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Clinical characteristics of complex aortic plaque in patients with non-valvular atrial fibrillation

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ABSTRACT

Background: Although complex aortic plaque (CxAoP) is a component of the CHA_2DS_2-VASc score in patients with atrial fibrillation (AF), it is underestimated without detection by trans-esophageal echocardiogram (TEE). We have evaluated the incidence and significance of CxAoP among patients with non-valvular AF (NVAF).
Methods: We included 981 patients with NVAF who underwent catheter ablation (59.1 ± 11.1 years old, 73.7% male, 70.2% paroxysmal AF). All of the patients underwent pre-procedural TEE evaluation. Left atrial (LA)-cardioembolic (CE) milieu was defined as a dense spontaneous echo-contrast or LA appendage flow velocity ≤ 20 cm/s.
Results: CxAoP was present in 8.3% of patients, and independently associated with age (OR 1.07, 95% CI 1.03–1.10, $p < 0.001$), male sex (OR 2.34, 95% CI 1.29–4.24, $p = 0.005$), and CHA_2DS_2-VASc score ≥ 2 (OR 3.33, 95%CI 1.42–7.77, $p = 0.005$). The presence of LA-CE milieu overlapped with CxAoP in only 11% of patients. Patients with CxAoP had a higher prevalence of hypertension ($p = 0.004$), smoking history ($p = 0.008$), paroxysmal AF (PAF, $p < 0.001$), and a smaller LA volume index ($p < 0.001$) than those with LA-CE milieu. The prevalence of persistent AF among patients with a history of stroke was significantly lower in the presence of CxAoP than in those with LA-CE milieu ($p = 0.014$). CHA_2DS_2-VASc score was underestimated in 11% of high-risk patients (CHA_2DS_2-VASc score ≥ 2) due to undetected CxAoP.
Conclusions: CxAoP may contribute to the risk of stroke by a different mechanism than LA-CE milieu in patients with NVAF. Imaging assessment for CxAoP affects thromboembolic risk stratification and decision making for stroke prevention in patients with NVAF.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmic source of thromboembolism, which is associated with a high risk of mortality and morbidity [1]. CHA_2DS_2-VASc score has demonstrated a modest improvement for the prediction of ischemic stroke in patients with non-valvular AF (NVAF) over the $CHADS_2$ score. This improvement can be attributed to the increased emphasis on the age factor, and to adding atherosclerotic vascular disease such as complex aortic plaque (CxAoP) and female sex as risk factors [2–6]. The main mechanism of thromboembolism in patients with AF is loss of left atrial (LA) booster pump function [7–9]. Therefore, transesophageal echocardiographic (TEE) markers of LA cardioembolic (CE) milieu, including low LA appendage (LAA) flow velocity (mean peak antegrade flow velocity ≤ 20 cm/s) and dense spontaneous echo contrast (SEC), have been considered as stroke surrogates [10,11]. However, the CHA_2DS_2-VASc score can predict the risk of ischemic stroke among the non-AF population [12,13], and a non-CE mechanism can contribute to the onset of ischemic stroke in addition to the LA-CE milieu in patients with NVAF [14–16]. Previous studies have shown that aortic plaques are common in NVAF patients [17]. CxAoP is an important non-CE risk factor for stroke and thromboembolism in high-risk patients with NVAF [18]. The presence of CxAoP can be easily missed in calculating a CHA_2DS_2-VASc score without additional imaging such as TEE, which may affect the physician's *anti*-thrombotic strategy [4,19]. Therefore, we investigated the incidence and clinical characteristics of NVAF patients with CxAoP and compared them to those with TEE markers of LA-CE milieu. We also evaluated the effect of CxAoP on the CHA_2DS_2-VASc score when the diagnosis is missed because the patient did not undergo TEE.

2. Methods

2.1. Study population

The study protocol adhered to the Declaration of Helsinki and was approved by the Institutional Review Board of Yonsei University Health System. All patients provided written informed consent. We enrolled 981 patients from the Yonsei AF Ablation Cohort from March 2009 to March 2015 who underwent TEE for pre-procedural evaluation of AF ablation (age: 59.1 ± 11.1 years, male: 73.7%, paroxysmal AF: 70.2%). The study's exclusion criteria were as follows: 1) patients with valvular AF (rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or a mitral valve repair), 2) patients with prior AF ablation, 3) patients who did not undergo pre-procedural TEE and 4) patients with

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inadequate evaluation for thromboembolic risk factors (aortic plaque, SEC, and LAA flow velocity) during their TEE.

2.2. Clinical variables and CHA_2DS_2-VASc score

We collected clinical variables from each patient to calculate their CHA_2DS_2-VASc score: age, sex, AF type, body surface area (BSA), body mass index (BMI), dyslipidemia, hypertension, diabetes mellitus, a history of congestive heart failure, stroke or transient ischemic attack (TIA) and vascular disease. We assigned 1 point for a history of congestive heart failure, hypertension, diabetes mellitus, vascular disease, age 65–74 and female sex, and 2 points for age ≥ 75 and a history of stroke/TIA. The definition of vascular disease used for the CHA_2DS_2-VASc score is a previous myocardial infarction, peripheral vascular disease or existence of a CxAoP. Although all patients in this study underwent TEE before AF catheter ablation, CxAoP was not considered in the initial CHA_2DS_2-VASc score to evaluate the effects of potentially undetected CxAoP when we omitted TEE. TEE is an uncomfortable diagnostic imaging method for the patient, so risk stratification by TEE is not a common clinical practice for patients with NVAF, except before emergency cardioversion or AF catheter ablation [19]. In the majority of NVAF patients, decision for anticoagulation treatment is made without TEE. Smoking status was also collected. Patients were classified as current smokers or as former smokers if they have smoked at least 100 cigarettes in their lifetime. Information regarding the use of medications such as statins, beta-blockers, angiotensin-converting enzyme inhibitors (ACEI), and angiotensin receptor blockers (ARB) was also obtained.

2.3. Transthoracic echocardiography (TTE) and TEE evaluation

TTE was executed just before conducting TEE. Chamber size, left ventricular ejection fraction, transmitral flow velocity, and tissue Doppler images of the mitral annular septal area were acquired according to the American Society of Echocardiography and the European Association of Cardiovascular Imaging guidelines. TEE was carried out for pre-procedural evaluation of AF ablation to measure LAA flow velocity (mean peak antegrade flow velocity in the LAA), and to evaluate the presence of thrombus or degree of SEC (none/faint/dense). After routine examinations by TEE, the transducer was gradually withdrawn from the descending aorta to the level of the aortic arch for the assessment of aortic plaques. We evaluated the presence, thickness and characteristics of plaques in the thoracic aorta. Plaques were defined as protrusions different in appearance and echogenicity from the adjacent intimal surface of the aorta. CxAoP were defined as large (≥4 mm in thickness measured in the horizontal plane), or having ulcerations or mobile components. TTE and TEE were conducted using commercially available echocardiography systems (iE33, Philips Medical System, Bothell, WA, USA; Vivid 7 or Vivid E9, GE Vingmed Ultrasound, Horten, Norway). All echocardiographic images were automatically saved in a picture archiving and communications system (PACS) and were double-checked by two National Board of Echocardiography-certified cardiologists.

2.4. Statistical data analysis

Continuous variables are expressed as mean ± standard deviation (SD) and categorical variables as counts and percentages. A student's *t*-test for continuous variables or Fisher exact test for categorical variables was used to determine the significance of differences in variables between two groups. *p* values for trend were calculated using the Cochran–Armitage test. Multivariate logistic regression analysis was used to identify the independent predictors of the presence of CxAoP in patients with NVAF. The multivariate logistic regression model was based upon the age, sex, and clinical variables of the patients that had statistical significance after univariate analysis. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using GraphPad Prism 6 (Graphpad Software, San Diego, CA, USA) or SPSS (IBM SPSS Inc., Chicago, IL, USA) version 20.0.

3. Results

3.1. Clinical characteristics of patients with CxAoP

Table 1 lists the characteristics of the 981 participants in the study (age: 59.1 ± 11.1 years, 73.7% male, 70.2% paroxysmal AF), and compares AF patients with CxAoP ($n = 81$, 8.3% of the study population) to those without ($n = 900$). Patients with CxAoP were older ($p < 0.001$) with a higher prevalence of hypertension ($p < 0.001$), diabetes ($p = 0.004$), heart failure ($p = 0.010$), chronic kidney disease ($p < 0.001$), vascular disease ($p < 0.001$), and stroke/TIA ($p = 0.009$). They had a higher CHA_2DS_2-VASc score ($p < 0.001$), and larger LA diameter ($p = 0.011$) and LA volume index ($p = 0.010$). They also more commonly took statins ($p < 0.001$), β-blockers ($p = 0.006$) or ACEI/ARB ($p < 0.001$). There were no significant differences with regard to sex, BSA, BMI, incidence of paroxysmal AF, dyslipidemia, and smoking history between the two groups (Table 1).

In multivariate logistic regression analysis, age (OR 1.067, 95% CI 1.033–1.103, $p < 0.001$), male sex (OR 2.338, 95% CI 1.290–4.239, $p = 0.005$) and a CHA_2DS_2-VASc Score ≥ 2 (OR 3.327, 95% CI 1.424–7.771,

Table 1
Patient characteristics according to the presence of CxAoP.

Characteristic	All NVAF patients ($n = 981$)	NVAF patients with CxAoP ($n = 81$)	NVAF patients without CxAoP ($n = 900$)	p-value
Age (years)	59.1 ± 11.1	68.2 ± 9.9	58.2 ± 10.9	<**0.001**
Male	723 (73.7%)	63 (77.8%)	660 (73.3%)	0.384
Paroxysmal AF	688 (70.2%)	58 (71.6%)	630 (70.1%)	0.762
BSA (m^2)	1.80 ± 0.18	1.79 ± 0.17	1.81 ± 0.18	0.400
BMI (kg/m^2)	24.9 ± 3.1	24.8 ± 2.7	24.9 ± 3.1	0.695
Heart failure	74 (7.5%)	12 (14.8%)	62 (6.9%)	**0.010**
Hypertension	481 (49.0%)	64 (79.0%)	417 (46.3%)	<**0.001**
Diabetes	137 (14.0%)	20 (24.7%)	117 (13.0%)	**0.004**
Dyslipidemia	240 (24.5%)	21 (25.9%)	219 (24.3%)	0.749
Vascular diseases*	83 (8.5%)	17 (21.0%)	66 (7.3%)	<**0.001**
Stroke/TIA history	145 (14.8%)	20 (24.7%)	125 (13.9%)	**0.009**
Current or former smoker	444 (45.3%)	41 (50.6%)	403 (44.8%)	0.312
eGFR ($mL/min/1.73\ m^2$)	79.7 ± 17.4	72.1 ± 19.9	80.4 ± 17.0	<**0.001**
CKD (eGFR ≤60)	113 (11.5%)	20 (24.7%)	93 (10.3%)	<**0.001**
CHA_2DS_2-VASc score	1.75 ± 1.61	3.07 ± 1.70	1.63 ± 1.55	<**0.001**
Echocardiography				
LA diameter (mm)	41.3 ± 5.9	42.8 ± 5.5	41.2 ± 5.9	**0.011**
LAVI (mL/m^2)	35.0 ± 11.9	38.6 ± 12.8	34.7 ± 11.8	**0.010**
LVEF (%)	63.2 ± 8.4	62.2 ± 9.7	63.3 ± 8.3	0.321
E/Em	10.4 ± 4.6	12.5 ± 5.5	10.3 ± 4.5	**0.001**
LAA flow velocity (cm/s)	51.6 ± 22.0	47.9 ± 21.3	51.9 ± 22.1	0.111
Medications				
Statin	285 (29.1%)	43 (53.1%)	242 (26.9%)	<**0.001**
Beta-blocker	283 (28.8%)	34 (42.0%)	249 (27.7%)	**0.006**
ACEI or ARB	345 (35.2%)	46 (56.8%)	299 (33.2%)	<**0.001**

Values are presented as mean ± SD or as n (%). *p*-values <0.05 are denoted by bold font. *Vascular diseases: previous myocardial infarction, peripheral artery disease (CxAoP was not included). ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; BMI: body mass index; BSA: body surface area; CKD: chronic kidney disease; CxAoP: complex aortic plaque; E/Em: ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (Em); eGFR: estimated glomerular filtration rate; LA: left atrium; LAA: left atrial appendage; LAVI: left atrial volume index; LVEF: left ventricular ejection fraction; NVAF: non-valvular atrial fibrillation; TIA: transient ischemic attack.

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