Novel Index for Determining the Development of Electrophysiological and Structural Atrial Remodeling in Patient with Atrial Fibrillation

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1. Introduction

The development of atrial remodeling process could contribute to the structural and electrophysiological changes in pulmonary veins (PVs) and atrium; which could promote local conduction abnormalities and cause an increased the arrhythmogenecity resulting in atrial fibrillation (AF) persistency. The efficacy of treatment strategy to restore sinus rhythm such as catheter ablation (CA) might be quite decreased in such cases with advanced atrial remodeling, therefore it is crucial to know the information associating with atrial electrical and structural remodeling for promoting AF.
In this study, we attempted to determine the novel factors relating the process of structural and electrophysiological remodeling in patients with AF in the inflammatory and anatomical views.

2. Novel index as increased inflammation determining the development of atrial remodeling

2.1 Backgrounds

The causes and pathogenesis of AF recurrences are multifactorial and are related to technical factors and a multitude of clinical factors; some studies have explored the possible role of inflammatory mechanisms in the pathogenesis of AF. The C-reactive protein (CRP) is a sensitive maker for reflecting a local or systemic inflammatory response, and some clinical studies also support the association of an elevated CRP level and an increase in AF episodes. In this study, we examined the association between a pre-existent inflammatory response and the recurrence of AF after CA, and clarified the clinical and electrophysiolocgical factors related to the CRP elevation.

2.2 Method

2.2.1 Study population

The study population consisted of 257 consecutive patients with drug-refractory episodes of AF who underwent radiofrequency catheter ablation. The patients' mean age was 61 years,

187 (73%) were male, and 77 (30%) had persistent AF defined as recurrent episodes of AF lasting more than 3 months. The exclusion criteria was as follows, 1; a left atrial diameter (LAD) of more than 55mm, 2; significant valvular disease requiring surgery, 3; an ejection fraction of less than 40%, and 4; hypertrophic obstructive cardiomyopathy. All antiarrhythmic agents (AAAs) were generally discontinued for at least 3 days before the CA. Vaugham-Williams Class I (Ia 47.9%, Ic 60.7%) AAAs was prior medicated in 80.9%, class II was 15.2%, class III was 10.5%, and class IV was 12.5%.

2.2.2 Electrophysiological study and catheter ablation

Transesophageal echocardiography was performed to exclude any left atrial (LA) thrombi. A 10-pole or 20-polar diagnostic catheter was positioned in the CS for pacing and recording. A 20-pole catheter was located in the right atrium to cover the area around the tricuspid annulus or superior vena cava (SVC). The LA and PVs were accessed by a transseptal approach. We introduced 3 steerable catheters including two spiral curve catheters into the left atrium through a single transseptal puncture site. The PVs were mapped with a circumferential 10-pole or 20-pole catheter (IBI, Irvine, CA, USA). The surface ECG and intracardiac electrograms filtered between 30 to 500 Hz were recorded simultaneously with a polygraph (DUO EP Laboratory; Bard Electrophysiology, Lowell, MA, USA). A single bolus of 150 IU/kg of heparin was administered after the transseptal puncture and repeated to maintain an activated clotting time of >300 seconds.

We initially performed a PV isolation procedure by using a double circular mapping technique during an isopreterenol administration (1-2 μg/min). We confirmed the success of the electrical PV isolation by monitoring the circumferential electrical isolation at the antrum level: approximately 1 cm from the ostium of both the right and left PVs. The complete disappearance of the potentials from all 4 PVs was confirmed in all patients. In case of burst-inducible AF after the PV isolation procedure, an additional roof line was created. Then, additional RF energy applications were appropriately applied for any mitral isthmus, induced atrial tachycardia circuits and complex fractionated electrical activity. If the arrhythmogenic foci were suspected to have originated from a non-PV area, they were located by searching with a roving catheter.

Radiofrequency (RF) energy was delivered for 30 to 60 seconds at each site using an 8mm tip catheter (Japan Life Line Co., Ltd., Fantasista, Tokyo, Japan). The RF energy was delivered with the power limited to 35 W. The temperature was limited to 55°C.

2.2.3 CRP measurement

The assessment of the CRP level was assessed by a high sensitive radio-immunoassay one day before the CA procedure. The CRP level was classified into 4 quartile levels (Quartile 1; <0.02 mg/dl, Quartile 2; 0.03-0.07 mg/dl, Quartile 3; 0.08-0.27 mg/dl, and Quartile 4; 0.28< mg/dl).

2.2.4 The evaluation of cardiac parameters

We measured the end-systolic LA diameter and the left ventricular parameters with 2D-echocardiography. LA volume and PV diameter was measured by integrating the volume traced in each slice of the 64-slice-MDCT scan (Philips Medicals Systems) one day before the CA.

2.2.5 Follow-up

All patients were discharged to home 3 days after the CA procedure and were seen in our hospital at 1-2 month intervals. The in-hospital AF episodes were carefully monitored for at least 2 days after the CA, and the AF episodes after discharge were adequately assessed by the patients' complaints, 12 lead ECG and 24 hour Holter ECG recordings. AF recurrence was defined as the occurrence of atrial tachyarrhythmias after a 2 month blanking period following the CA procedure. AAAs were given for 3 to 6 months to the patients with long-lasting persistent AF or to those with paroxysmal AF and easily induced residual AF. Following that, the AAAs were withdrawn and the AF episodes were further assessed without AAAs.

2.3 Result

2.3.1 CRP level relating clinical, structural, electrophysiological findings

Table 1 shows the association between the CRP quartiles and clinical characteristics. In clinical characteristics, the age, prevalence of structural heart disease, prevalence of hypertension, and number of prior anti-arrhythmic agents were significantly increased when the CRP level was elevated.

	Quartile 1 <0.02 (N=65)	Quartile 2 0.03-0.07 (N=64)	Quartile 3 0.08-0.27 (N=64)	Quartile 4 0.28< (N=64)	p value
Age (y.o)	59±11	62±10	61±10	64±10	0.026
Male (%)	74	71	75	71	0.95
SHD(%)	32	43	29	69	0.001
HT(%)	33	37	44	51	0.27
AF duration(y)	4.8	5.8	6.5	5.7	0.33
Persistent AF	36	21	35	27	0.21
Co-AFL(%)	25	29	34	30	0.77
# of AAAs	1.6	2.1	1.7	2.1	0.035

SHD; structural heart disease, HT; hypertension, Co-AFL; coexistent atrial flutter,
# of AAAs; number of anti-arrhythmic agents

Table 1. Patient characteristics and CRP quartiles

Table 2 shows the association among the CRP quintiles and structural, electrophysiological, procedural findings. In structural findings, the left atrial diameter was significantly increased for an elevated CRP level, and the LA volume also tended to be increased with a CRP elevation. IN electrophysiological findings, arrrhythmogenisity from PVs were significantly decreased when the CRP level was increased. However, the atrial substrate after PV delineation to maintain AF were highly observed when the CRP level was elevated.

	Quartile 1 <0.02 (N=65)	Quartile 2 0.03-0.07 (N=64)	Quartile 3 0.08-0.27 (N=64)	Quartile 4 0.28< (N=64)	p value
Structural findings					
LA diameter, (mm)					
(A-P)	35.1±5.5	35.6±5.6	36.5±5.5	38.1±5.5	0.001
(S-L)	38.1±6.6	39.3±5.8	40.0±7.4	40.0±6.9	0.25
(MV-PV)	53.7±8.3	52.2±8.8	54.0±9.0	51.7±8.3	0.46
LA volume, (cm3)	76.8±42	86.8±34	91.4±34	94.4±40	0.14
PV diameter, (mm)					
(LSPV)	19.1±2.8	18.3±2.5	18.5±3.5	19.3±3.7	0.76
(LIPV)	16.0±3.0	6.4±2.5	16.2±2.5	15.9±2.2	0.80
(RSPV)	19.1±3.4	18.4±3.1	19.0±2.9	18.4±2.4	0.66
(RIPV)	16.6±3.2	16.4±2.8	16.0±2.7	6.5±2.3	0.78
LVEF, %	64.3±12	65.1±12	64.7±8.3	59.5±13.2	0.08
Electrophysiological findings					
(Triggered AF)					
AF triggered by AFC (%)	75	71	68	61	0.38
AF triggered from PVs (%)	67	65	56	55	0.04
AFC from PVs (%)	93	90	84	0.19	
(Burst inducible AF)					
Pacing induced AF (%)	63	56	62	72	0.40
Pacing induced AT (%)	54	59	70	76	0.04
Residual inducible AF (%)	8	19	9	36	0.004
Procedural findings					
(Additional CA strategy)					
Roof line creation (%)	67	71	83	74	0.22
Mitral isthmus line (%)	22	33	32	26	0.60
SVC isolation (%)	25	15	13	16	0.41

LA; left atrium, A-P; anterior-posterior. S-L; septal-lateral, MV-PV; mitral valve-upper pulmonary vein
AFC; arrhythmogenic foci, AT; atrial tachycardia, CA; cathter ablation,

Table 2. Structural, electrophysiological and procedural findings and CRP quartiles

2.3.2 CRP level and clinical course

Figure 1 represents the relation between the AF occurrence after the CA and the CRP quartiles. AF occurrence after CA was significantly higher when the CRP level was elevated (quintile 1; 11%, quintile 2; 13%, quintile 3; 20%, and quintile 4; 30% $p<0.001$).

The univariate analysis revealed that the CRP quartile, left atrial diameter, persistent AF, AF duration (m), number of prior AAAs, mitral isthmus line and superior vena cava isolation were significant factors for an AF recurrence. The multivariate analysis revealed that the CRP quartile [Odds ratio (95% CI); 2.06 (1.02-4.22)] was an independent factor to AF recurrences, as well as, the left atrial diameter [1.31(1.12-1.52)] and persistent AF[1.09(1.01-1.19)].

Figure 2 represents the effects of statins on the AF recurrence. The use of statins was significantly associated with a decreased incidence of an AF recurrence (7% vs. 19%, $p<0.05$), whereas the use of ACE or AII antagonists was not significantly associated with an AF recurrence (16% vs. 16%, $p<0.05$).

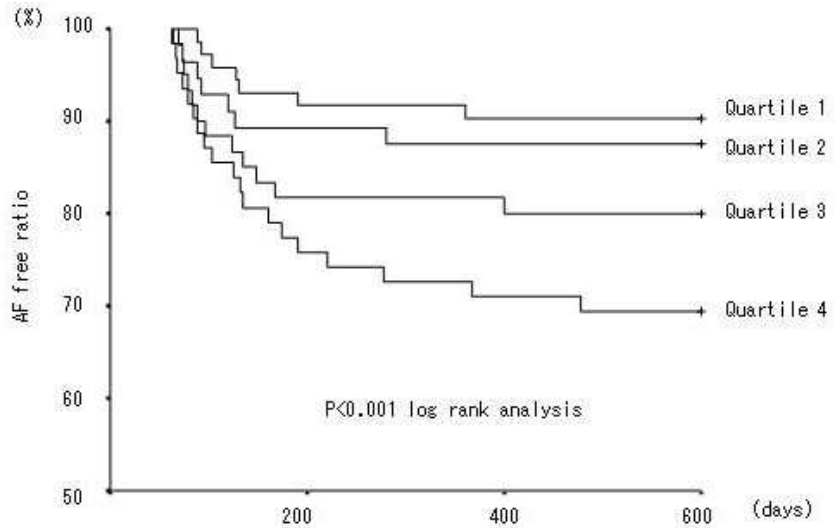

Fig. 1. The relation between the AF occurrence after the CA and the CRP quartiles.

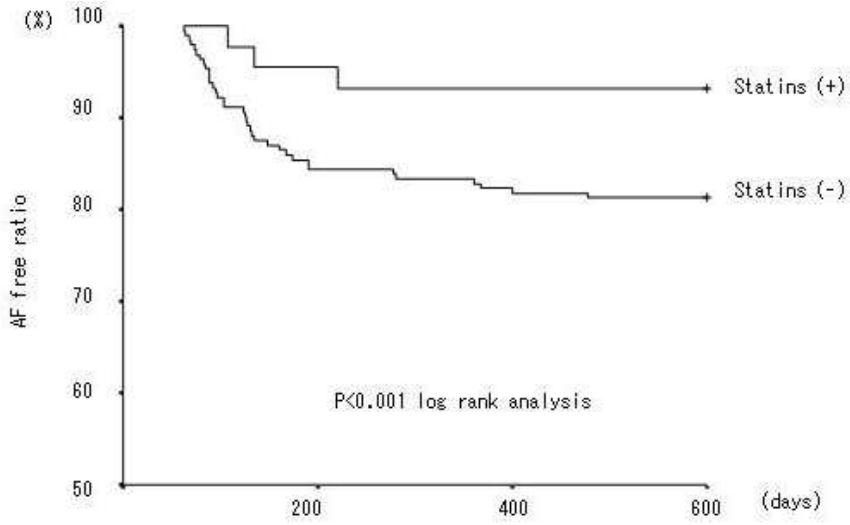

Fig. 2. The statin use and the AF occurrence after the CA.

2.3.3 The comparison of parameter and outcome between paroxysmal and persistent AF

CRP level (0.18±0.26 vs. 0.33±0.89 mg/dl, p=0.042) and left atrial diameter (35.1±5.4 vs. 38.9±5.2, p<0.001) were significantly lower in patients with paroxysmal than persistent AF. As procedural findings, the additional roof line creation (64% vs. 95%, p<0.001) and mitral isthmus line creation (13% vs. 37%, p=0.038) were significantly lower in patients with

paroxysmal than persistent AF. The residual burst pacing inducible AF at the end of CA was significantly lower in patients with paroxysmal than persistent AF (14% vs. 36%, $p<0.001$). Figure 3 demonstrated the comparison of AF recurrence between paroxysmal and persistent AF. AF recurrence was significantly lower in patients with paroxysmal than persistent AF (15 % vs. 24%, $p<0.01$), although several clinical bias relating to structural remodeling were included between both groups.

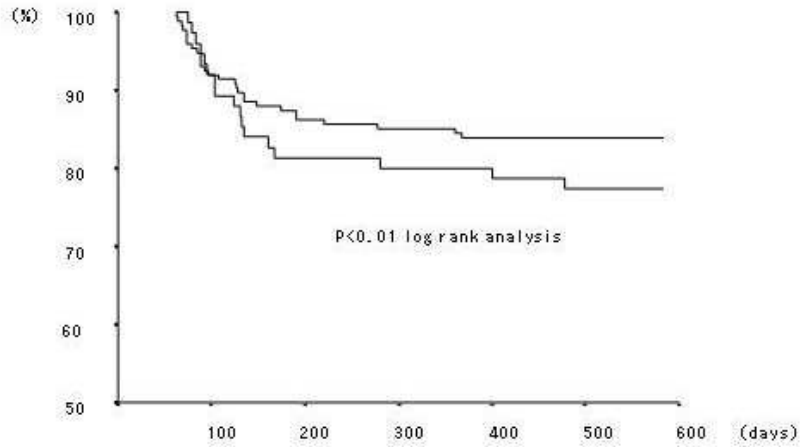

Fig. 3. The comparison of AF recurrence between paroxysmal and persistent AF.

2.4 Discussion

2.4.1 Epidemiological significance of inflammation on AF

Epidemiological studies have demonstrated that during an inflammatory response the CRP level is significantly higher in AF patients than in non-AF patients, and the increased CRP level is an independent contributing factor for the future development of an AF occurrence (Chung et al. 2001). The concept that inflammation contributes to at least some types of AF is supported by the frequent occurrence of AF after cardiac surgery (Bruins et al. 1997), a genetic study (Gaudino et al. 2003), and the association of AF with pericarditis (Spodick 1976). In particular, AF occurrences were highly observed in 5 to 70% of patients after cardiac surgery (Hogue et al. 1999); which may explain the clinically significant impact of the inflammatory response on AF occurrences, whereas hemodynamic intolerance and neuro-hormonal factors may also basically be associated with the development of AF by promoting the atrial functional and anatomical remodeling process.

2.4.2 Inflammation and the AF occurrence after CA

It has been reported that the electrical reconnection of isolated PV potentials might mainly be related to the AF occurrence after CA in patients with paroxysmal AF (Cappato et al. 2003). However, a PV electrical isolation strategy alone for patients with an enlarged atrium or persistent AF might be quite limited. It is now recognized that the development of AF leads to electrical and structural changes within the atria that perpetuate the atrial tachyarrhythmia. Shortening of the atrial refractory period and prolongation of the atrial conductivity as the result of a remodeled atrium could allow for the promotion and

maintenance of multiple wavelet-re-entry circuits. The structural changes, including left atrial dilatation, further increase the fibrotic process with deposition of increased amounts of connective tissue, and promote the inconsistency and prolongation of the atrial conduction which leads to maintaining the perpetuation of AF. Previous studies have shown that AF recurrence after CA is significantly higher in patients with inducible AF after the PV isolation than in those without AF (Wright et al. 2008), and a younger age, smaller left atrial diameter(Van Gelder et al. 1991), and shorter duration of AF(Wijffels et al. 1995) are predictors of sinus rhythm maintenance. The results of those studies suggest that many of the AF recurrences are thought to be secondary to electrical and structural remodeling. In this study, the increased CRP level was significantly associated with an advanced age and structural heart disease with a significant relationship to a high AF inducibility after the PV isolation during the CA. Thus, these findings indicate that an increased CRP level might be a useful marker for the atrial remodeling process which would promote the future development of AF after the CA.

2.4.3 The mechanism of AF occurrence caused by inflammation

The precise mechanism for the increased circulating CRP level in AF is uncertain, but might reflect the active participation of CRP in the local inflammatory response within the atrial myocardium. In this study, AF recurrence was clearly associated with increased CRP levels even after the adjustment for confounding factors; which implies that the CRP may have a direct linkage to the AF occurrence, and not only be a secondary marker for atrial remodeling. Historical evidence to support a direct association between AF and inflammation can be extracted from the frequent association of AF to inflammatory conditions of the heart, such as myocarditis and pericarditis. Transient AF episodes were frequently observed after open heart surgery, and the results of the atrial biopsies taken from patients in AF have demonstrated evidence of inflammatory infiltration within the atrial tissue (Frustaci et al. 1997). The CRP could possibly bind to the membranes of the myocardial cells in inflamed tissues, and release an activating complement, leading to tissue damage. Data from ischemic heart disease also supporting the deposits of CRP, have also been demonstrated on immunohistochemical staining, in the vascular wall of active atherosclerotic plaques, where it is co-localized with the complement complex (Lagrand et al. 1997). Moreover, CRP has been shown to act as an opsonin and may participate in the clearance of apoptotic myocyte loss (Mevorach 2000). Myocyte loss is typically accompanied by replacement fibrosis. Thus, that local inflammatory response in the atrium may also be a part of the structural remodeling process associated with an increased occurrence of AF.

2.4.4 Anti-inflammatory agents for preventing AF occurrences

Recently studies have shown that the use of anti-inflammatory agents is associated with a decreased incidence of AF. The capacity of statins to reduce inflammation, CRP levels and oxidative stress is well-established (Strandberg et al. 1999) (Plenge et al. 2002). In a retrospective study, statins decreased the recurrence after successful external cardioversion of persistent lone AF (Siu et al. 2003); in a prospective analysis, statins protected against atrial fibrillation in patients with stable coronary artery disease (Young-Xu et al. 2003). The use of statins has recently been related to a 3-fold decrease in the odds of AF after noncardiac thoracic surgery (Amar et al. 2005), and has a lower incidence of AF (Marin et al. 2006) or other cardiac arrhythmias (Dotani et al. 2000) after coronary artery bypass surgery.

Pretreatment with statins, which significantly reduces the inflammatory cytokines and prevents the adhesion between the inflammatory cells and endocardium, is likely to facilitate the prevention of inflammatory mediated AF episodes.
There is evidence suggesting an association between AF and an enhanced renin angiotensin system activity. Experimental studies have revealed that angiotensin II possesses several pro-inflammatory properties which is the key mediatory factor in the inflammatory cascade (Healey et al. 2005). Further, angiotensin II exhibits a growth-enhancing effect on cardiac myocytes as well as on vascular smooth muscle cells and fibroblasts, thus resulting in the remodeling and fibrosis of the atria that could serve as a potential arrhythmogenic substrate for the development of AF. ACE-Is or angiotensin II antagonists have been shown to decrease the inflammatory response. (Brull, Sanders et al. 2002) (Hernandez-Presa et al. 1997), and prevent the development of myocardial fibrosis related to the electrical and structural remodeling process (Nakashima, Kumagai et al. 2000) (Fortuno et al. 1998) (Lopez et al. 2001).
In the data from this study, the patients with a pre-statin treatment experienced a significant decrease in AF episodes after the CA, however the patients with a pre-ACE-I or AII antagonist treatment did not experience that beneficial effect. The patients medicated with statins tended to include younger patients, whereas those medicated with ACE-Is or AII antagonists tended to include older patients with hypertension or a reduced ventricular function; which may have modified the results of the analysis of our data.
Recent clinical studies have demonstrated that the CRP level is transiently elevated after CA (Marcus et al. 2008), and that the short-term AF episodes were transiently increased (Oral et al. 2002). These reports also suggested that the increased inflammatory response from the CA procedure may increase the following transient occurrences of AF. Pretreatment with statins significantly improved the short-term outcome within 3 days, and not only the long-term outcome after the CA in this study; which may be expected to facilitate a reduction in the AF occurrences after CA and improve the symptoms due to tachyarrhythmias with the avoidance of any unnecessary second CA procedures. Further studies are required to examine the beneficial effect of anti-inflammatory agents on improving the short and long term outcome after CA.

3. Novel index as left atrial roof shape determining the development of atrial remodeling

3.1 Backgrounds

The preexistent morphology of the PVs could modify their arrhythmogenicity (Lin et al. 2000; Lee et al. 2005; Pak et al. 2006). The development of the remodeling process could contribute to the structural and electrophysiological changes in the PVs and atrium; which could promote local conduction abnormalities and cause an increased PV/non-PV arrhythmogenecity resulting in AF persistency (Lee et al. 2005) (Wijffels et al. 1995) (Hoit et al. 1998) (Chen et al. 2002) (Johnson et al. 1986). This evidence supports the observation that the morphological findings of the PVs and atrium may include a crucial role of helping to identify the characteristics of their pre-existing arrhythmogenicity (Kurotobi et al. 2011). However, there is a methodological limitation of the PVs and atrium in order to evaluate the morphological characteristics in a quantitative manner because of their own unique, variable and asymmetrical features.
The part of the left atrial (LA) roof which consists of the upper wall of the left atrium and upper PVs, incorporating the LA, was described as the LA roof silhouette, and could easily be visualized by pulmonary angiography or CT imaging. The morphological findings of the PVs and atrium may include a crucial role of helping to identify the characteristics for the

electrical and structural remodelling. In this study, we examined the hypothesis that the LA roof shape could be used as a novel predictor in patients with AF to allow us to determine the characteristics of the PVs, atrial arrhythmogenicity and substrate for promoting AF.

3.2 Methods

3.2.1 Study population

The study population consisted of 153 consecutive patients with drug-refractory episodes of AF who underwent radiofrequency catheter ablation (CA). The patients' mean age was 62 years, 122 (80%) were male, and 58 (38%) had persistent AF defined as recurrent episodes of AF lasting more than 3 months. The exclusion criteria was same as CRP study.

3.2.2 Electrophysiological study and catheter ablation

Electrophysiological study and ablation procedure was same as CRP study, and had already stated in the section of 2.2.2.

3.2.3 The induction and detection of the arrhythmogenic foci

The induction of arrhythmogenic foci was performed according to our previously reported paper (Kurotobi, Iwakura et al.). In brief, spontaneous arrhythmogenic foci in both atria were induced and carefully mapped before and after the PV isolation procedure using an intravenous infusion of high dose isoproterenol (ISP) of up to 20 μg/min without any sedation. If AF persisted or spontaneously occurred under the ISP, we attempted to cardiovert the AF up to 3 times. To detect the location of the arrhythmogenic foci, we simultaneously used five multipolar catheters to record the electrograms from the PVs and outside the PVs to search for any arrhythmogenic foci. A 20-pole catheter (2 mm inter-electrode spacing) covered the area from the SVC to the crista terminalis, coronary sinus, and ostium of the left PVs. A roving catheter was located at the right superior PV ostium. During the ablation procedure, the ISP administration was maintained at 1-2 μg/min. At the end of the procedure, the same induction maneuvers as in the initial protocol (up to 20 μg/min) were repeated. Arrhythmogenic foci were defined as direct AF triggers or spontaneous reproducible atrial premature beats with coupling intervals of < 350ms or frequent repetitive firings.

3.2.4 The evaluation of left atrial volume

We measured the end-systolic LA diameter and left ventricular parameters with 2D-echocardiography. The LA volume and PV diameter were measured by integrating the volume traced in each slice of the 64-slice-MDCT scan (Philips Medicals Systems) during several days prior to the CA. To enhance the cardiac cavity, contrast medium was injected at a flow-rate of 2.5 mL/s through an antecubital vein using an injector. The LA volume was measured by integrating the volume traced in each slice of the CT scan from the level of the mitral annulus to the roof of the left atrium with commercially available software (EP planner, Philips Medical Systems, Haifa, Israel). Each slice was automatically traced with digital markers to exclude the PVs and LA appendage at their ostial level. The LA appendage was excluded from the volumetric analysis.

3.2.5 The assessment of the LA roof shape

According to the PVs and LA dominant level, we classified the LA roof shape into a deep V shape (group A; Possible PV dominant type), shallow V shape (group B) and flat-coved

shape (group C; Possible LA dominant type) using both PVs cine angiography (Figure 4). Cine angiography was performed by spontaneous contrast medium injection from the long sheath located at the upper right and left PVs. The shape of LA roof was determined by using antero-posterior projection, and was assessed by an upper angle between the right and left side LA wall silhouette. Deep V shape (A) was defined an less than 140°, shallow, V shape (B) was 140°-180°, and flat-coved shape was more than 180°(C).

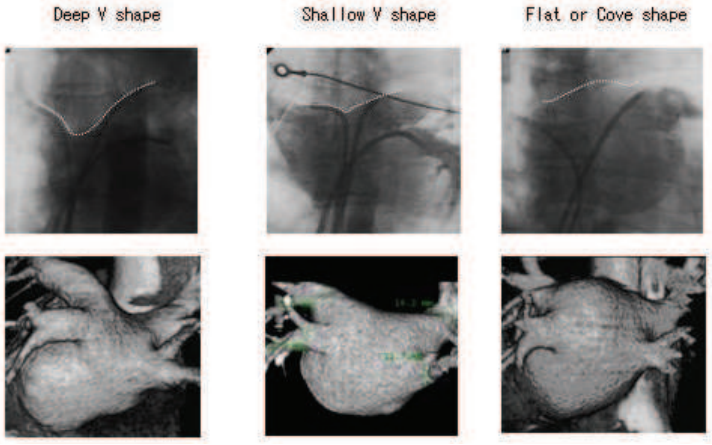

Fig. 4. Classification of roof shape.

3.3 Results

3.3.1 Patient characteristics and roof shape

The comparison of the patient characteristics among group A, B and C are shown in Table 3. Group A was observed in 35 patients (23%), B in 76 (50%), and C in 42 patients (27%). There were no significant differences in the mean age, mean AF duration, or clinical coexistence of atrial flutter, among the 3 groups. As the LA roof silhouette became flat, the number of prior of AAD's (A; 2.1±0.9 vs. B; 1.7±1.4 vs. C; 1.2±0.8, p=0.003) significantly decreased, and the prevalence of structural heart disease (A; 19% vs. B; 40% vs. C; 68%, p=0.002) and persistent AF (A; 26% vs. B; 35% vs. C; 52%, p=0.014) significantly increased.

	d-V (n=35)	s-V (n=76)	F-C (n=42)	p value
Age (years)	64.7±8.9	61.4±11.3	62.8±8.7	0.40
Male (%)	83	75	86	0. 69
SHD (%)	19	40	68	0.002
Hypertension (%)	30	24	46	0.10
AF period (m)	63.8	67.1	67.0	0.83
Per-AF	26	35	52	0.014
The duration of pe-AF	14.3	22.7	37.8	0.108
Co-AFL(%)	27	26	39	0.42
# of AAD	2.1±0.9	1.7±1.4	1.2±0.8	0.003

SHD; structural heart disease, Co-AFL; coexistent atrial flutter, AAD; anti-arrhythmic drug per-AF; persistent AF

Table 3. Clinical background and roof shape

3.3.2 Relationship among the LA roof shapes and electrophysiological and structural findings

The electrophysiological and structural findings of each roof shape group are shown in Table 4.

As the LA roof silhouette became flat, the incidence of AF arising from the PVs (A; 70% vs. B; 57% vs.C; 40%, p=0.003), AF from the upper PVs (A; 63% vs. B; 41% vs. C; 38%, p=0.046) and from arrhythmogenic foci including reproducible premature beats (A; 94% vs. B; 84% vs. C; 76%, p=0.033) significantly decreased. On the other hand, the incidence of AF arising from non-PV sites (A; 6% vs. B; 13% vs. C; 22%, p=0.041) and from arrhythmogenic foci from non-PV sites (A; 26% vs. B; 46% vs. C; 54%, p=0.016) significantly increased as the LA roof silhouette became flat. A multivariate analysis demonstrated that the deep V shape was an independent contributing factor to AF triggers from PV [Odds ratio (95% CI); 2.94 (1.27-6.80), p=0.012]. As the LA roof silhouette became flat, the incidence of pacing inducible AF just after the PV isolation (A; 51% vs. B; 65% vs. C; 79%, p=0.001) and at the end of the CA (A; 12% vs. B; 24% vs. C; 36%, p=0.016) significantly increased.

The LA diameter (A-P; 33.1±2.8 mm for A vs. 37.4±5.6mm for B vs. 40.2±6.3mm for C, p<0.001;. S-L; 36.1±5.8 mm for A vs. 39.4±6.6 mm for B vs. 43.2±6.8 mm for C, p<0.001; MV-PV; 48.2±6.0 mm for A vs. 55.3±8.7 mm for B vs. 58.4±7.6 mm for C, p<0.001.) and entire LA volume (A; 69.5±24.1 ml vs. B; 85.2±34.9ml vs. C; 105.7±45.4, p<0.001) became significantly larger, as the LA silhouette became flat. The PV diameter of each PV and left ventricular ejection fraction did not differ between the three roof shape groups.

	deep V (n=35)	shallow V (n=76)	flat or cove (n=42)	p value
Electrophysiological findings				
Trigger inducible AF (%)				
AF from 4PVs	70	57	40	0.003
AF from upper PVs	63	41	38	0.046
AF from non-PV sites	6	13	22	0.041
AFCs from 4PVs	94	84	76	0.033
AFCs from upper PVs	90	76	64	0.02
AFCs from non-PV sites	26	46	54	0.016
# of AF foci from PVs	0.86	0.76	0.80	0.82
# of all AF foci	2.03	1.93	2.29	0.28
Pacing inducible AF (%)				
Just after PVI	51	65	79	0.001
At the end of the CA	12	24	36	0.016
Structural findings				
Left atrial diameter, (mm)				
(A-P)	33.1±2.8	37.4±5.6	40.2±6.3	0.001
(S-L)	36.1±5.8	39.4±6.6	43.2±6.8	0.001
(MV-PV)	48.2±6.0	55.3±8.7	58.4±7.6	0.001
LA volume, cm^3	69.5±24.1	85.2±34.9	105.7±45.4	0.001
PV diameter (mm)				
(LSPV)	18.5±2.8	19.0±2.9	18.5±4.8	0.19
(LIPV)	15.3±2.4	15.8±2.2	15.5±3.2	0.74
(RSPV)	18.6±2.6	19±3.2	19.3±3.7	0.32
(RIPV)	15.8±2.2	15.9±2.6	15.7±2.9	0.83
LVEF, %	66.1±8.6	63.3±13.7	59.7±13.1	0.08

PVs; pulmonary veins, PVI; pulmonary vein isolation, CA; catheter ablation procedure
AF; atrial fibrillation, AFCs; arrhythmigenic foci,
AFCs include reproducible atrial premature beats as the possible AF trigger.

Table 4. Relation between the LA roof shapes and electrophysiological and strictural findings

3.3.3 Clinical outcome

An in-hospital recurrence was observed in 28/152 (18%) patients, and a long-term AF recurrence was observed in 29/152 (19%) patients. The mean follow-up period after the CA was 567 days (360-1065 days). The AADs were used were administrated after the CA in 30% of the patients (persistent; 47%, paroxysmal; 23%). The ratio of additional LA roof line (A; 64% vs. B; 84% vs. C; 88%, $p<0.05$), and mitral isthmus line (A; 14% vs. B; 22% vs. C; 34%, $p<0.05$) during CA were significantly highly required as the LA silhouette became flat, whereas the AF recurrence was not significantly different among three groups (A; 18% vs. B; 18% vs. C; 23%, n.s.) .

3.4 Discussion

3.4.1 LA roof shape and PV/LA dominancy

From the embryological view, the PV trunks are shown to derive from a common vessel, which becomes absorbed within the LA from superior-posterior direction. This incorporation transforms the branches of this common PV into separately inserting individual 4 PV trunks, first into the right and left PV trunks and subsequently into the superior and inferior trunks (DeRuiter et al. 1995) (Neill 1956) (Yamane et al. 2008). Anatomical PV structure could be caused by either anomalous branching of the common PV or by the variable absorption level of the common PV into the LA, therefore the incorporation level could mainly determine the LA roof shape according to the PV/LA dominancy level. When the common PV was incorporated into LA with a greater dominancy PVs, the silhouette of LA roof could be expressed by the upper wall of superior PVs; which the roof shape may be expressing as a V. On the other side, that was incorporated into LA with a less dominancy PVs, the silhouette of LA roof could be mainly expressed by the existent upper LA wall; which the LA roof may tend to be a flat shape.

In this study, an enlarged LA volume has a significant association with flat or coved LA roof shape. The development of the atrial structural remodeling process may also change the LA roof shape. Vertical LA enlargement could modify LA roof shape and sometimes overlap the PV silhouette as a component of LA roof, because the location of PVs is strictly stick to right and left lungs. Horizontal LA enlargement may promote the development of flat LA roof. Moreover, the advancement of cardiac rotation as a result of aging or hypertensive change; which is possibly related to atrial remodeling process, may also change the LA roof silhouette.

3.4.2 LA roof shape and PV arrhythmogenicity

AF is mainly initiated by PV triggers (Haissaguerre et al. 1998), and a rapidly firing source located within the PVs could be responsible for initiating, and in some cases, maintaining arrhythmias in patients with AF. The mechanism underlying such rapid discharges from PVs, including enhanced automaticity or triggered activity mechanisms may be involved in the initiation of AF (Patterson et al. 2005). In this study, AF triggers from PVs were highly observed in the patients with a deep V LA roof shape and PV dominancy. A previous paper reported that AF tended to originate from larger pulmonary veins (PVs) (Yamane et al. 2002). Especially in the superior PVs, the enlargement may often be consistent with the site of the arrhythmogenic PVs (Lin et al. 2000). PV enlargement caused by the stretch mechanism may increase the PV's automaticity and/or triggered activity to initiate AF (Satoh and Zipes 1996). However, there was no significant relation between the LA roof

shape and PV diameter in this study. These findings may imply the novelty and independence of the LA roof shape as an index of the PV's arrhythmogenicity, as compared with the prior reports which discussed the PV features.

3.4.3 LA roof shape and non PV arrhythmogenicity

Non-PV foci could arise from the superior vena cava, left atrial posterior free wall, crista terminalis, ostium of the coronary sinus, inter atrial septum, or Marshall bundle (Hwang, Wu et al. 2000) (Chen et al. 1999) with an incidence of those ranging from 3.2 to 47% (Lin et al. 2003) (Mangrum et al. 2002) (Schmitt et al. 2002). The predominant non-PV triggering sites have a slow diastolic depolarization that enhances spontaneous depolarization (Chen et al. 2002), and the triggered activity of the non-PV triggers could also be involved in the onset and perpetuation of AF..

Because triggered activity is likely to occur in the presence of underlying disease such as cardiomyopathy (Boyden et al. 1984), the development of the atrial remodeling process may enhance the triggered activity of non PV lesions. A previous study reported that multiple PV arrhythmogenic foci may be associated with an older age, longer AF duration, and larger atrial all triggers (Lee et al. 2005), and persistent AF is more frequently triggered by foci from the LA side of the LA–PV junction than is paroxysmal AF(Pak et al. 2006). These findings could explain why the flat and cove LA roof as a result of advanced atrial remodeling increased the non PV arrhythmogenisity in this study.

3.4.4 The significance of LA roof shape as ablation strategy

It is now recognized that the development of AF leads to electrical and structural changes within the atria that perpetuate the atrial tachyarrhythmia. The structural changes, including the enlarged LA, further promote the inconsistency and prolongation of the atrial conduction which leads to maintaining the perpetuation of AF. In this study, the incidence of pacing inducible AF just after PV isolation and at the end of the CA significantly increased, as the LA roof silhouette became flat. A previous paper reported that AF recurrence after CA was significantly higher in patients with inducible AF after the PV isolation than in those without AF (Wright et al. 2008), therefore that evidence indicates the importance of a flat or coved LA roof shape as a reflection of any latent AF substrate in the atrium. And also, the development of the atrial remodeling process could enhance the triggered activity of non-PV lesions(Lee et al. 2005) (Boyden et al. 1984). In this study, non-PV foci were significantly more often observed in patients with a flat-coved LA roof shape.

P V isolation is the cornerstone of the treatment especially in patients with paroxysmal AF, however the PV electrical isolation strategy alone in patients with a remodeled atrium might be quite limited. Many of the AF recurrences are thought to be secondary to electrical and structural remodeling (Wijffels et al. 1995) (Van Gelder et al. 1991). Thus, a further additional extensive intervention following the PV isolation might be required to improve the outcome of the CA in patients with a flat-coved LA roof, whereas only a PV isolation strategy could lead to a favorable outcome in patients with a deep V LA roof.

4. Conclusion

Pre-exsistent CRP level and the shape of the LA roof shape as novel factors allowed us to understand the structural and the electrophysiological information of the pulmonary vein

and atrium. This information is useful for determining the appropriate strategy for the CA of AF.

5. Ackonowledgements

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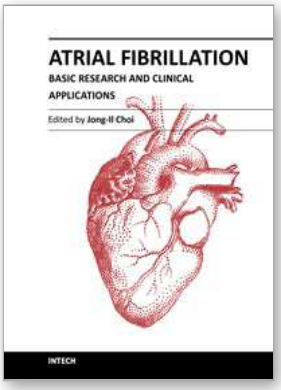

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