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Association Between Plaque Thickness of the Thoracic Aorta and Recurrence of Atrial Fibrillation After Ablation

Hui-Jeong Hwang, MD, Man-Young Lee, MD, Ho-Joong Youn, MD, Yong-Seog Oh, MD, Tae-Ho Rho, MD, Wook-Sung Chung, MD, Chul-Soo Park, MD, Yun-Seok Choi, MD, Woo-Baek Chung, MD, Jae-Beom Lee, MD, Hyun-Keun Park, MD, KeunJoon Lim, MD, and Jae Hak Lee, MD

Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea

ABSTRACT

Background and Objectives: Several predictors of recurrence of atrial fibrillation (AF) after ablation have been identified, including age, type of AF, hypertension, left atrial diameter and impaired left ventricular ejection fraction. The aim of this study was to investigate whether the atherosclerotic plaque thickness of the thoracic aorta is associated with a recurrence of AF after circumferential pulmonary vein ablation (CPVA). **Subjects and Methods:** Among patients with drug-refractory paroxysmal or persistent AF, 105 consecutive (mean age 58±11 years, male : female=76 : 29) patients who underwent transesophageal echocardiography and CPVA were studied. The relationships between the recurrence of AF and variables, including clinical characteristics, plaque thickness of the thoracic aorta, laboratory findings and echocardiographic parameters were evaluated. **Results:** A univariate analysis showed that the presence of diabetes {hazard ratio (HR)=3.425; 95% confidence interval (CI), 1.422-8.249, p=0.006}, ischemic heart disease (HR=4.549; 95% CI, 1.679-12.322, p=0.003), duration of AF (HR=1.010; 95% CI, 1.001-1.018, p=0.025), type of AF (HR=2.412, 95% CI=1.042-5.584, p=0.040) and aortic plaque thickness with ≥4 mm (HR=9.514; 95% CI, 3.419-26.105, p<0.001) were significantly associated with the recurrence of AF after ablation. In Cox multivariate regression analysis, only the aortic plaque thickness (with ≥4 mm) was an independent predictor of recurrence of AF after ablation (HR=7.250, 95% CI=1.906-27.580, p=0.004). **Conclusion:** Significantly increased aortic plaque thickness can be a predictable marker of recurrence of AF after CPVA. **(Korean Circ J 2011;41:177-183)**

KEY WORDS: Atrial fibrillation; Catheter ablation; Atherosclerosis; Aorta, thoracic.

Introduction

Atrial fibrillation (AF) is an important risk factor for stroke, thromboembolism and congestive heart failure, leading to substantial morbidity and mortality from cardiovascular and cerebrovascular events.[1-3] The development of AF is influenced by age,[4)5)] gender,[4)6)] ischemic heart disease (IHD),[7)] valvular heart disease and cardiovascular risk factors, such as hypertension,[8)] diabetes[7)] and obesity.[9)] Some reports have also suggested that atherosclerosis is associated with the occurrence of AF.[10-13)]

Catheter ablation has emerged as a therapeutic option in patients with symptomatic, drug-resistant AF. However, the recurrence rate of AF after an ablation procedure has been reported to be variable, ranging from 15-30%.[8)14)15)] Prior studies have identified a number of predictors of outcome following AF ablation, including age,[5)] type of AF,[5)] hypertension,[8)] left atrial (LA) diameter[5)8)] and impaired left ventricular ejection fraction (LVEF).[8)16)] The aim of this study was to investigate whether aortic plaque thickness measured by transesophageal echocardiography (TEE), is associated with the recurrence of AF after circumferential pulmonary vein ablation (CPVA).

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Correspondence: Man-Young Lee, MD, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, 62 Yeouido-dong, Yeongdeungpo-gu, Seoul 150-713, Korea
Tel: 82-2-3779-1325, Fax: 82-2-3779-1374
E-mail: myleecardio@catholic.ac.kr

• The authors have no financial conflicts of interest.

Subjects and Methods

Patient population

We retrospectively evaluated 105 consecutive patients (mean age 58±11 years, male : female=76 : 29) who underwent circumferential pulmonary vein (PV) mapping and ablation because of symptomatic, drug-refractory paroxysmal AF (PAF) or persistent AF (PeAF), between June 2005 and January 2009. All the patients had been refractory to the treatment with at least one antiarrhythmic agent, including class I or class III drugs. Transthoracic echocardiography (TTE) and TEE were performed before the ablation procedure. Clinical data were collected from the patients' through telephone interviews, and from the medical records during follow-up.

The duration of AF was determined based on the clinical symptoms and or electrocardiographic documentation. PAF was defined as the occurrence of two or more episodes of AF during the previous 12 months, typically lasting <7 days and terminating spontaneously. PeAF was defined as the occurrence of episodes of AF sustained beyond 7 days, and usually requiring pharmacological therapy or cardioversion for the restoration of a normal sinus rhythm.[17] The recurrence of AF was defined as a documented episode of AF lasting for >30 seconds on electrocardiography (ECG) or 24-hour Holter monitoring.[18] AF episodes within the first three months after the ablation procedure were not considered in the evaluation of the final success rates because they are often described as transient recurrences related to the atrial inflammatory processes following ablative lesions.[18][19]

The patients were informed of the investigative nature of the study and their written consent was obtained prior to their participation in the study. This study was approved by the Institutional Review Board of St. Mary's Hospital, The Catholic University of Korea (SC10RISI0031).

Transesophageal echocardiographic assessment of the thoracic aorta

TEE was performed according to standard practice guidelines[20] using commercially available ultrasonographic instruments (GE Healthcare Vivid 7 Pro equipped with 5 MHz transesophageal probe and Hewlett-Packard SONOS 5500 equipped with 6 MHz probe). Peak velocity (Vmax) of the left atrial appendage (LAA) flow was recorded within 1 cm of the orifice of the appendage with pulse-wave Doppler interrogation, and evaluated in antegrade (emptying) directions, averaged over three consecutive cardiac cycles. Plaque was defined as an irregular intimal thickening of ≥1 mm protruding into the lumen with echogenicity. The plaque thickness was defined as the distance between the medial-adventitial border of the thoracic aorta and the internal side of the plaque. For examining the aortic plaque thickness, the transducer was pulled back from the level of the aortic valve (35-40 mm from the incisor) to the level of the aortic arch (15-20 mm from the incisor). The largest plaque measured in any region of the thoracic aorta was selected and plaques were classified into three categories based on the definition of simple vs. complex plaque depending on the plaque size:[20][21] <1 mm, 1-4 mm and >4 mm thickness (Fig. 1).

Transthoracic echocardiographic assessment

Prior to the ablation procedure, all the patients underwent TTE for assessment of cardiac structure and function. TTE was performed using the aforementioned echocardiographic instruments equipped with 4- to 5-MHz transthoracic transducers.

Left ventricular end diastolic diameter, left ventricular end systolic diameter and anteroposterior left atrial diameter (LAD) were measured by M-mode echocardiography in the parasternal view. LVEF was calculated using Simpson's method.[22]

Catheter ablation procedure

The patients were given oral anticoagulation for at least one month; this was stopped three days before the ablation procedure, intravenous heparin was infused from the day of admission to one day before the ablation procedure. Antiarrhythmic agents were stopped at least five half-lives before the ablation procedure, but amiodarone was stopped at least three weeks before the procedure. A PV CT was performed before the ablation procedure to integrate the anatomy of the left atrium (LA) and PV into a three dimensional (D) mapping system (CARTO, Biosense-Webster, Diamond Bar, CA, USA). Catheters were introduced through the left femoral vein and

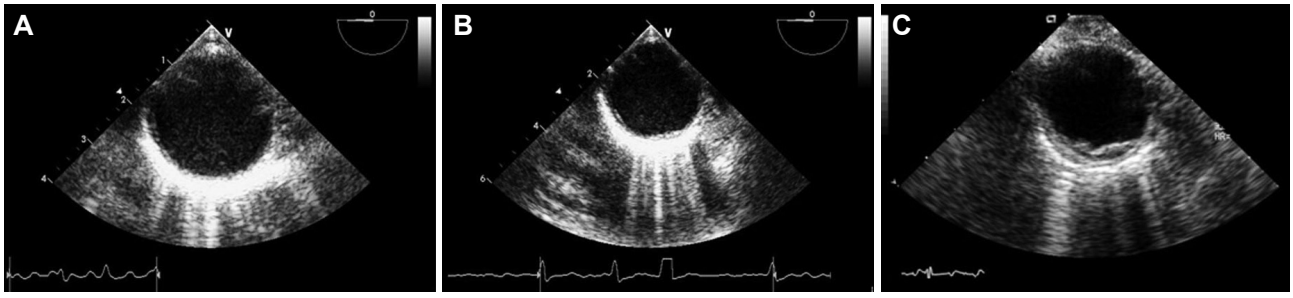


Fig. 1. Short-axis transesophageal echocardiographic views of the thoracic aorta showing aortic plaque thickness. A: plaques with <1 mm thickness. B: 2.2 mm plaque thickness (1-3.9 mm). C: 7 mm plaque thickness (≥4 mm).

right jugular vein. A 7 French (Fr) decapolar electrode catheter was positioned in the coronary sinus, a 6 Fr quadripolar catheter was placed in the right atrium and a hexapolar catheter was positioned in the His bundle recording area. A pigtail catheter was introduced into the main pulmonary artery through the right femoral vein. Pulmonary venograms were then obtained during the venous phase of the ipsilateral pulmonary angiography. After obtaining a transseptal access to the LA, an intravenous bolus of heparin (5,000 IU) was administered, and an additional bolus injection was delivered to maintain an activated clotting time between 250-350 seconds during the procedure. Mapping was performed during sinus rhythm. An irrigation tip catheter (7 Fr NaviStar thermocool, Biosense Webster Diamond Bar, CA, USA) was used for electroanatomical 3D mapping and ablation. A Lasso catheter was placed in each ipsilateral PV antrum (Fig. 2A). CPVA was performed along the ipsilateral PV antrum using a Lasso catheter as an electrical reference for electrical PV isolation using the CartoMerge mapping system, and roof line ablation was then added (Fig. 2B). Supplementary linear lesions were deployed along the mitral isthmus, if the induced AF persisted or was repeatedly induced. A target temperature for the ablation was 42°C at a maximal power output of 35 W. The end point of the ablation was defined by the disappearance of PV potentials and non-inducibility of sustained AF during isoproterenol infusion and coronary sinus pacing.

Follow-up

The patients were followed up in the outpatient clinic at 1-2 weeks after the ablation procedure and every 1-3 months thereafter. A routine 24-hour Holter monitoring was performed before each visit, and a 12-lead ECG was obtained at each visit. The patients were asked to report to the emergency room for an ECG if any symptoms suggestive of a recurrence occurred between the scheduled visits.

After the ablation, all patients received anti-arrhythmic treatment for at least one month to protect against early recurrences and continued oral anticoagulation for a minimum of two months to maintain an international normalized ratio between 2.0 and 3.0. A minimum follow-up of three months was required.

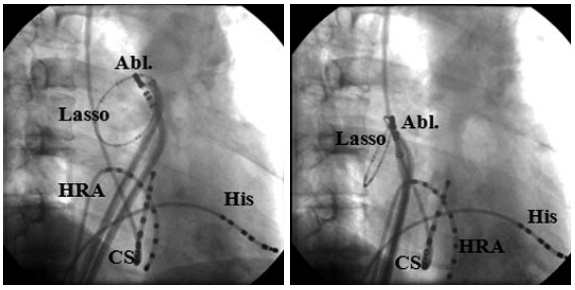
Statistical analyses

The Statistical Package for the Social Sciences (SPSS) for Windows, version 12.0 was used for all analyses. The continuous variables are presented as the mean values±standard deviations. For continuous variables, the groups were compared using a Student's t-test, and for categorical variables, the differences between the groups were analyzed using the chi-squared test or Fisher's exact test. A Cox multivariate regression analysis was performed to determine the predictors of the recurrence of AF after CPVA. Statistical significance was considered at p of less than 0.05.

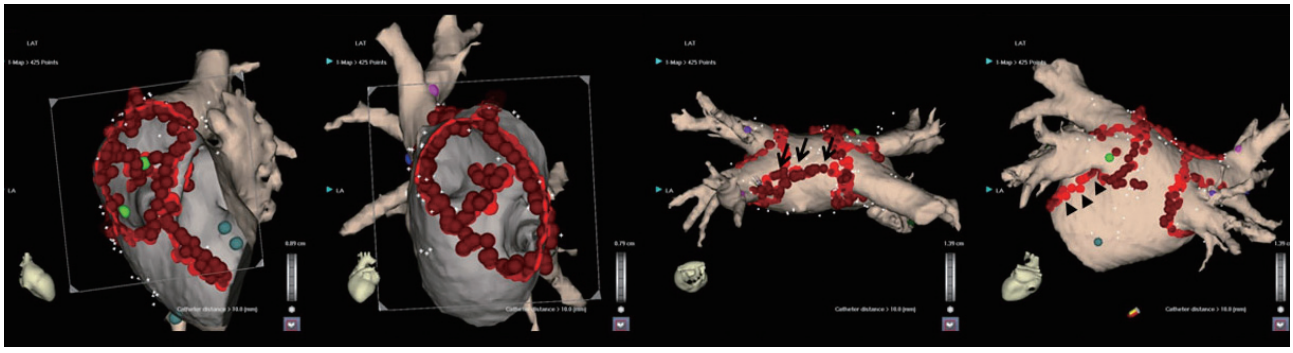
Results

Baseline clinical characteristics

Baseline clinical characteristics of the patients are shown



35 mm Lasso at Lt. PV antrum 35 mm Lasso at Rt. PV antrum



Lt. Antral Ablation Rt. Antral Ablation Roof Line (↑) Ablation Mitral isthmus (▲) Ablation

Fig. 2. Catheter ablation procedure for AF. A: a large sized Lasso catheter placed at the left and right ipsilateral circumferential pulmonary vein antrum. B: electroanatomic mapping and ablation (red dots) of the left and right antrum, roof line and mitral isthmus of the left atrium. Abl.: ablation catheter, HRA: high right atrium, CS: coronary sinus, His: His bundle, Lt.: left, Rt.: right, PV: pulmonary vein.

Table1. Baseline clinical characteristics and variables associated with recurrence of AF

Baseline clinical characteristics	All subjects (n=105)	AF recurrence (-) (n=79)	AF recurrence (+) (n=26)	p
Clinical characteristics				
Age (years)	58±11	57±11	62±13	0.055
Sex (M : F)	76 : 29	57 : 22	19 : 7	0.927
DM (N, %)	12 (11.4)	5 (6.3)	7 (26.9)	0.009*
Hypertension (N, %)	41 (39)	28 (35.4)	13 (50)	0.187
Stroke (N, %)	5 (4.8)	4 (5)	1 (3.8)	1.000
IHD (N, %)	7 (6.7)	2 (2.6)	5 (20.8)	0.008*
VHD (N, %)	17 (16.2)	13 (18.3)	5 (22.7)	0.758
Smoking (N, %)	9 (8.6)	8 (10.1)	1 (3.8)	0.446
Duration of AF (months)	35.0±66.8	18.1±27.9	32.3±44.3	0.134
Type (PAF : PeAF)	56 : 49	45 : 34	11 : 15	0.194
Mitral isthmus line	37 (35.2)	31 (39.2)	6 (23)	0.135
Plaque thickness (N, %)				<0.001*
<1 mm	56 (53.3)	49 (62.0)	7 (26.9)	
1-4 mm	33 (31.4)	25 (31.6)	8 (30.7)	
>4 mm	16 (15.2)	5 (6.3)	11 (42.3)	
Laboratory findings				
FBS (mg/dL)	103.3±18.2	102.3±17.1	106.3±21.0	0.336
hsCRP (mg/L)	2.13±3.57	2.3±4.0	1.6±1.6	0.399
BNP (pg/mL)	312.7±508.8	241.8±436.0	519.7±645.2	0.059
Cr (mg/dL)	1.02±0.20	1.0±0.2	1.1±0.2	0.191
TC (mg/dL)	176.4±35.4	178.6±35.9	170.0±33.8	0.272
TG (mg/dL)	147.0±85.2	156.4±84.8	118.7±81.3	0.050
HDL-C (mg/dL)	49.2±27.5	46.7±12.9	48.2±16.0	0.640
LDL-C (mg/dL)	103.8±27.2	105.3±29.1	99.1±20.0	0.329
Echocardiographic parameters				
LVEDD (mm)	49.2±5.5	49.3±5.1	48.9±6.7	0.741
LVESD (mm)	30.7±5.9	30.4±5.8	31.5±6.6	0.506
LAD (mm)	41.3±6.9	41.1±6.9	43.3±7.7	0.221
EF (%)	62.5±6.9	62.5±6.3	62.5±8.6	0.994
Vmax of LAA (cm/s)	55.3±22.0	57.2±21.8	49.6±22.3	0.141

Data are expressed as mean±SD or number (%) of patients. *p<0.05. AF: atrial fibrillation, DM: diabetes mellitus, IHD: ischemic heart disease, VHD: valvular heart disease, PAF: paroxysmal atrial fibrillation, PeAF: persistent atrial fibrillation, FBS: fasting blood sugar, hsCRP: high sensitive CRP: C-reactive protein, BNP: brain natriuretic peptide, Cr: creatinine, TC: total cholesterol, TG: triglyceride, HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol, LVEDD: left ventricular end diastolic diameter, LVESD: left ventricular end systolic diameter, LAD: anteroposterior left atrial diameter, EF: left ventricular ejection fraction, Vmax of LAA: peak velocity of left atrial appendage flow

in Table 1. The mean age of the 105 patients was 58±11 years of whom 72% were men. Diabetes, hypertension, stroke, IHD and valvular heart disease were present in 11.4%, 39%, 4.8%, 6.7% and 16.2%, respectively. Only one patient had an impaired systolic function with a LVEF <45%. The type of AF was PAF in 56 patients (53%) and PeAF in 49 patients (47%).

Atrial fibrillation recurrence and predictive variables

Linear lesions along the mitral isthmus were deployed in 37 patients (35% of all patients); 31 patients were free of symptoms of recurrence of AF and 6 patients had recurrence of AF, but there was no significant difference between both the groups (p=0.135) (Table 1). After the ablation procedure, the mean follow-up duration was 23 months (range 6-40). The recurrence of AF developed in 26 patients (25%); of this 57.6% of patients had PeAF. Patients with recurrence of AF had a significantly higher prevalence of diabetes (26.9% vs. 6.3%, p=0.009), IHD (20.8% vs. 2.6%, p=0.008) and a thicker aortic plaque (>4 mm plaque; 42.3% vs. 6.3%, p<0.001) than in the patients without recurrence of AF (Table 1).

Table 2. The relationship between recurrence of AF and the variables

	Hazard ratio (95% CI)	p
Age (years)	1.039 (0.999-1.081)	0.057
Sex (M : F)	0.975 (0.407-2.335)	0.954
DM	3.425 (1.422-8.249)	0.006*
Hypertension	1.509 (0.687-3.316)	0.306
Stroke	0.652 (0.088-4.830)	0.675
IHD	4.549 (1.679-12.322)	0.003*
VHD	1.405 (0.507-3.895)	0.513
Smoking	0.480 (0.065-3.555)	0.473
Duration of AF (months)	1.010 (1.001-1.018)	0.025*
Type of AF (PeAF : PAF)	2.412 (1.042-5.584)	0.040*
Plaque thickness		<0.001*
<1 mm	1 (reference)	
1-4 mm	2.419 (0.834-7.017)	0.104
>4 mm	9.514 (3.479-26.015)	<0.001*
Echocardiographic parameters		
LVEDD (mm)	0.970 (0.888-1.059)	0.493
LVESD (mm)	1.027 (0.947-1.113)	0.522
LAD (mm)	1.037 (0.975-1.104)	0.250
EF (%)	1.000 (0.938-1.065)	0.989
Vmax of LAA (cm/s)	0.987 (0.968-1.006)	0.188

*p<0.05. AF: atrial fibrillation, CI: confidence interval, DM: diabetes mellitus, IHD: ischemic heart disease, VHD: valvular heart disease, PAF: paroxysmal atrial fibrillation, PeAF: persistent atrial fibrillation, LVEDD: left ventricular end diastolic diameter, LVESD: left ventricular end systolic diameter, LAD: anteroposterior left atrial diameter, EF: left ventricular ejection fraction, Vmax of LAA: peak velocity of left atrial appendage flow

A univariate analysis showed that the presence of diabetes {hazard ratio (HR)=3.425; 95% confidence interval (CI), 1.422-8.249, p=0.006}, IHD (HR=4.549; 95% CI, 1.679-12.322, p=0.003), duration of AF (HR=1.010; 95% CI, 1.001-1.018, p=0.025), type of AF (HR=2.412; 95% CI, 1.042-5.584, p=0.040) and aortic plaque thickness with >4 mm (HR=9.514; 95% CI, 3.479-26.015, p<0.001) prior to the ablation procedure were significantly associated with the recurrence of AF after ablation (Table 2). In the Cox multivariate regression analysis, only the aortic plaque thickness (with >4 mm) was an independent predictor of the recurrence of AF after ablation (HR =7.250; 95% CI, 1.906-27.580, p=0.004) (Table 3).

Table 3. Multivariate Cox proportional hazards model for recurrence of AF after catheter ablation

	Hazard ratio (95% CI)	p
DM	1.191 (0.279-5.089)	0.814
IHD	2.509 (0.665-9.464)	0.175
Duration of AF (months)	1.007 (0.996-1.018)	0.240
Type of AF (PAF : PeAF)	1.816 (0.689-4.788)	0.228
Plaque thickness		0.015*
<1 mm	1 (reference)	
1-4 mm	2.451 (0.769-7.816)	0.130
>4 mm	7.250 (1.906-27.580)	0.004*

*p<0.05. AF: atrial fibrillation, CI: confidence interval, DM: diabetes mellitus, IHD: ischemic heart disease, PAF: paroxysmal atrial fibrillation, PeAF: persistent atrial fibrillation

Discussion

AF is not only the most frequently encountered arrhythmia in clinical practice but it can also cause fatal complications, such as stroke, thromboembolism and congestive heart failure.[1-4] For patients with drug-refractory AF, catheter ablation could be recommended as a therapeutic option, but the rate of procedural efficacy was variable according to the report, to represent the success rate of 60-85%.[8)14)15)] According to the results of several studies, the risk factors for the recurrence of AF after ablation could be different based not only on the methods of the ablation procedure,[5)8)] but also could be different from the traditional risk factors even after chemical- or electrical-cardioversion.[5-9)] This study intended to investigate the factors influencing the recurrence of AF after 3D-guided CPVA and roof line and supplementary mitral isthmus isolation procedures.

The relationship between the occurrence of AF and the degree of atherosclerosis has been reported in several studies.[11-13)] Heeringa et al.[11)] demonstrated that intima-media thickness (IMT) of the common carotid artery and the presence of carotid plaque are associated with the development of AF. Blackshear et al.[12)] showed that aortic plaque is prevalent in patients with AF and is associated with risk factors of atherosclerosis such as age, tobacco smoking, DM, hypertension and peripheral arterial disease. Agmon et al.[13)] demonstrated that AF is associated with aortic atherosclerosis and this association is related to age since both AF and aortic atherosclerosis are more frequent in the elderly population. In this study, we also observed that degree of aortic atherosclerosis is associated with recurrence of AF after ablation. It has been suggested that AF and atherosclerosis share common risk factors such as age, hypertension and DM.[12)13)] Furthermore, several reports demonstrated that oxidative stress and inflammation can play an important role in fibrosis and atrial structural remodeling, which results in the occurrence of AF.[23-25)] Oakes et al.[26)] reported that the degree of fibrosis of LA myocardial tissue estimated on delayed enhancement magnetic resonance imaging is an independent predictor of recurrence of AF after ablation. Likewise, it has been accepted that fibrosis, including oxidative stress and inflammation is also one of well known pathophysiologies of atherosclerotic progression.[27)28)] In other words, recurrence of AF is associated with the degree of fibrosis in LA,[26)] and atherosclerotic plaque is a product of the inflammatory and fibrous response of the aorta.[27)28)] Consider-

ing the similarity in the underlying pathophysiology between these two processes, the close association between recurrence of AF and aortic plaque thickness, therefore, can be surmised.

Regarding the other risk factors such as the presence of diabetes and IHD, duration of AF and type of AF which showed significant association with the recurrence of AF after ablation on univariate analysis: Firstly for diabetes and IHD; the number of patients who had DM and/or IHD was maybe too small to show any significance on multivariate analyisis. Secondly for the duration of AF; the duration of AF which had been estimated based on the patient's symptoms and ECG documentation was thought to have some inherent limitations, and thirdly for the type of AF; there was more recurrence in the cases with PeAF, but failed to show any statistically significant difference between the cases with PAF and the cases with PeAF.

Berruezo et al.[8] demonstrated that an age of >50 years and the presence of PeAF (compared to PAF) were not independent predictors of recurrence of AF after CPVA. In addition, there was a report showing no significant associations between the recurrence of AF and variables, such as age and type of AF after ablation.[29] The results of these studies were consistent with our results. But, we should consider the fact that the clinical utilization of this procedure was mostly limited to the patients with AF who were not too elderly.

LA structural and electrical remodeling induces atrial dilatation and occurrence of AF respectively.[23-26] Increase in LA dimension has been known to be a traditional risk factor for recurrence of AF as well as occurrence of AF.[23-26] However, in our study we couldn't find any association between the LA size and recurrence of AF. The reason for this discrepancy couldn't be clarified by the results of this study, but it may be related to the limitation that the LA dimension measured by TTE correlates poorly with the true LA volume,[29][30] or it may be related to the selection bias, since the ablation procedure is usually reserved for those patients with no structural heart disease, and not for those patients with huge LA.

The limitations of this study are as follows:

1) We did not perform the other imaging studies, such as dynamic aortic CT. Therefore, the aortic plaque located in the blind spot of the upper ascending aorta could not be detected. Fortunately, plaque lesions are more common in the descending versus the ascending or aortic arch portion of the thoracic arota.[12]

2) Aortic plaque thickness does not represent the absolute degree of atherosclerosis in the aorta. Further studies on the atheroma volume should be helpful.

3) This was a retrospective and a single center study in a relatively small group of patients. Therefore, large-scale, prospective, randomized studies are required.

4) This study showed clinical outcomes of the patients with a heterogeneous and a relatively short term follow-up duration of a period of 23±17 months. The predictors of recurrence of AF in the patients followed up for long term may be different than those seen in these results.

In conclusion, the results of the present study demonstrated that a significantly increased aortic plaque thickness may be a predictable factor of recurrence of AF after CPVA in patients with PAF or PeAF. Therefore, an assessment of the aortic plaque thickness can be incorporated into the pre-procedural evaluation in order to make an assumption regarding the disease prognosis.

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