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Clinical Significance of Arrhythmogenic Foci in Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) is initiated by pulmonary vein (PV) and non-PV foci, which could be associated with initiating and maintaining AF. The development of the remodeling process and preexistent anatomical structures are likely to relate to the structural and electrophysiological changes in the PVs and non-PV area, which could promote the local conduction abnormalities and cause an increased PV/non-PV arrhythmogenicity. In this section, we assessed the features and relating factors of PV/non-PV arrhythmogenicity in patients with AF and evaluated its clinical implication. As a result, we realized the atrial anatomical features, such as the left atrial roof shape, left lateral ridge, and Marshall vein provided us with an understanding of PV and non-PV arrhythmogenicity in patients with AF. In addition, the presence of residual arrhythmogenic non-PV foci is associated with increased AF recurrence after catheter ablation; therefore, the information of arrhythmogenic foci (AMF) is also useful for determining the appropriate strategy of ablation for AF.

Keywords: atrial fibrillation, catheter ablation, arrhythmogenic foci, structural remodeling, Marshall bundle

1. Introduction

Atrial fibrillation (AF) is caused by triggers from pulmonary veins (PVs) [1], and a rapid firing from the PVs could be responsible for initiating and maintaining arrhythmias in patients with

AF. The enhanced automaticity or triggered activity mechanisms could be involved in the initiation of AF [2, 3]. In addition, the PV's circumference is also most likely crucial for sustaining the reentry of maintaining AF [4], which can enhance a condition for persistent AF.

Non-PV foci can also arise from the crista terminalis, ostium of the coronary sinus, interatrial septum, superior vena cava, left atrial posterior free wall, and Marshall bundle [5, 6] with the incidence ranging from 3.2 to 47 % [7, 8, 9]. The dominant triggering sites of non-PV have a slow diastolic depolarization, increasing the chance of the spontaneous depolarization [10], and the triggered activity from the non-PV sites could also be involved in the initiation and perpetuation of AF. Previous studies have reported that the increased delay after depolarizations has been documented from the superior vena cava [10], coronary sinus (CS) [11], Marshall bundle and the coronary sinus [12], atrial muscle that extends into the mitral valve [13], and working muscle [14]. Especially, the Marshall bundle may be a crucial structure to initiate catecholamine-sensitive AF.

The development of the remodeling process and preexistent anatomical structures seems to be related to the structural and electrophysiological remodeling in the PVs and atrium, which can increase the local abnormal conduction and develop an increased PV/non-PV arrhythmogenicity leading to AF persistency [15, 16, 17, 10, 11].

In this section, we assessed the features and relating factors of PV/non-PV arrhythmogenicity in patients with AF and evaluated their clinical implication during catheter ablation procedure.

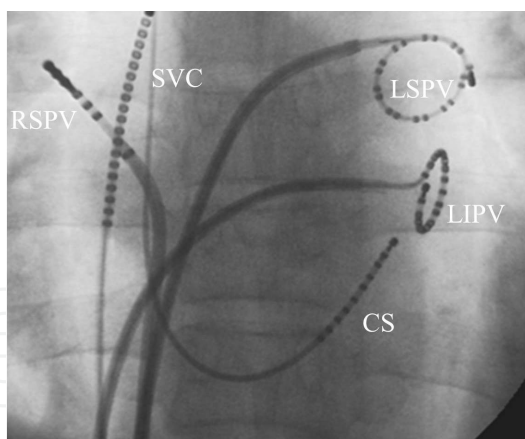
2. The feature and clinical implication of arrhythmogenic foci of atrial fibrillation

2.1. The method of induction and detection of PV/non-PV arrhythmogenic foci

We used five multipolar catheters recording the electrograms to search for the location of the arrhythmogenic foci (AMF). A 20-pole catheter covered the SVC to the crista terminalis, CS, and the left PVs. A mapping catheter was located at the right superior PV (Figure 1). When the AMF have originated from a non-PV area uncovered by the catheters, we searched the location with a mapping catheter. The 12-lead ECG and intracardiac electrograms were filtered between 30 to 500 Hz (DUO EP Laboratory; Bard Electrophysiology, Lowell, MA, USA).

The occurrence of PV/non-PV foci could be influenced by the induction methods, and PV arrhythmogenicity may be enhanced by the stimulation with acetylcholine or isoproterenol (ISP) [2, 18]. The relationship between the ISP dose and arrhythmogenicity remains unclear; however, the PV/non-PV foci are likely to be revealed with a high-dose isoproterenol up to 20 g/min or subsequent cardioversion of AF [19, 20]. High-dose ISP can cause the vagally mediated nerve reflex bradycardia, which seems to increase arrhythmogenicity after autonomic nerve competition.

Both atrial spontaneous AMF were carefully searched before the PV isolation procedure under an intravenous infusion of isoproterenol (ISP) without sedation. During sinus rhythm, ISP was



LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; CS, coronary sinus; RSPV, right superior pulmonary vein; SVC, superior vena cava.

Figure 1. Catheter locations for detecting AMF. Twenty-pole circular catheters were positioned at the left superior and inferior PV. A 10- or 20-pole catheter was located in the CS, and then terminal crest and the SVC were covered with a 20-pole catheter. The mapping catheter was located at the RSPV. When arrhythmogenic foci arise from the RIPV or a non-PV area, the suspected area was confirmed by a mapping catheter. The location of the PV/non-PV foci showing the earliest atrial focus was referred to the local electrogram or onset of the ectopic P wave. In addition, the direction of the earliest activated site of the PV/non-PV foci could be also determined by the sequence of the activation recorded from multipolar catheters allowing to detect the non-PV sites in both atria.

initially delivered at 1–2 g/min for 5 min, and then the dose was gradually increased up to 20 g/min with careful monitoring of the blood pressure. When the blood pressure dropped under 70 mm Hg, the dose of ISP was reversed to the basal level. When AF persisted and/or spontaneously occurred, direct cardioversion (DC) was attempted up to three times. The DC energy was delivered by using an external biphasic wave up to 270 J, and sinus rhythm was temporarily or successfully restored in all enrolled patients.

The ISP administration was maintained at basal level (1–2 g/min) during the ablation. At the end of the session, the increased dose of ISP was administered up to 20 g/min. AMF were confirmed as direct AF triggers and/or reproducible atrial premature beats with coupling intervals of <350 ms or frequent firings (Figure 2).

2.2. The location of PV/non-PV arrhythmogenic foci

Two hundred fourteen consecutive patients with drug-refractory AF episodes were enrolled in this study (mean age of 61 years, male, 71 %; persistent AF, 21%). The clinical and electrophysiologic characteristics of the AMF were demonstrated in Figure 3. Five hundred AMF were observed. PV and/or non-PV foci were detected in 201 of 214 (93.9 %). Two hundred sixty-three foci (52.6 %) in 174 patients (81.3 %) were confirmed as the triggers directly shifted to AF, and 237 foci (47.4 %) in 150 patients (70.1 %) showed reproducible premature atrial beats with an interval of <350 ms or repetitive firings. PV foci were confirmed in 195 of 214 patients (91 %) and non-PV foci in 107 of 214 (50 %), accounting for one third of all the AMF. Foci originating from only PVs were detected in 95 of 214 patients (44 %), both PV and non-PV origins in 98 of 214 (46 %), and only non-PV origins in 8 of 214 (3.7 %). Non-PV foci are located

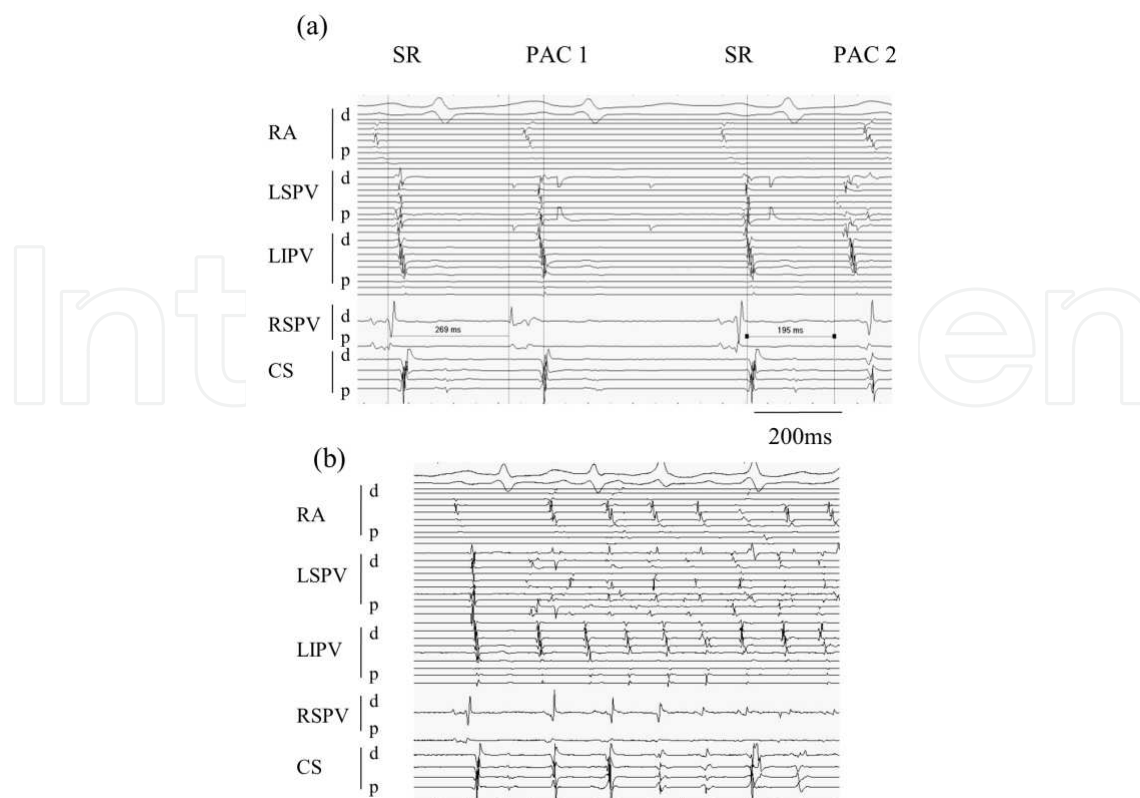


Figure 2. Multiple foci from the right and left PVs. The electrogram exhibiting the PV foci is a two-component electrogram during sinus rhythm. Premature atrial beats one from the right superior PV (a). The electrogram of the ectopic beat exhibits a reversal polarity and a rapid deflection with a coupling interval of 269 ms and apparently precedes the P-wave onset recorded in the 12 ECG. The following PAC 2 originating from the left superior PV spontaneously occurred with a coupling interval of 195 ms. The frequency of PAC 1 and PAC 2 gradually developed, and then PAC 2 was finally shifted to AF (b).

in the superior vena cava (21 %), LA posterior wall (14 %), terminal crest (7.4 %), coronary sinus (7.4 %), left lateral area (6.9 %), LA roof (4.6 %), atrial septum (3.7 %), and other sites (1.5 %). Non-PV foci were detected before the PV isolation procedure in 55 of 109 foci (50 %) (superior vena cava (77 %), atrial septum (39 %), terminal crest (38 %), coronary sinus (38 %), LA roof (24 %), left lateral area (20 %), LA posterior wall (13 %)). The roving catheter had to be relocated to search for the foci uncovered by the catheters in 58 of 214 patients (27 %). PV foci were significantly more related to AF occurrence than non-PV foci (PV foci 61 % vs. non-PV foci 28 %, $p < 0.001$). The mean coupling interval of PV foci was significantly shorter than that of non-PV foci (196 ± 68 vs. 255 ± 90 ms, $p < 0.001$). The number of inducible foci was significantly higher in patients with non-PV foci than without those (3.1 ± 1.7 vs. 1.5 ± 1.4 , $p < 0.001$).

Non-PV foci were induced 15 % of the time with no ISP, 30 % with 1–2 g/min, and 55 % with 2–20 g/min. PV foci were revealed 25 % of the time with no ISP, 43 % with 1–2 g/min, and 32 % with 2–20 g/min. The distribution of the inducibility according to the ISP dose significantly differed between PV foci and non-PV foci ($p < 0.001$).

In half of the enrolled patients, non-PV foci were confirmed and accounted for one third of all AMF. High-dose ISP could improve the ratio of the detection of both PV and non-PV foci;

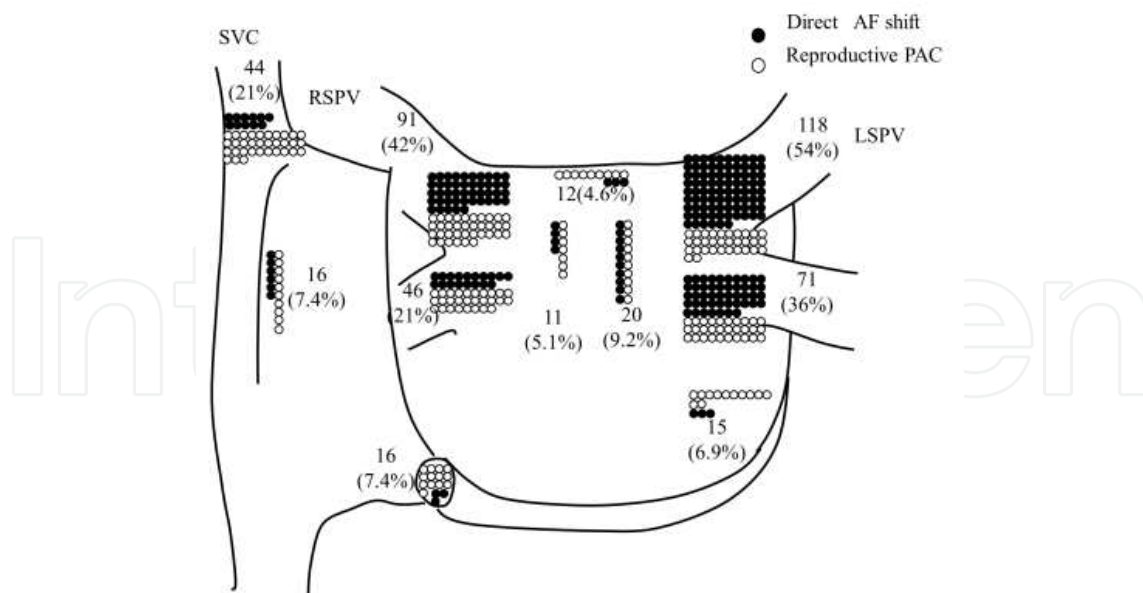


Figure 3. The location of induced AMF. AMF were determined as direct AF triggers or spontaneous reproductive premature atrial premature contraction (PAC) with the coupling interval less than 350 ms or repetitive firing in arrhythmogenic foci. Black circle represents foci which directly shifted to AF; white circle represents reproductive PAC and repetitive firing. To detect the location of foci, we simultaneously used five multipolar catheters to record the electrograms outside the PVs, coronary sinus, SVC, and crista terminalis to search for the AMF during isoproterenol administration.

however, the dose of the ISP was significantly higher for the non-PV foci than the PV foci. The predominant non-PV trigger sites seemed to be related to anatomical structures such as the terminal crest or ligament/vein of Marshall, known to be catecholamine-sensitive structures [5]. These evidences may explain why a high dose of ISP was needed to reveal non-PV foci.

2.3. The PV/non-PV arrhythmogenic foci between paroxysmal and persistent AF

. The incidence of PV foci and non-PV foci from the left atrium was not significantly different between paroxysmal and persistent AF patients. The incidence of non-PV foci, the sum number of foci, the number of non-PV foci, the incidence of right atrial foci, and the occurrence of multiple foci were significantly higher in the persistent than paroxysmal AF. In a multivariate analysis, multiple foci were one of the independent contributing factors to persistent AF as well as the left atrial dimension.

Furthermore, Figure 4 demonstrated that the number of foci was significantly higher in >24 h than < 24 h (1.77 ± 0.16 vs. 2.64 ± 0.14 , $p < 0.001$) in the paroxysmal AF patients and also significantly higher <1 year than >1 year (3.62 ± 0.15 vs. 1.92 ± 0.16 , $p = 0.038$) in persistent AF patients. In the data of comparing the AF incidence from PV/non-PV foci between paroxysmal and persistent AF, PV foci were confirmed in 86 % >24 h and in 94 % < 24 h in paroxysmal AF patients and in 96 % <1 year and in 86 % >1 year in persistent AF patients. Non-PV foci were confirmed in 32 % >24 h and in 58 % < 24 h in the paroxysmal AF and in 66 % <1 year and in 59 % >1 year in the persistent AF. The number of foci was significantly increased with a longer AF period in paroxysmal AF, whereas it had significant association on a short AF period in

persistent AF. Therefore, these findings may imply that the presence of increased foci may possibly facilitate the development of a shift from paroxysmal to persistent AF, although that may gradually become less significant as long-lasting AF develops.

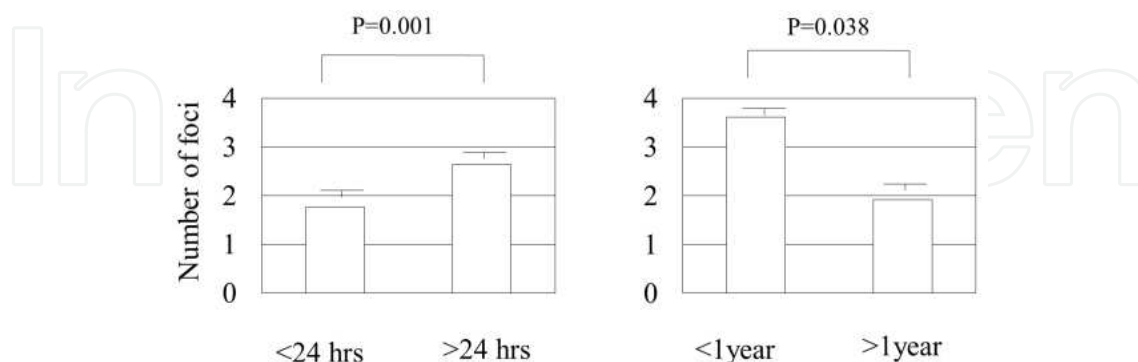


Figure 4. The number of induced foci between paroxysmal and persistent AF. The left graph demonstrates the comparison of the number of foci between those with episodes of < 24 h (n=70) and > 24 h (n=82) in patients with paroxysmal AF. The right graph shows the comparison between AF episodes < 1 year (n=19) and those > 1 year (n=21) in persisted AF patients. The number of foci was significantly higher in >24 h than < 24 h (1.77 ± 0.16 vs. 2.64 ± 0.14 , $p < 0.001$) in the paroxysmal AF patients and significantly higher <1 year than >1 year (3.62 ± 0.15 vs. 1.92 ± 0.16 , $p = 0.038$) in the persistent AF patients. These evidences may imply that the presence of multiple foci may help the promotion from paroxysmal to persistent AF state, and long-lasting AF might reduce the significance of the multiple foci in the perpetuation of AF.

AF occurrence after ablation was significantly higher in patients with multiple foci than without it (sum; 26 % vs. 11 %, $p = 0.024$, paroxysmal; 22 % vs. 14 %, $p = 0.087$, persistent; 26 % vs. 19 %, $p = 0.630$). The hazard ratio of multiple foci being associated with recurrent AF demonstrated that those foci were not a significant relating factor for recurrent AF (2.03 (0.92–3.76), $p = 0.106$).

The multiple triggers may allow a greater chance of reinitiating AF even after the AF self-termination and may facilitate the progression to the persistency from a paroxysmal to persistent AF. In the meantime, the enhanced triggered activity of multiple sites as the cause of AF persistency could also beget AF perpetuation by making new wavelets and less likelihood of AF self-termination. Furthermore, the enhanced dispersion of the atrial refractoriness may also be a crucial factor for AF persistency. The presence of increased atrial dispersion might promote the progression from paroxysmal to persistent AF state [21]. These observations may provide a clue as to why multiple triggers are associated with the development of the fibrillatory process in AF persistency.

2.4. Mutual linkage of left PV AMF

PV myocardial sleeves with complex muscle bundle orientations or specific autonomic nervous system may have the same interactions between each PV. Thus, we determined the mutual linkage of AMF around PVs. AFC from the left superior PV were significantly associated with AFC of the left inferior PV (42 % vs. 23 %, $p < 0.05$), left-sided left posterior wall (20 % vs. 5 %, $p < 0.05$), and roof area (8 % vs. 2 %, $p < 0.05$) (Figure 5). In case of foci from LSPV, the occur-

rence of AMF was 68 % in LIPV, 85 % in the left side LA posterior wall, and 75 % in the roof. Right PVs had no significant mutual association for AFC between each other (Figure 6).

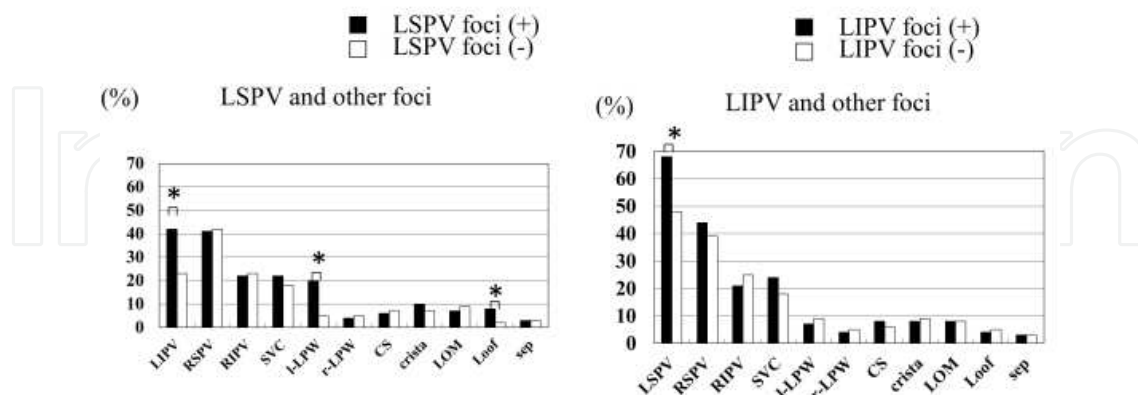


Figure 5. The relation between left PV foci and other foci. The incidence of foci from LIPV (42 % vs. 23, $p < 0.05$), left-side left atrial posterior wall (20 % vs. 5 %, $p < 0.05$) and left atrial roof (8 % vs. 2 %, $p < 0.05$) was highly detected in patients with LSPV than without LSPV foci.

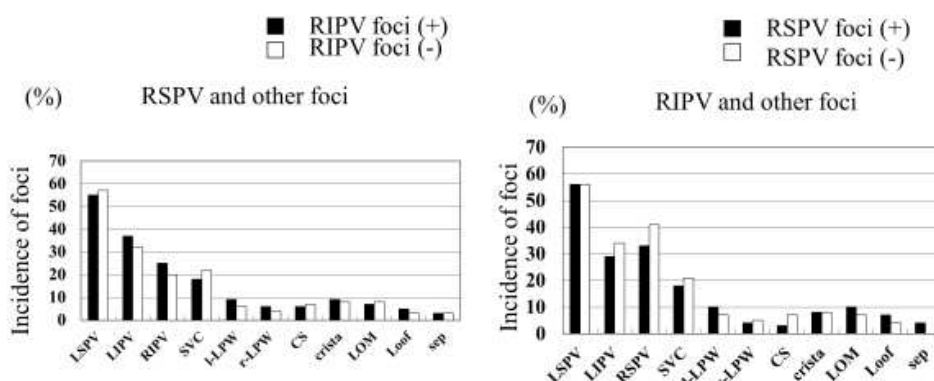


Figure 6. The relation between right PV foci and other foci. There is no significant relation between right PV foci and other foci.

Left lateral ridge as the anterior wall of left PVs facilitating to connect both superior and inferior PV may contribute the mutual arrhythmogenic linkage of them. Thus, we examined the relation between the shape of left lateral ridge and LPV's arrhythmogenicity in 120 AF patients.

Morphology of the left lateral ridge was determined by the endoscopic view of 64-MDCT. From the relation to superior and inferior PVs, the characteristics of the ridge was classified into 3 groups: long (connecting both PVs, $n=44$), intermediate (half of PV distance, $n=53$), and poor (only around PV, $n=23$) (Figure 7). The incidence of AF foci from the left inferior PV (29 % vs. 9 %, $p < 0.05$) and spontaneous AF occurrence from both PVs (23 % vs. 5 %, $p < 0.05$) were significantly higher in the long type than in the intermediate and short types. The number of AF foci around the ridge was significantly greater in patients with long type than those without it (1.2 ± 0.9 vs. 0.6 ± 0.7 , $p < 0.01$).

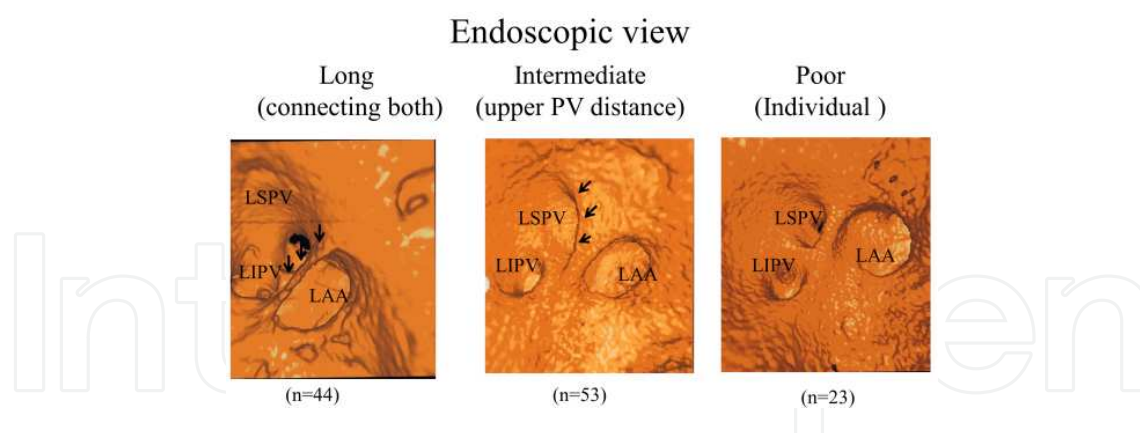


Figure 7. Endoscopic view of left PVs ostium. LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; LAA, left atrial appendage.

2.5. Left atrial roof shape and PV/non-PV foci

The remodeling process is associated with the structural and electrophysiological abnormality in the PVs and atrium, which could promote local conduction delay and lead to an increased PV/non-PV arrhythmogenicity developing to AF persistency [15, 16, 17, 10, 11]. These evidences might imply that the morphological features of the PVs and atrium can contain a crucial role to detect their preexisting arrhythmogenicity, although the evaluation of the morphological features is limited in a quantitative manner because of their variable and unique structure.

The left atrial (LA) roof consisting of the upper wall of the left atrium and upper PVs was demonstrated as the silhouette of LA roof and could simply be visualized by PV angiography or left atrial CT imaging. In addition, the dominance of morphological PVs/LA and the features of the LA roof silhouette could be easily determined in patients with AF. Thus, the relation between PV/non-PV arrhythmogenicity and LA roof silhouette was examined in this study.

Based on the PVs and LA dominance, The LA roof shape was classified into a deep V shape (possible PV dominance), shallow V shape, and flat-covered shape (possible LA dominance) by cine angiography (Figure 8). Angiography was conducted by both contrast media from the long sheath locating at the right and left superior PVs. The LA roof shape was assessed by A–P projection and was determined by the angle of the LA roof silhouette between the right and left LA wall. The deep V shape was defined as $<140^\circ$, shallow V shape was 140° to 180° , and flat-covered shape was $>180^\circ$.

Table 2 shows the relation between AMF and roof-shape group. In results, 335 AMF were detected. PV/ non-PV foci were observed in 136 of 152 (89 %) AF patients. AF triggers immediately shifting to AF were found in 114/152 (75 %) AF patients, and AF from PV foci was in 84 of 152 (55 %) AF patients. PV foci containing reproducible atrial premature contractions were observed in 135 of 152 AF patients (89 %) and non-PV foci in 77 of 152 (44 %). The location of non-PV foci was in the superior vena cava (25, 28 %), left atrial posterior wall (19, 21 %), terminal crest (10, 11 %), CS (10, 11 %), left lateral area (9, 10 %), LA roof (7, 8 %), atrial septum (4, 4 %), and other areas (6, 7 %).

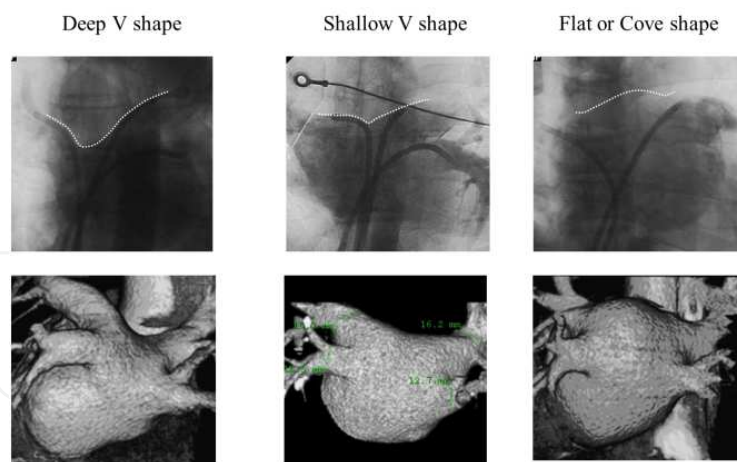


Figure 8. According to the PV and LA dominant level, the LA roof shapes into a deep V shape, shallow V shape, and flat-coved shape which were classified by using cineangiography and 64-slice MDCT. The upper figure is the cineangiography, and the lower is the 3D-constructed image of the MDCT. The deep V shape seemed to be dominated by the segment of both trunks of the upper PVs, whereas the flat-coved LA roof shape shows less incorporation into the LA.

As the silhouette of LA roof got to flat, the incidence of AF from the PVs (deep V 70 % vs. shallow V 57 % vs. flat 40 %, $p=0.003$), AF of the upper PVs (deep V 63 % vs. shallow V 41 % vs. flat 38 %, $p=0.046$), and PV foci including reproducible premature contractions (deep V 94 % vs. shallow V 84 % vs. flat 76 %, $p=0.033$) significantly decreased. The incidence of AF from non-PV sites (sharp V 6 % vs. shallow V 13 % vs. flat 22 %, $p=0.041$) and non-PV foci including atrial premature contractions (sharp V 26 % vs. shallow V 46 % vs. flat 54 %, $p=0.016$) were significantly increased as the LA roof silhouette got to flat. In a multivariate analysis, the deep V was an independent relating factor to PV AF triggers (OR 2.94 (1.27–6.80), $p=0.012$). These findings may include the novelty of the LA roof silhouette as an index of the PV's arrhythmogenicity.

AF is likely to originate from larger PVs [22], and the enlarged PVs may often be associated with the arrhythmogenic PVs [23]. Enlarged PV by the atrial stretch can enhance the PV's automaticity and triggered activity for AF initiation [24]. In addition, the atrial remodeling process may promote the increased triggered activity of non-PV lesions. The presence of multiple PV/non-PV foci could be related to longer AF duration, an older age, and larger atrial dimensions [25]. And also, LA enlargement could predispose LA posterior wall triggers [15].

3. Marshall bundle and arrhythmogenic foci

Marshall reported that a “vestigial fold of the pericardium” lies dorsal to the left atrial appendage in 1850. The small oblique vein of Marshall (VOM) is often connected to the vestigial folds going around the ostium of the left PVs. VOM drains into CS and separates the great cardiac vein and CS. The muscle sleeves of the VOM are also connected to CS musculature [26]. The vein or its ligament of Marshall is usually connected to the left PVs [27, 28, 29], and its distal ends are directly connected to the posterior wall of the left atrium [27, 30].

AF can originate from VOM or its ligament because of its catecholamine-sensitive structure [31, 5]. Preserved persistent left superior vena cava as a remnant of VOM can also include the similar electrical and anatomical features [32]. VOM or its ligament has connections to muscle bundles of the left atrium as well as of the surrounding coronary sinus (CS) in histological studies. The distal end often connects to the LA lateral area and to the left PVs [27, 29]. Therefore, recognition of the VOM anatomy in AF patients would help access to non-PV foci around the left PVs, which would lead to favorable clinical procedural result.

3.1. Angiographic vein of Marshall and AMF

In 100 AF patients, we examined the anatomy of VOM with balloon-occluded venography of coronary sinus using a balloon wedge pressure catheter (Goodtec, Huntington Beach, CA). The landmark of VOM orifice was identified at the junction of the CS and great cardiac vein. The right anterior oblique, left anterior oblique, and anteroposterior views were obtained in enrolled AF patients (Figure 9). To identify the anatomical association for VOM to both the superior and inferior left PVs, we performed selective superior and left inferior left PVs angiography by using injection of 5–10 ml of contrast medium from long sheaths. The grade of VOM development was measured from the AP view and classified into two grades (poor, reaching below superior left PV distributed in LA, and good, above superior left PVs).

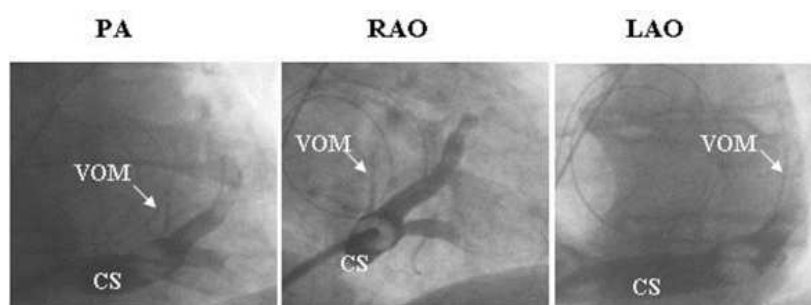


Figure 9. Representative results of VOM angiography. The location of the VOM is indicated by arrows. VOM runs obliquely between the left atrial appendage and LSPV.

VOM was visualized by balloon-occluded CS venography in 73 AF patients (73 %). There were no significant differences in clinical characteristics of the two groups. VOM development was poor in 55 patients (75 %) and good in 18 patients. In the anteroposterior image, the VOM running behind the mitral isthmus line was confirmed. VOM going through the mitral isthmus area was observed in 51 patients (51 %). The branches originating from the end of VOM was observed in 49 patients (67 %).

The incidence of PV foci from the left superior PV was significantly higher in patients with VOM than in those without it (66 % vs. 42 %, $P=0.05$). And also, the incidence of left superior PV foci as direct AF initiator was significantly higher in patients with VOM than in those without it (50 % vs. 30 %, $P<0.05$). The incidences of the left superior PV foci were 41 % in none, 69 % in poor VOM, and 56 % in good VOM. The incidences of the left superior PV foci as direct AF initiator were 30 % in none, 56 % in poor VOM, and 33 % in good VOM.

Twelve patients had non-PV foci in the LA posterior wall, and nine (75 %) of these patients also had PV foci in the left superior PV around VOM structure even after the successful PV isolation procedure at PV ostium level. The correlation between angiographic VOM anatomy and surrounding non-PV foci is shown in Figure 4. After ablating the site at the branch of VOM connecting to the LA wall, we can often successfully terminate AF. Twenty-eight patients had 30 non-PV foci surrounding left superior PVs including LA posterior free wall, LA roof, and LA lateral wall, and 12 of 30 non-PV foci were directly shifted to AF.

The branches of the VOM were a good landmark to identify the location of non-PV foci around left PVs (Figure 10). We could successfully ablate the residual non-PV foci at the distal end of VOM in 11 patients (39 %) after PV ostial isolation (AF termination after RF delivery, 3; disappearance of reproductive atrial premature contractions, 8). Successful terminations of non-PV foci were observed in 5 in left LA posterior wall, 4 in LA lateral wall, and 2 in LA roof. Among 28 patients with non-PV foci surrounding left PVs, non-PV foci were successfully deleted in 17 patients, whereas 11 patients of them had AF recurrence. Seven of 11 (67 %) with successful non-PV foci termination were free from AF recurrence.

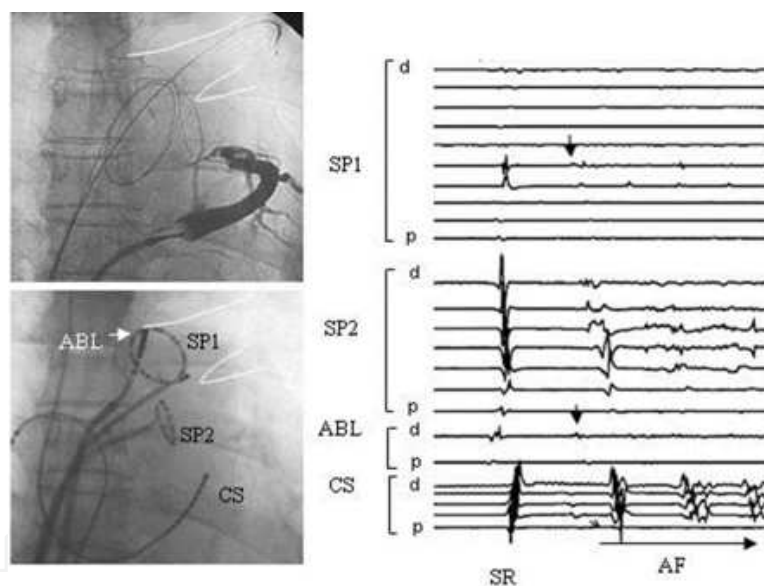


Figure 10. Spontaneous PV and coronary sinus angiography (3a). The VOM reached between LSPV and LIPV and ran laterally to the LIPV ostium. Super-selective VOM angiography revealed that the end of VOM had a branch that spreads in the area of the lateral and posterior wall below the LSPV ostium (3b). Arrows indicate the end of the VOM.

The presence of VOM is associated with a higher incidence of AF triggers of the left superior PVs. The incidence of left superior PV foci was significantly higher in patients with visible VOM than in those without visible VOM. In angiographic findings, the distal branches of VOM are commonly distributed around both the left superior and inferior PVs, especially in patients with good visual VOM. The VOM and its ligament richly innervated by sympathetic nerves could be served as a cause of isoproterenol-sensitive automatic activity [5, 33]. These evidences support arrhythmogenic foci from the VOM, and its ligament can be inducible by using high-dose isoproterenol administration.

Left PVs foci and non-PV foci adjacent to the left PVs can have an influence on each other. Approximately 40 % of non-PV foci around the left superior PV were successfully ablated by targeting the distal end of VOM or its branches. These evidences demonstrate the angiographic data of VOM, and its branches may indicate the site of catheter ablation of non-PV foci. Radiofrequency energy applied to the areas of VOM distal ends occasionally delineated non-PV foci originating from the surrounding area of left PVs. Thus, we believe that understanding of the VOM anatomy can improve the clinical outcome of ablation in cases with catecholamine-sensitive AF.

3.2. Conduction along the left lateral ridge and the arrhythmogenicity of the left pulmonary veins

The ligament and VOM containing the Marshall bundle (MB) with richly innervates the sympathetic and parasympathetic nerves is within the left lateral ridge (LLR) which is longitudinally running between the left atrial appendage and left pulmonary vein (LPVs), and they can serve as a source of triggers and the substrate of reentry of atrial fibrillation (AF) [1,2]. If the distinctive dominant conduction along the LLR is present, possibly due to the continuous and/or partial MB conduction, its conduction may be associated with the increased arrhythmogenicity of the LPVs. In this study, we examined the relationship between the preferential conduction properties of the MB and the arrhythmogenicity of the LPVs in 40 AF patients.

A 20-pole diagnostic catheter was positioned in the CS for pacing and recording. The upper and lower LPVs were simultaneously mapped with two adjustable 20-pole catheters (Optima, Irvine, USA) (Figure 11a). At first, RF energy during CS pacing was delivered along the LLR as a part of the LPV ablation (Figure 11b), and each ablation site and the conduction pattern during the RF delivery were monitored and recorded by fluoroscopy and a 3D electroanatomical system.

The earliest activated site of the upper LPV during CS pacing was observed at the carina lesion in 32 of 40 patients (80 %), anterior wall in four of 40 (10 %), and posterior wall in four of 40 (10 %). The earliest activated site was at the upper LPV in 34 of 40 (85 %), bottom of the lower LPV in four of 40 (10 %), and posterior site in two of 40 (5 %).

After the RF delivery along the LLR, the PV potentials of the upper LPV completely disappeared in one patient and that of the lower LPV in two patients. The conduction time between the LPVs and CS stimulus site was significantly prolonged during the RF delivery (before vs. after; upper, 91 ± 26 ms vs. 127 ± 38 ms, $p < 0.001$; lower, 86 ± 21 ms vs. 103 ± 22 ms, $p < 0.001$). A remarkable prolongation of more than 30 ms was observed in 19 of 40 patients (48 %) (both LPVs, 6; only the upper LPVs, 12; and only the lower LPV, 1). The sites of the remarkable prolongation during the RF delivery were observed at the carina between the LPVs [4], anterior site of the upper LPV carina [10], anterior wall of the lower LPV [3], and bottom of the lower LPVs [2].

Thirty-three AMF from LPVs (upper, 22; lower, 11) were observed in 23/40 patients (56 %). Fifteen of the detected foci directly shifted to AF, and 16 of them exhibited premature atrial contractions and/or transient frequent repetitive firings. The earliest activated site of the AMF

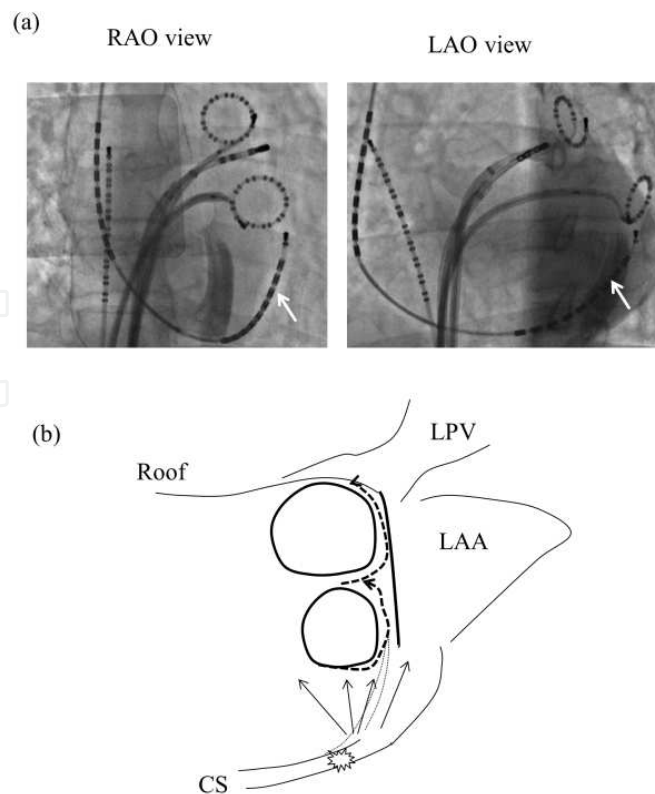


Figure 11. The location of the PV/non-PV foci showing the earliest atrial focus was determined by a reference for the local electrogram and the earliest activation site of the foci. The earliest activation sites from arrhythmogenic foci and during CS pacing were determined by the direction of the spontaneous activation recorded by double spiral catheters located in both LPVs. The pacing site during the RF application was delivered from the posterolateral CS, possibly from the takeoff site of the MB. The RF application along the LLR was sequentially delivered in a lower to upper manner (from the bottom of the inferior LPV, anterior wall of the inferior LPV, and LPV carina to the anterior wall of the superior LPV) during CS pacing.

from the upper LPV was found at the carina region in 12 of 22 (55 %), anterior wall in three of 22 (14 %), roof site in three of 22 (14 %), and posterior wall in four of 22 (18 %). The earliest activated site of the AMF from the lower LPV was found at the carina region in six of 11 (55 %), anterior wall in two of 11 (18 %), bottom in one of 11 (9 %), and posterior wall in two of 11 (18 %).

The conduction time from the CS to the earliest activated upper PV after the RF delivery was significantly longer in patients with AMF from the upper LPV than in those patients without (107 ± 36 ms vs. 146 ± 40 ms, $p<0.01$), and the conduction time from the CS pacing site to the earliest activation site of the upper LPV was significantly prolonged in the patients with AMF than in those without during the RF delivery (44 ± 22 ms vs. 17 ± 11 ms, $p<0.01$).

In this study, the earliest site of AMF from the LPVs was often determined to be around the carina region. These observations are likely to be consistent with the previous report [9]. In addition, the complex crossing of the muscular connections, bridges, neural inputs, and the adjoining muscle sleeves, possibly related to the MB conduction in the inter-PV carina, might promote electrical arrhythmogenicity including spontaneous ectopies of AF [10]. And also, the earliest activated site of the upper LPVs during CS pacing was highly observed around the

carina region, and also a remarkable prolongation jump during the RF delivery was highly observed around the carina and/or adjacent anterior area. A previous report suggested that the distal exit of the MB into the upper LPV is commonly located around the inter-PV junction, possibly bypassing the LPV junction to the left atrium [34]. These specific muscle orientations and the dominant MB conduction toward the carina region could promote the preferential conduction properties.

In addition, the prolongation of the conduction time between the CS and LPVs during the RF delivery was significantly more commonly observed in patients with upper LPV AMF than in those without. The preferential properties of the MB connecting to the LPVs might involve cross talk that promotes an increased LPV arrhythmogenicity [3, 4, 11]. A larger amount of preserved MB muscle as a remnant of the LSVC, which is related to the conduction properties of the LPVs, may be crucial for determining the increased arrhythmogenicity of the LPVs.

4. The efficacy of the sinus restoration strategy to detect arrhythmogenic foci for persistent AF

Catheter ablation (CA) of persistent AF may commonly be performed during ongoing AF, mainly targeting sites exhibiting complex atrial fractionated electrograms (CFAEs) and/or dominant frequencies (DFs) in addition to pulmonary vein (PV) isolation [35, 36, 37]. However, CA during ongoing AF may be limited especially in patients with a trigger dominant-type AF [20, 38, 19]. The rapid firing from the PVs and non-PV foci may beget enhanced automaticity, triggered activity, and localized micro-reentry as AF initiation and maintenance [37, 3, 10].

Our prior data suggested that an increased number of AMF are more highly observed during a vigorous sinus rhythm (SR) restoration strategy in persistent rather than paroxysmal AF [39], and the failure of the elimination of the AMF initiating an immediate recurrence of AF was significantly associated with the recurrence of persistent AF [40]. In this study, we performed CA based on a vigorous SR restoration strategy for persistent AF and evaluated the relationship between the electrophysiological features of the inducible AMF and recurrent AF episodes after the CA in 117 persistent AF patients.

The AF ablation strategy is summarized in Figure 12. We initially performed the PV isolation procedure by using a double circular mapping catheter technique. The DC energy was delivered with an external biphasic waveform of up to 270 J before the PV isolation. The electrical PV isolation was successfully accomplished with monitoring the circumferential electrical isolation at the antrum level: approximately 1–2 cm from of both the right and left PVs ostium.

After the PV isolation procedure, an additional RF energy application was primarily applied to create an LA roof line. When the AF was still persisted or inducible after LA roof line, additional mitral isthmus line or ablation of the area showing complex fractionated atrial electrograms (CFAEs) in left atrium was accomplished. When AF could not be terminated in

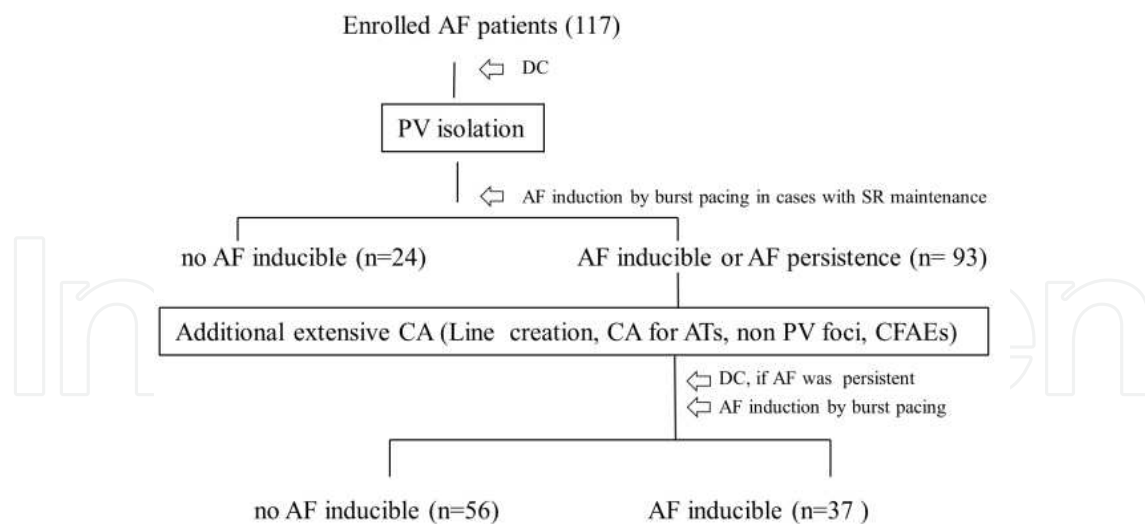


Figure 12. The summarized vigorous SR restoration strategy during the ablation according to the pacing-oriented AF inducibility. SR rhythm was restored by using external direct cardioversion before the PV isolation and line creation at the end of the ablation. AF was no longer inducible after only the PV isolation procedure in 24 of 117 patients (20.5 %). During the PV isolation, SR shifted to AF spontaneously and/or was triggered by the roving catheter in 68 of 117 patients

these series of procedures, direct cardioversion was delivered to restore SR again in such cases. Then, we confirmed whether complete block lines were created at the roof and mitral isthmus.

Extensive electrical isolation for PVs was successfully performed in all enrolled patients. An LA roof line was additionally created in 93 of 117 (80 %) patients after the extensive PV delineation, and the successful block line was confirmed in 86 of 93 patients (92 %). ATs were inducible in 61 of 117 patients (52.1 %) during the CA (tricuspid-dependent AT, 30; mitral annulus-dependent AT, 15; septal through, 5; LA anterior, 5; and upper loop in right atrium, 3). ATs with an unstable circuit were observed in five patients. A mitral isthmus line was additionally created in 34 of 117 patients (29 %). We confirmed a successful mitral block in 22 of 34 patients (65 %). Epicardial approach from the CS was needed in 18 out of 34 patients (53 %). Ablation targeted to the CFAEs was performed in 19 of 117 patients (16 %). Three common atrioventricular nodal reentry tachycardias (AVNRT) and one sinus nodal tachycardia (SANRT) were induced and successfully terminated.

At the end of the CA, residual AF could still be induced in 37 out of 117 patients (31.6 %), and also residual ATs were still inducible in 30 of 117 (25.6 %) (MI-dependent AT, 5; localized in LA anterior, 3; LA septal, 1; stable unknown, 11; and unstable, 11). Cardiac tamponade occurred in one of 117 (0.85 %) patients during the ablation. A nonsurgical drainage was successfully performed in those cases. The mean procedural time was 174±35 min, and the mean fluoroscopic time was 52±16.8 min.

At the end of the CA, residual AMF were still found in 48 of 117 patients (41.0 %) (directly shifted to AF, 22; reproducible atrial premature beats, [26]. The locations included the left atrial posterior wall [6], superior vena cava [3], crista terminalis [4], left lateral area [1], interatrial septum [1], coronary sinus ostium [1], and unknown [32]. The number of AMF during the CA

was significantly higher in the patients with residual AMF than in those without (2.3 ± 1.2 vs. 3.0 ± 1.2 , $p=0.041$).

The incidence of non-PV AMF was significantly higher in the patients with pacing inducible AF than in those without [69 % vs. 47 %, $p=0.032$]. The residual AMF were significantly higher in the patients with pacing-inducible AF than in those without (67 % vs. 29 %, $p<0.001$).

The mean follow-up period after the CA was 937 days. The follow-up ratio was 106 out of 117 patients (90.6 %) at one year and 86 of 117 patients (73.5 %) at two years after the CA. In-hospital AF episodes were observed in 17 of 117 (14.5 %) patients, and a long-term AF recurrence was observed in 42 of 117 (35.9 %) patients. AT episodes after the CA were observed in 31 of 117 patients (26.4 %), and those were only observed within 3 months after the CA in 11 of 31 patients (35.4 %). AT episodes coexisted with the AF episodes in 16 of 31 patients (52 %). In the multivariable analysis, the AF duration (1.01 (1.00–1.02), $p=0.012$), LA volume (1.01 (1.01–1.02), $p=0.006$), and residual AMF (3.95 (1.32–11.8), $p=0.004$) were independent risk factors for recurrent AF. Figure 13 demonstrates the AF recurrence ratio in the patients with and without residual AMF. AF episodes after the CA were significantly greater in the patients with residual AMF than in those without (50 % vs. 26 %, $p=0.002$). The result of the study demonstrated that the residual AMF was a useful predicting parameter for the outcome of CA, and the clinical course was impressively favorable in patients without residual AMF (AF recurrence after initial session at two years was 26%). (58.1 %). At the end of the ablation, residual AF was still inducible in 37 of 117 patients (31.6 %).

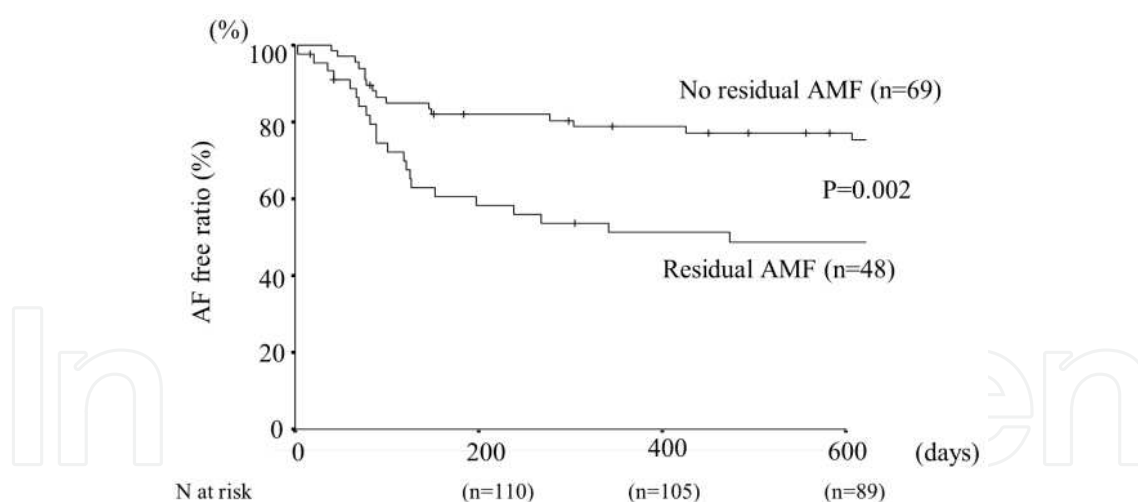


Figure 13. The AF recurrence ratio in the patients with and without residual arrhythmogenic foci during the follow-up. Residual foci were observed in 48 of 117 patients (41 %). The AF free ratio between both groups was compared by a log rank analysis, and AF episodes after the CA were significantly higher in the patients with residual foci than in those without (50 % vs. 26 %, $p=0.002$). The mean follow-up period was 937 days.

After only a PV isolation, AF was no longer inducible in approximately one fifth of the patients with a favorable outcome even though they underwent a less aggressive intervention. This information might allow us to reduce the number of unnecessary additional RF applications during CA. On the other hand, non-PV foci were also highly confirmed even in patients with

persistent AF [39]. Several studies have also addressed the importance of modifying the non-PV foci to improve the outcome of CA for AF [20, 23]. A vigorous SR restoration strategy might facilitate determining the non-PV arrhythmogenicity.

The data from this study also showed that non-PV AMF were closely associated with the AF pacing inducibility during CA. The development of the atrial remodeling process might enhance the triggered activity of the non-PV lesions, because the increased non-PV arrhythmogenicity may be associated with the atrial remodeling process including an enlarged LA [25, 41]. A recent study demonstrated that the response to ISP after CA more accurately predicted AF recurrences in patients with paroxysmal AF [38]. Residual AMF could increase the chance of AF initiation, and the significance of those may be especially pronounced particularly in cases that develop atrial remodeling.

In conclusion, these data support the role of arrhythmic triggers in determining eventual recurrences in patients with persistent AF and point to AMF as a potentially valuable early index of long-term ablation success.

5. Conclusions

AMF could be involved in mechanism of the AF development. In addition, atrial anatomical structure such as left atrial roof shape, left lateral ridge, and Marshall vein provided us with an understanding of the arrhythmogenicity of the PVs and non-PVs in patients with AF. Because the presence of residual AMF is associated with increased AF recurrence after ablation, the information of AMF is useful for determining the appropriate strategy of ablation for AF.

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