Aortic Atherosclerotic Plaque and Long-Term Prognosis in Patients With Atrial Fibrillation
– A Transesophageal Echocardiography Study –
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Background: Both left atrial spontaneous echo contrast (LASEC) and aortic atherosclerotic plaque (AoP) ≥4.0 mm in thickness are predictors of cardiovascular events after stroke. The aim of this study was to investigate impact of AoP ≥4.0 mm or LASEC on cardiovascular events in patients with atrial fibrillation (AF).

Methods and Results: One hundred and eight consecutive patients with AF were enrolled and studied. Patients were grouped according to the presence or absence of AoP ≥4.0 mm in the proximal aortic arch on transesophageal echocardiography (TEE). Cardiovascular events included death, myocardial infarction, ischemic stroke, systemic embolism and congestive heart failure. During a follow-up period (median, 3.9 years), cardiovascular event-free survival rate was significantly lower in patients with AoP ≥4.0 mm than in patients without AoP ≥4.0 mm (log-rank, P=0.01). In contrast, patients with LASEC showed a trend toward lower cardiovascular event-free survival than those without LASEC (log-rank, P=0.10). Univariate TEE predictors of cardiovascular events were AoP ≥4.0 mm, LASEC and left atrial appendage flow velocity. On multivariate Cox regression analysis, AoP ≥4.0 mm was the only TEE predictor of cardiovascular events during follow-up (P=0.02, hazard ratio, 2.6; 95% confidence interval: 1.1–6.0).

Conclusions: In the present unselected patients with AF, AoP predicted long-term cardiovascular events. (Circ J 2013; 77: 68–72)

Key Words: Arrhythmia; Diastole; Echocardiography; Prognosis

Aortic atherosclerotic plaque (AoP) of the proximal aortic arch is one of the sources of embolism responsible for ischemic stroke.1–10 Presence of large (≥4.0 or 5.0 mm) AoP has been shown to predict recurrent stroke events in patients with ischemic stroke.1–4,9–11 Left atrial (LA) thrombus associated with atrial fibrillation (AF) is another important source of embolism for patients with cardiogenic ischemic stroke.7,8,12–15 Although AoP may play some role even in patients with AF, its long-term prognostic impact is unknown.7,8 We hypothesized that AoP may affect long-term clinical outcome in patients with AF independent of findings of LA blood stasis. Accordingly, this study was undertaken to investigate the impact of AoP (≥4.0 mm) or LA spontaneous echo contrast (LASEC)/LA thrombus on long-term cardiovascular events in patients with AF.

Methods

Subjects
Between January 2000 and December 2004, the Bell Land General Hospital echocardiography database was probed to find patients with AF who were referred for transesophageal echocardiography (TEE). A total of 108 consecutive patients were enrolled. Mean age was 65.6±9.6 years (male, n=70; female, n=38). Informed consent for TEE was obtained from all patients.

TEE
TEE was performed using a commercially available echocardiography machine (VIVID 7, GE Medical) with use of multiplane TEE probe. After topical anesthesia using lidocaine, the TEE probe was advanced and echocardiographic images were obtained. The following measurements were performed: LA appendage (LAA) flow velocity,7,8,16 maximum thickness...
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Figure 1. Transesophageal echocardiographic images of (Left) aortic atherosclerotic plaque (AoP) ≥4 mm and (Right) AoP <4 mm.

Table 1. Clinical Subject Characteristics

|                          | AoP ≥4.0 mm (n=21) | AoP <4.0 mm (n=87) | P-value |
|--------------------------|---------------------|--------------------|---------|
| Age (years)              | 72.1±8.5            | 64.0±9.3           | 0.0005  |
| M/F                      | 15/5                | 56/31              | NS      |
| Etiology of AF           |                     |                    |         |
| Rheumatic heart disease  | 2 (9.5)             | 9 (10)             | NS      |
| Non-rheumatic AF         | 2 (9.5)             | 16 (18)            | NS      |
| Non-valvular AF          | 17 (81)             | 62 (72)            |         |
| Hypertension             | 7 (33)              | 37 (43)            | NS      |
| Dyslipidemia             | 6 (29)              | 14 (16)            | NS      |
| Diabetes mellitus        | 6 (29)              | 20 (23)            | NS      |
| Smoking                  | 3 (15)              | 21 (24)            | NS      |
| MI                       | 4 (19)              | 4 (5)              | 0.023   |
| Stroke                   | 10 (48)             | 14 (16)            | 0.002   |
| Congestive heart failure | 3 (14)              | 28 (32)            | NS      |

Data given as mean±SD or n (%).
AF, atrial fibrillation; AoP, aortic atherosclerotic plaque; MI, myocardial infarction.

of the AoP, presence or absence of LASEC or LA thrombus. Study patients were grouped according to presence or absence of AoP ≥4.0 mm in the proximal aortic arch (Figure 1).

Clinical Follow-up
The primary outcome of the study was cardiovascular event, defined as a composite of all-cause death, acute myocardial infarction, ischemic stroke, peripheral embolism or congestive heart failure.

Statistical Analysis
Quantitative data are presented as mean±SD, and qualitative data are presented as frequencies. Continuous variables were compared using unpaired t-test or Mann-Whitney U-test, as appropriate. Binary variables were examined using Fisher’s exact and chi-square tests. Statistical significance was set at P<0.05. Survival and cardiovascular event-free survival curves during follow-up in patients with vs. without AoP ≥4 mm were obtained using the Kaplan-Meier method with log-rank test. Cox proportional hazards regression was used to analyze the impact of covariates derived from TEE on cardiovascular event. Variables entered into the Cox proportional hazard models were those with a univariate probability of P<0.15 (AoP ≥4 mm, LAA flow velocity, LASEC and LA thrombus). All statistical analysis was performed with Statview version 5.0 (SAS Institute).

Results
Clinical Characteristics and Medications
AoP ≥4 mm was present in 21 patients (19%) and absent in 87 (81%) of 109 patients. Clinical characteristics are listed in Table 1. Patients with AoP ≥4 mm were significantly older, more frequently had a prior history of myocardial infarction, and stroke. In contrast, there were no significant differences in gender, dyslipidemia and family history between the 2 groups.

Medications are listed in Table 2. Warfarin and aspirin were similarly prescribed in the 2 groups. Digitalis and loop diuretics were less frequently used in patients with AoP ≥4.0 mm. Antihypertensive medications, nitrates and statins were similarly used in both groups.
TEE Results

TEE results are summarized in Table 3. LASEC was more frequently observed in patients with AoP ≥4 mm. Otherwise, indices of LA blood stasis were similar between the 2 groups. As expected, patients with AoP ≥4 mm in the proximal aortic arch frequently had AoP ≥4 mm in the descending aorta.

Cardiovascular Events

Cardiovascular events during follow-up (median, 3.9 years) are summarized in Table 4. Kaplan-Meier plot of survival rate was significantly lower in patients with AoP ≥4 mm than in patients with AoP <4 mm (log-rank, P=0.01; Figure 2A). Kaplan-Meier cardiovascular event-free survival rate was also significantly lower in patients with AoP ≥4 mm than in patients with AoP <4 mm (log-rank, P=0.02; Figure 2B).

Univariate predictors (P<0.15) of cardiovascular events were AoP ≥4 mm (P=0.01), LAA flow velocity (P=0.08), LASEC (P=0.13) and LA thrombus (P=0.13). On multivariate analysis, AoP ≥4 mm was the only independent predictor of cardiovascular events (χ²=5.98; relative risk, 2.86; 95% confidence interval: 1.23–6.65; P=0.02; Table 5).

Discussion

The present study shows that AF patients with AoP ≥4.0 mm had significantly lower cardiovascular event-free survival. In contrast, findings of the LA blood stasis, such as decreased LAA flow velocity, 7,8,14–16 presence of LASEC, 7,8,14,15,17 and LA thrombus were not independently associated with long-term cardiovascular events. These results suggest that AoP rather than LA blood stasis may be a marker of poor clinical outcome in patients with AF.

The present results are concordant with those of a substudy of the Stroke Prevention in Atrial Fibrillation (SPAF)-III, showing that AoP was associated with future stroke in patients with AF. 18 Previous studies have suggested that age and hypertension were independent risk factors for AoP. 1,7,8 Similarly, age and hypertension are strongly associated with the development of AF. 19 Because prevalence of AF increases with age, it follows that elderly patients with AF also have a higher chance of having AoP. 7 It has also been reported that age is related to left ventricular relaxation, left ventricular filling pressure and prevalence of physiological valvular regurgitation. 20–22 In the present subjects, patients with both AF and AoP ≥4.0 mm were significantly older, in agreement with previous studies. It has been reported that LA thrombus associ-
ated with AF is the major cause of ischemic stroke/transient ischemic attack (TIA) and peripheral embolism. Recently, several studies have suggested that inflammation is associated with LA thrombus formation and risk profile determined by clinical characteristics (ie, CHADS2 score). C-reactive protein (CRP) in patients with AF is significantly higher in patients with LA thrombus than in patients without LA thrombus. Therefore, AF patients with elevated CRP may have more cardiovascular events. In the present study, however, CRP was measured in only a subset of subjects at the time of TEE and, as a result of the small sample size, CRP was not directly related to AoP or cardiovascular events. A larger subject number will be required to assess the relationship between systemic inflammation and AoP or cardiovascular events.

There are several possible explanations for the stronger impact of AoP rather than LA blood stasis on long-term out-

Table 5. Predictors of Cardiovascular Events

|                  | Univariate | Multivariate |
|------------------|------------|--------------|
|                  | P-value    | chi²         | P-value | RR (95%CI) |
| AoP ≥4.0 mm      | 0.01       | 5.98         | 0.02    | 2.86 (1.23–6.65) |
| LAA velocity     | 0.08       | 2.78         | 0.10    | 0.98 (0.96–1.00) |
| LASEC            | 0.11       | 0.11         | 0.74    | 1.16 (0.48–2.80) |
| LA thrombus      | 0.13       | 1.16         | 0.28    | 1.74 (0.63–4.81) |

CI, confidence interval; RR, relative risk. Other abbreviations as in Table 3.

Figure 2. Kaplan-Meier plot of (A) survival rate and (B) cardiovascular event-free survival rate during follow-up in patients with aortic atherosclerotic plaque (AoP) <4.0 mm and AoP ≥4 mm. (A) Patients with AoP ≥4 mm had significantly lower survival rate. (B) Patients with AoP ≥4 mm had significantly lower cardiovascular event-free survival rate.
come. First, the presence of AoP may represent extensive systemic atherosclerosis. Therefore, it is possible that patients with AoP have a more extensive atherosclerosis burden throughout the entire body. Second, most of the high-risk AF patients were treated with warfarin. Therefore, the negative impact of LA blood stasis may be modified and weakened by effective anticoagulation. In contrast, no effective therapeutic option for AoP has been established as yet. In the present study, no specific medications were related to long-term cardiovascular events, possibly because of the non-randomized study design and the relatively lower event rate. Therefore, further study is needed to assess and establish therapeutic strategies to lower cardiovascular events in AF patients with AoP.

Patients with AoP ≥4.0 mm in the proximal aorta had significantly higher prevalence of AoP ≥4.0 mm in the descending aorta. AoP in the descending aorta, however, was not an independent predictor of cardiovascular events, possibly because the descending aorta itself cannot be a source of cerebral embolism.

**Study Limitations**

There were several limitations in this study. First, this is a single-center study with a small number of subjects. Therefore, these results should be confirmed by a multicenter study with a larger subject number. Second, anticoagulation was used based on each primary care physician’s discretion at the time of study entry. Therefore, a substantial number of patients with high-risk profiles were not treated with warfarin. This is, however, comparable to a previous real-world survey showing that only 40% of AF patients with ≥intermediate risk were actually treated with warfarin. Third, patients with AoP ≥4.0 mm had a higher prevalence of previous history of TIA/stroke or myocardial infarction. These clinical characteristics may also be associated with worse prognosis in the patients with AoP ≥4.0 mm. Because of the small sample size and the relatively lower event rate, the present study was not sufficiently powered to perform multivariate analysis including both TEE indices and clinical characteristics. Finally, as mentioned earlier, no specific therapeutic strategy could be drawn from the study to improve the outcome of the patients with AF and AoP. Although medication at the time of initial TEE is given (Table 3), medication status throughout the entire follow-up period is not known. Therefore, a prospective, randomized study is necessary to test the efficacy of anti-thrombotic therapy or lipid-lowering therapy to prevent cardiovascular events in AF patients with large AoP.

In conclusion, AoP predicts long-term clinical outcome of AF patients independent of findings of LA blood stasis or thrombus. Further study is warranted to improve prognosis of these higher risk AF patients.

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