2. LVZ size, distribution, and risk factors.

An average of 750 points were taking per map, with LA surface area of 162.94cm2, and LA volume of 152.5ml (containing LA body, LAA, and PV trunk within 1cm from ostium). LVZ presence was found in 92 patients. Factors including age, gender, BMI, CHA2DS2-VASC score, LA diameter, LA volume were analyzed for the risk factor of LVZ presence. Patients with LVZ presence tended to be older, more of persistent type, bigger atrium and longer ERP mean. After multivariate analysis, higher LA volume remained to be the risk factor of LVZ presence (Table 3).

The LVZ distribution was not homogeneous. Overall LA LVZ% was 14.9 ± 19.9%, which was highest in septum but lowest in lateral wall (figure 3). LVZ% was positively associated with CHA2DS2-VASC score (correlation coefficient =0.227, p=0.007), LA volume (correlation coefficient =0.422, p<0.001) and ERP mean (correlation coefficient =0.378, p=0.003), but negatively associated with ERP dispersion (correlation coefficient=-0.577, p<0.001).

3. AF inducibility, sustainability, and termination.

In 86 patients underwent ERP measurement, AF could be induced in 38, however, 6 were less than 30 seconds that would not be counted as inducible AF. In remaining 32 inducible AF,

24 were sustained (Table 4). The coupling interval that induce AF was 180±29ms. The most common site to induce AF was the left PV ostium (43%), while the least was in CS ostium (24%). Neither atrial flutter nor paroxysmal supraventricular tachycardia was induced.

In 36 patients underwent ibutilide administration, no Torsade de points happened. 1mg ibutilide was administered in all patients. AF was terminable in 12 patients, in whom cardioversion into sinus rhythm happened in all cases. The duration between cardioversion and initiation ibutilide administration was 17±24 minutes. Re-initiation of AF happened in one patients during ablation, in whom, LA voltage mapping in sinus rhythm completed.

4. Relationship between LVZ with AF dynamics.

Comparing patients with inducible AF and those without, demographic characteristics, morbidities and heart structural parameters were similar, LVZ% were not significantly different between two groups (table 4). However, ERP mean was shorter (176±32 vs. 226±26, P<0.01) and ERP dispersion was higher (98.9±34.7 vs. 67.7±39.0, P=0.038) in patients with inducible AF. Similar pattern was observed in patients with induced AF of any duration. However, in patients with sustained AF over 300 seconds, LVZ% was significantly larger (10.6±12.1 vs. 0.8±0.8, P=0.001).

Risk factors of inducible AF, sustained AF were evaluated, shorter ERP mean was the risk factor for inducible AF. Even though LVZ% was larger with sustained AF, however, no risk factor for sustained AF was identified after multivariate analysis (Table 4).

Comparing terminable and interminable AF, more classification of persistent AF and higher degree of LVZ% (40.6±24.5 vs. 17.1±13.5, P=0.016) was identified to be risk factor preventing AF from termination, which held true in multivariate analysis (Table 4).

5. Association of LVZ distribution with AF dynamics.

Comparing uninducible AF, inducible AF patients had higher LVZ% in anterior wall (18.6 ±24.6 vs 7.9±7.0±12.1, p=0.014). Sustainable AF had larger LVZ% in more areas including roof, anterior wall, septum, floor, compared with those unsustainable. In interminable AF patients, LVZ% in roof, anterior wall, posterior wall, and floor were larger (figure 3 and Table 5). Compared with sustainable AF patients, significantly higher LVZ% in anterior wall, septum, posterior wall and floor were observed in interminable AF patients (P<0.05 in all).

Discussion:

Previous works suggested low voltage areas are important substrates[4, 5]. But the specific relationship between different electroanatomic substrates with AF inducibility and sustainability were not fully understood. Our study have following major findings: (1) LVZ was important AF substrates, predicting poor outcome after AF ablation; (2) for AF inducibility, LVZ% didn't differ significantly between inducible and non-inducible AF patients, but larger LVZ% in anterior wall was observed in inducible AF patients; (3) LVZ% were significantly larger in patients with sustained AF and interminable AF, larger LVZ% was independent risk factor for interminable AF. The relationship between LVZ with AF inducibility, sustainability, and termination were different.

1 LVZ in AF

The pathology of LVZ in AF were multiple. Certain correlation between LVZ with scars, epicardial adipose tissue, and contact areas of neighboring structures were reported[13-15]. Presence of LVZ predict poor outcome after ablation[2, 12]. The finding of our study complied with previous reports. Left atrial substrate modification targeting LVZ for catheter ablation of AF resulting in a higher AF free rate[5]. The implication of LVZ in AF ablation was important, however its association with AF initiation, sustainability and termination needs to be specified.

2 LVZ and AF inducibility and sustainability.

The inducibility of AF varied because of different induction protocol and definition of AF among centers. Previously described protocol mainly classified as two ways: extrastimulus protocol or rapid pacing protocol[8, 10, 16-19]. Previous report found that rapid pacing protocol could result in AF inducibility in 25-67% of people without history of AF, which indicate that rapid atrial pacing could be unspecific to asses AF inducibility[17, 19]. Jones et al[20] observed patterns of spontaneous AF initiation in AF patients. They found that most of the spontaneous AF were initiated by short runs of atrial extrastimulus before break into fibrillation. Continuous source firing only happened in 32% of spontaneous AF. This indicate that AF induction with extrastimulus protocol are more similar to the spontaneous initiation process. As other previous works[8, 10, 18], we assessed the AF inducibility with the extrastimulus protocol because it is more physiological.

The relationship between AF initiation and LVZ have been in dispute. Study by Masuda et al[21] have demonstrate that AF was more often induced in atrium with LVZ. However, Kosiuk et al[22] found that in patients with redo-ablation, new-appearing LVZ didn't associated with inducibility of AF, which was similar to the finding in our study.

One reason might account for the dispute was the variable cut-off value used for the definition of inducible AF. In patients with paroxysmal AF, it was reported 43% of patients for a definition >10 seconds[23]. 36% of patients for a definition of $\geqslant$5 minutes[24]. In our study, the cut-off value was 30 seconds for the definition of inducible AF. The rate of inducible AF was 37.2%, which was comparable with the previous study[8]. When we used the cut-off value of induced AF with any duration or over 30 seconds, the LVZ% differences between groups were insignificant. However, it became significant when we divide patients with the cut-off value over 300 seconds. Similar findings were observed in the report by Medi et al.[25] that in patients with hypertension, induced AF over 30 seconds was observed in 30% of the patients. However, brief AF less than 30 seconds were inducible in 20% and repetitive initiating AF in 10% of

patients without hypertension. which indicate that LVZ% were more likely to be the factor affecting the AF duration rather than the inducibility itself. Besides, Jadidi et al.[4] observed that repetitive rotational activity with coverage over 70% of AF cycle length are often recorded in border zone around LVZ. 80% of AF could be terminated in LVZ and 20% in the LVZ border, suggesting the sustaining nature of LVZ. In our study, LVZ% were higher in patients with sustained AF. Previous study has found that LVZ was often associated with more fragmented signal, and slow conduction[26]. This could help to facilitate reentry sustainability by increasing the excitable gap between wavefronts and wave-tails.

Besides, in our study the risk factor for AF inducibility was ERP mean shortening, which is in accordance with the previous studies[10, 19]. Shortening of ERP and widening of ERP dispersion may cause heterogeneous conduction, facilitating fibrillatory wave breakup.

3. LVZ and AF termination.

Ibutilide is a potassium channel blocker that prolongs phase 3 of the cardiac action potential, resulting in increased refractoriness of atrial myocytes, Promoting reentry conduction block. clinical indication for administering ibutilide is recent onset AF or atrial flutter with a routine dose of 1 to 2 mg. low dose Ibutilide can decrease negative CFAE, displaying active CFAE sustaining AF. Low dose ibutilide guided CFAE ablation have also been reported[27]. our previous study found that interminable AF during ibutilide guided CFAE ablation predict poor outcome after ablation, suggesting more complex substrates in ibutilide interminable AF patients[27]. In our present study, larger LVZ% was larger in interminable AF patients. The possible mechanism for LVZ to prevent AF termination still need to be studied. Previous study found that the electric activation during AF would be unstable after ibutilide administration[28]. Possibly due to the facilitated spiral wave drifting, collision, and followed by AF termination[29].

In scared atrium, LVZ could act as the anchoring site for spiral waves, decreasing spiral drifting, and preventing AF termination[30, 31].

4. LVZ distribution and AF dynamics:

Different LVZ distribution may be associated with specific arrhythmia. Masuda et al.[21] found that in patients with AF, burst pacing induced AF were associated with vast distribution of LVZ in all atrial segments. Anterior wall and septum dominant LVZ distribution were associated with mitral valve isthmus flutter, while posterior wall and roof dominant LVZ distribution were associated with roof flutter. In our study, similar finding was observed that vast distribution of LVZ and higher degree of LVZ% were associated with AF sustaining.

As for AF initiation according to the observational study of spontaneous AF onset, Jones et al[20] observed that a consistent, complete, or near-complete line of block extended from the septal mitral annular region and oval fossa, passing posteriorly around the right inferior PV and then up the posterior wall, in 75% of cases reaching the LA roof. This septopulmonary line of block appeared critical to the formation and interaction of wavefronts in the evolution from initiating mechanism to established AF in all cases. Besides, Other functional line of blocks, not seen during sinus rhythm, were observed to form during initiating sequences in certain cases, typically on the anterior wall. In our study, patients with inducible AF were more likely to have higher LVZ% in anterior wall which may underlying the line of block.

In this study, comparing LVZ distribution in patients of sustainable AF, interminable AF patients have higher LVZ in posterior wall. previous study by kumagai et al[32] found that isolation of posterior wall facilitated AF termination in addition to PVI, suggesting great contribution of posterior wall in AF termination. Phase mapping of LA rotor and wavelets suggested that posterior wall isolation not only reduce the critical mass for maintenance of AF

within the posterior wall, but also decrease the rotors and multiple wavelets in the other regions[33].

Study limitations:

There are several limitations of our study. Firstly, the anatomic change of low voltage in atrium of AF cannot be determined because we are lacking imaging and biological proof. Secondly, the bipolar voltage of the right atrium was not collected, which may forbid further analysis of the contribution of right atrial LVZ in AF initiation, sustainability and termination, further studies are needed to elucidate the association. Thirdly, patients with prior ablation, previous radiotherapy or chemotherapy, surgeries in heart, lung and esophagus were not investigated in this study. Substrates underlying AF initiation, perpetuation, and termination may be different. Future study is needed to investigate relationship between LVZ and AF dynamics. Besides, different pacing protocol, varying pacing output and different pacing sites including LAA and SVC could result in different relationship between LVZ with AF initiation, perpetuation, and termination. Further studies were needed to elucidate different pacing protocol and sites on these relationships. Moreover, the relationships between LVZ and AF dynamics were not causal. But previous studies have identified that ablation targeting the LVZ could benefit the long-term outcome for persistent AF patients. This might suggest the causal relationship of LVZ on AF dynamics. Finally, the sample size of our study is relatively small, However, the sample size of our study was comparable to previous studies[8, 10, 18]. Larger studies might be needed to validate our findings.

Conclusion:

LVZ was important AF substrates underlying poor outcome after ablation. Its association with AF initiation, sustaining and termination were different depending on LVZ size and distribution.

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List of abbreviations

ERP: effective refractory period

LVZ: Low voltage Zone.

PV: Pulmonary veins.

PVI: pulmonary vein isolation

Figure Legends:

Figure1. Study protocol:

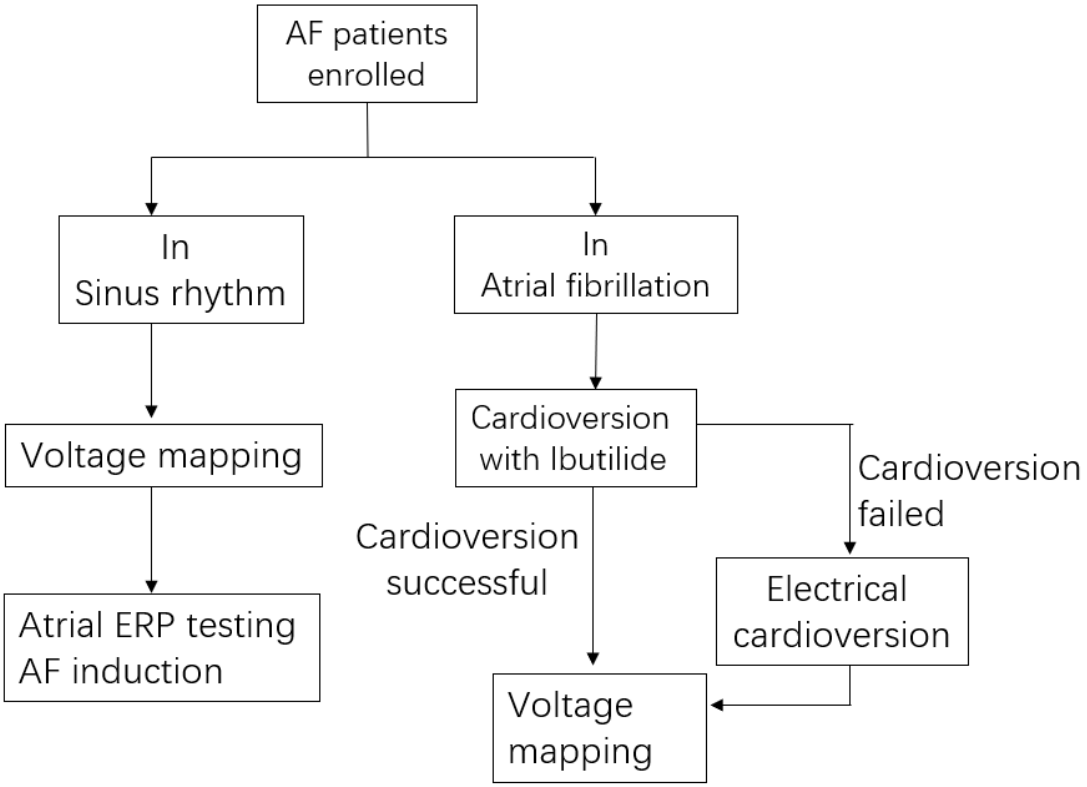


Figure 2. the definition of left atrium segments.

In the left column, we presented LA activation in sinus rhythm, which was earliest activated in the septum and anterior wall (in red) while latest activated in the lateral wall (in purple). In the right column, we presented the synchronized LA in voltage map, in which area in purple indicate healthy atrium, which area colored red to blue indicate low voltage zone (LVZ). To describe the LVZ distribution, we divided the left atrium (LA) into 6 segments: (1) roof between the left superior pulmonary vein (LSPV) and right superior pulmonary vein (RSPV),(2) anterior wall between roof and mitral valve annulus (MVA)，(3) LA septum that below fossa ovalis and anterior wall, (4) posterior wall between roof and Pulmonary veins, (5) LA floor that between Posterior wall and MVA, (6) Lateral wall between left PVs and MVA. In this case, we observed a large area of LVZ in the posterior wall.

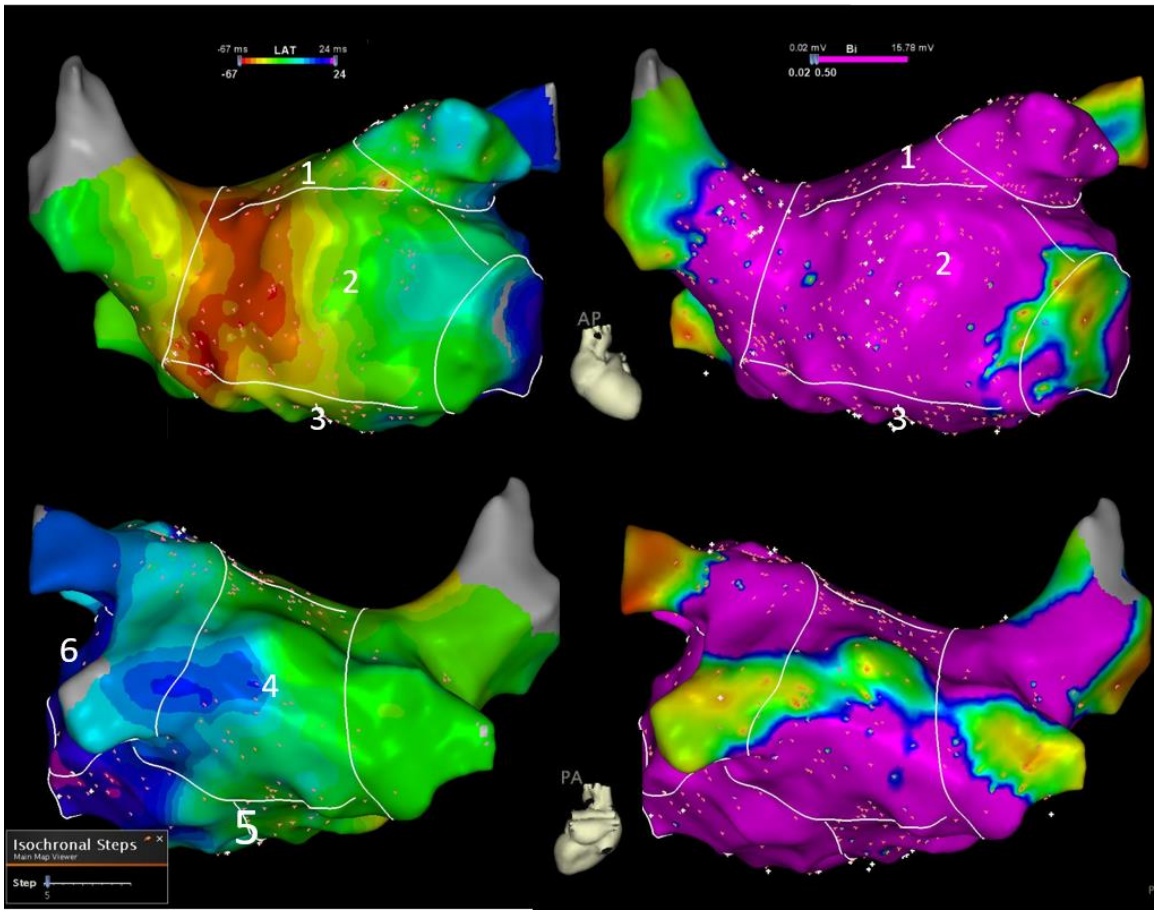
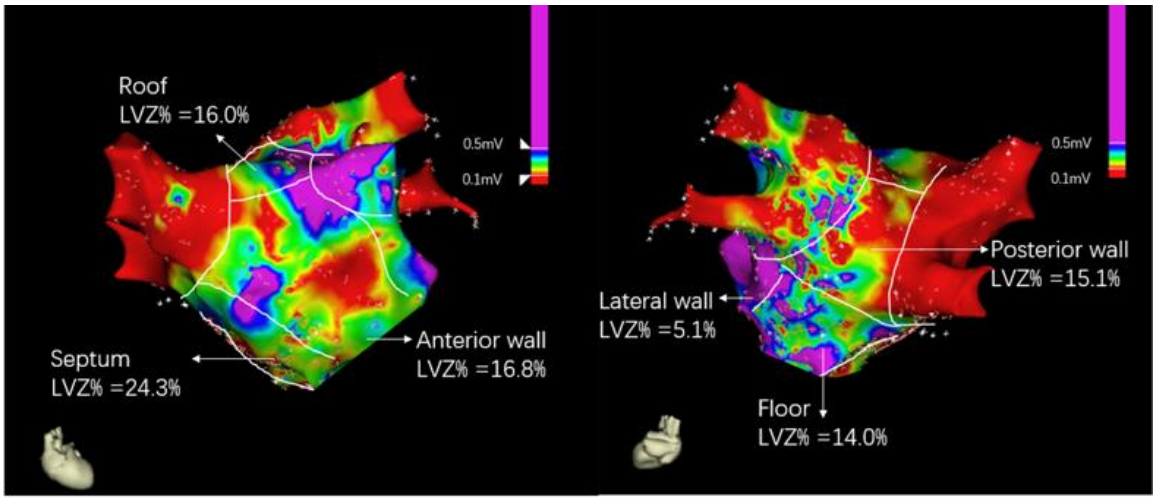


Figure 3. LVZ distribution in different atrial segments.

Areas in purple indicate healthy myocardial with sinus voltage ⩾0.5mV, area with color range from red to blue indicate low voltage zone with voltage < 0.5m V. septum was the major region harboring LVZ, while lateral wall harbors the least area of LVZ. The LVZ distribution in different protocol and deriving classifications was presented. Inducible AF had larger LVZ% in anterior wall even though global LVZ% were comparable to uninducible AF. LVZ% in sustainable AF were significantly larger than unsustainable AF. Interminable AF patients had largest area of LVZ.


Roof
LVZ% =16.0%
0.5mV
0.1mV
Septum
LVZ% =24.3%
Anterior wall
LVZ% =16.8%
Lateral wall
LVZ% =5.1%
Posterior wall
LVZ% =15.1%
Floor
LVZ% =14.0%

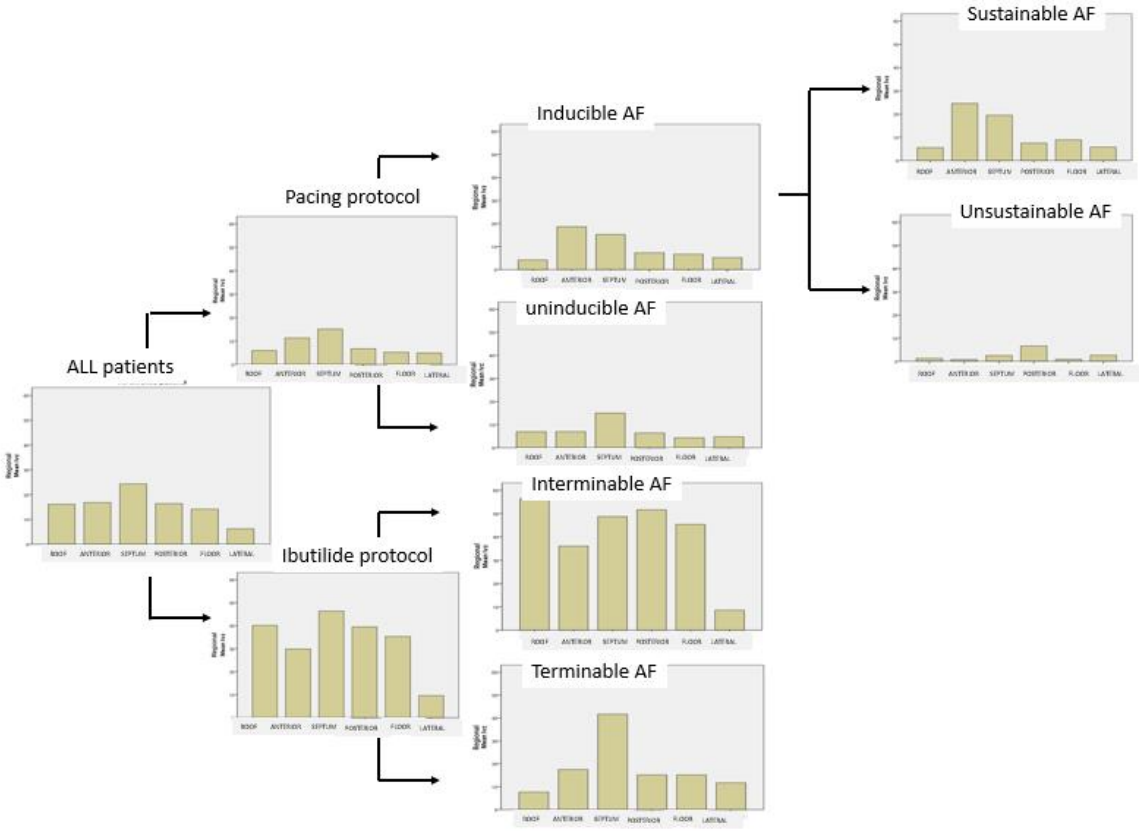

ALL patients
Pacing protocol
Ibutilide protocol
Inducible AF
uninducible AF
Interminable AF
Terminable AF
Sustainable AF
Unsustainable AF

Table 1：Characteristics of patients.

Variables	All Cases （n=122）	Persistent AF（n=36）				Paroxysmal AF （n=86）				P *
		Total	Induction protocol （n= 14）	Termination protocol (n=22)	P§	Total	Induction protocol (n=72)	Termination protocol (n=14)	P§	
Age（years）	65.8±10.2	63.2±7.7	61.6±8.6	64.0±8.2	0.402	66.9±10.9	66.7±10.0	68.0±12.8	0.732	0.062
Female（%）	46 （37.7%）	13(33.3%)	7	6	0.166	33(39.5%)	31	2	0.069	0.519
BMI （kg/m2）	29.4±3.0	29.5±3.2	30.3±2.0	29.0±3.8	0.200	29.3±2.9	29.5±3.0	28.2±2.4	0.130	0.685
CHA2DS2-VASC	3.9±2.1	4.9±2.2	5.1±2.5	4.7±2.1	0.667	3.5±1.8	3.5±1.9	3.4±1.6	0.915	<0.001
Without AAD	85	21	8	13	0.908	64	55	9	0.342	0.078
Propafenone history	34	14	6	8	0.697	20	16	4	0.607	0.079
Sotalol history	3	1	0	1	0.418	2	1	1	0.191	0.883
LA volume (ml)	152.6±40.7	165.8±47.9	166.1±64.7	169.8±36.5	0.826	147.1±26.2	144.5±35.8	153.2±31.9	0.402	0.020
LA diameter (mm)	41.5±5.7	45.6±5.3	44.5±4.5	46.2±5.7	0.361	39.7±5.0	38.7±4.4	44.8±5.0	0.001	<0.001
LVEF（%）	64.7±7.3	64.9±6.5	66.6±7.1	63.5±6.0	0.172	64.6±7.7	65.0±7.9	62.7±6.5	0.309	0.834
ERP mean（ms）	213.9±29.4	219.0±40.2	219.0±40.2	NA	NA	212.9±27.0	212.9±27.0	NA	NA	0.591
ERP dispersion (ms)	78.0±38.2	71.1±40.2	71.1±40.2	NA	NA	79.4±37.9	79.4±37.9	NA	NA	0.460
LVZ %	14.9±19.9	24.5±24.0	12.6±19.4	33.4±23.0	0.008	10.9±16.5	6.4±9.2	31.6±26.2	0.003	0.003

AAD: antiarrhythmic drugs; BMI: body mass index; ERP: effective refractory period; LVEF: Left Ventricle Ejection Fraction, LA: left atria; LVZ: Low voltage zone. * P value was for comparison of paroxysmal and persistent AF groups;

§ P value was for comparison of patients in induction protocol and termination protocol.

Table 2 risk factors of recurrence after AF ablation.

Variable	AF ablation recurrence		Univariate Analysis			Multivariate analysis		
	With n=(36)	without n=(86)	ORs	95% CI	P	ORs	95%CI	P-
Age (years)	65.9±10.6	65.8±10.0	0.986	0.942-1.033	0.559			
Female	9	37	1.002	0.957-1.165	0.312			
Persistent AF	16	20	1.529	0.777-3.009	0.219			
BMI (kg/m^2)	29.6±3.4	29.3±2.9	1.021	0.914-1.140	0.710			
CHA2DS2-VASC	3.8±1.6	3.9±2.2	1.021	0.765-1.364	0.887			
LA d (mm)	42.2±5.9	41.2±5.6	0.902	0.824-0.987	0.025	0.978	0.891-1.075	0.650
LA vol (ml)	173±46	143±35	1.015	1.006-1.024	0.001	1.009	1.002-1.017	0.015
ERP mean (ms)	202±23	218±30	0.984	0.969-0.998	0.029	0.979	0.939-1.022	0.333
ERP dispersion (ms)	87±40	75±37	1.008	0.997-1.020	0.148			
LVZ %	25.4±26.1	10.5±14.6	1.033	1.011-1.055	0.003	1.015	1.001-1.030	0.042

AF: atrial fibrillation, BMI: Body Mass Index, LVEF: Left Ventricle Ejection Fraction, LA D: left atrial diameter, LA VOL: left atrial volume, ERP: effective refractory period, LVZ: Low voltage zone. OR: Odds ratio, CI: confidence interval.

Table 3 risk factors of presence of LVZ.

Variable	LVZ presence		Univariate Analysis			Multivariate analysis		
	With n=(92)	without n=(30)	ORs	95% CI	P	ORs	95%CI	P-
Age (years)	67±10	62±9	1.053	1.010-1.097	0.015	1.031	0.978-1.087	0.259
Female	33	13	0.731	0.316-1.692	0.467			
Persistent AF	32	4	3.467	1.112-10.804	0.032	1.243	0.292-5.295	0.769
BMI (kg/m^2)	29.2±2.8	29.8±3.8	0.938	0.821-1.073	0.353			
CHA2DS2-VASC	4±2	3.4±2	1.174	0.948-1.454	0.141			
LA d (mm)	41.7±6.3	40.8±3.2	1.028	0.955-1.106	0.467			
LA vol (ml)	159±44	134±17	1.023	1.007-1.040	0.005	1.020	1.003-1.039	0.024
ERP mean （ms）	218±26	204±34	1.023	1.003-1.043	0.026	1.009	0.989-1.029	0.399
ERP dispersion (ms)	71±37	94±36	0.986	0.972-1.000	0.048	0.983	0.969-0.996	0.014

AF: atrial fibrillation, BMI: Body Mass Index, LVEF: Left Ventricle Ejection Fraction, LA D: left atrial diameter, LA VOL: left atrial volume, LVZ: Low voltage zone. ERP: effective refractory period. CI: confidence interval

Table 4. risk factors for inducible, sustained and terminable AF

Parameters	Induced AF with any duration			Inducible AF						Sustained AF						Terminable AF					
	With (n=38)	Without (n=48)	P	With (n=32)	Without (n=54)	P	Multivariate analysis			With (n=24)	Without (n=6)	P	Multivariate analysis			With (n=12)	Without (n=24)	P	Multivariate analysis		
							OR	95% CI	p				OR	95%CI	P				OR	95%	P
Age (years)	64.1±11.4	67.3±8.9	0.146	64.3±10.9	66.9±9.7	0.254				64.8±11.9	64.3±8.0	0.924				62.3±10.0	67.3±10.2	0.180			
female	16	22	0.730	13	25	0.609				11	2	0.580				4	4	0.397			
Persistent AF	4	10	0.199	4	10	0.465				2	2	0.254				4	18	0.029	0.090	0.012-0.671	0.019
BMI （kg/m2）	29.3±3.5	29.9±2.3	0.346	29.4±3.7	29.7±2.3	0.630				29.5±4.3	29.0±0.6	0.549				28.1±2.2	29.0±3.8	0.471			
CHA2DS2-VASC	3.2±1.4	4.2±2.4	0.024	3.4±1.2	4.0±2.4	0.141				3.3±1.3	4.0±0.9	0.203				3.8±2.4	4.4±1.9	0.427			
LA Volume (ml)	146.7±37.1	149.1±46.1	0.794	153.9±34.8	144.6±45.9	0.292				156.1±35.5	151.7±38.8	0.792				168.7±36.4	160.7±35.2	0.531			
LA diameter (mm)	39.5±3.8	39.6±5.4	0.896	39.2±3.5	40.0±5.6	0.408				39.1±3.8	39.0±2.7	0.961				48.0±4.3	44.5±4.7	0.079			
ERP mean (ms)	186±29	229±25	<0.001	176±32	226±26	<0.001	0.961	0.936-0.986	0.003	202±21	176±32	0.057				NA	NA	NA			
ERP dispersion (ms)	94±31	65±40	0.018	98.9±34.7	67.7±39.0	0.038	1.015	1.000-1.031	0.053	97±26	99±34	0.914				NA	NA	NA			
LA LVZ %	7.2±10.6	7.7±12.4	0.852	8.2±11.3	7.0±11.9	0.659				10.6±12.1	0.8±0.8	0.001	1.384	0.878-1.819	0.120	17.1±13.5	40.6±24.5	0.016	0.928	0.874-0.985	0.015

AF: atrial fibrillation, BMI: Body Mass Index, LVEF: Left Ventricle Ejection Fraction, LVZ: Low voltage zone.LA: left atrium ERP: effective refractory period

Table 5. LVZ distribution and AF dynamics

	Induced AF with any duration			Inducible AF			Sustained AF			Terminable AF		
	with (n=38)	Without (n=48)	P	With (n=32)	Without (n=54)	P	With (n=24)	Without (n=6)	P	With (n=12)	Without (n=24)	P
LVZ% in roof	3.5±9.9	7.9±19.1	0.155	4.2±7.4	6.9±18.2	0.327	5.5±8.1	0.3±0.9	0.003	7.6±13	56.4±40	0.001
LVZ% in anterior wall	15.7±23.5	7.9±12.6	0.071	18.6±24.6	7.0±12.1	0.014	24.5±25.8	0.7±1.4	0.001	17.5±18	36.1±34	0.044
LVZ % in septum	15.2±21.4	15.0±25.6	0.968	15.2±22.9	15.0±24.3	0.963	19.5±25.0	2.5±4.9	0.004	41.6±23	48.7±33	0.472
LVZ% in posterior wall	7.1±3.9	6.4±16.5	0.796	7.3±4.1	6.4±15.6	0.693	7.5±4.6	6.6±1.9	0.462	15.2±22	51.6±33	0.001
LVZ% in floor	5.6±15.8	4.9±13.3	0.810	6.7±17.0	4.3±12.6	0.466	8.9±19.3	0.5±1.3	0.033	15.2±19.6	45.4±32.7	0.006
LVZ% in lateral wall	5.0±5.6	4.9±9.9	0.929	5.2±6.0	4.8±9.3	0.791	5.8±6.8	3.5±1.7	0.143	11.6±18	8.6±14.7	0.614

AF: atrial fibrillation, LVZ: Low voltage zone