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Original Article

Transesophageal echocardiographic thromboembolic risk is associated with smoking status in patients with atrial fibrillation

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ABSTRACT

Background: Smoking is a risk factor for cardiovascular diseases, but it is unclear whether smoking status, including environmental tobacco smoke, increases stroke risk in patients with atrial fibrillation (AF). Abnormalities of the left atrium (LA) and aortic atherosclerosis, as detected by transesophageal echocardiography (TEE), are risk factors for stroke and thromboembolism in AF patients. We investigated the impact of smoking status on thromboembolic risk by TEE in patients with nonvalvular AF.

Methods: In 122 patients with AF (mean age, 63 years; chronic AF 50%) who underwent TEE before catheter ablation of AF or for detection of the potential cardioembolic source, urinary concentrations of cotinine and clinical variables including smoking status and the CHA_2DS_2-VASc score were determined.

Results: Severe aortic atherosclerosis and increased aortic wall thickness were more frequently detected by TEE in current smokers than in non-smokers ($p < 0.05$), though these findings did not significantly differ between non-smokers and environmental smokers. Patients in AF rhythm during TEE, who were environmental smokers and at relatively low risk, as stratified by their CHA_2DS_2-VASc score (≤ 2), showed lower LA appendage flow velocity than those without environmental smoking (47 ± 22 vs. 34 ± 13 cm/sec, $p < 0.05$).

Conclusions: TEE findings indicated that smoking status could be associated with thromboembolic risk in patients with AF.

1. Introductions

Atrial fibrillation (AF) is associated with an increased risk of ischemic stroke and cardiovascular events [1]. Aging, history of stroke, hypertension, diabetes mellitus, and heart failure are significant risk factors for stroke and thromboembolism in patients with AF [2,3]. Cigarette smoking is a well-known risk factor for cardiovascular diseases including ischemic and hemorrhagic stroke [4–7]. Smoking status is associated with atherosclerosis [8], vascular damage (e.g., endothelial dysfunction) [9,10], and incident AF [11,12]. We have previously shown a close relationship between cigarette smoking and adverse cardiovascular events in patients with AF [13], but the effects of exposure to environmental tobacco smoke, in particular, on cardiovascular risk remain to be determined. Despite the careful risk assessment and management that is required for patients with cardiovascular risk factors, the impact of smoking status on stroke risk remains unclear in AF patients. Abnormalities of the left atrium (LA) and aortic atherosclerosis, as detected by transesophageal echocardiography (TEE), are established risk factors for stroke and thromboembolism in AF patients [14]. TEE findings, such as dense LA echo contrast (LASEC), low LA appendage (LAA) flow velocity, LA thrombi, and aortic atherosclerosis, were used as risk markers for thromboembolism in AF [15]. Therefore, in the present study, we determined the impact of smoking status on TEE-detected risk factors in patients with nonvalvular AF.

2. Material and methods

2.1. Study population

This cross-sectional study included 122 consecutive patients with nonvalvular AF who underwent TEE at our University Hospital before catheter ablation of AF or for detection of the potential cardioembolic source. Patients in the acute phase of infection or cardiovascular diseases, as well as those receiving a kidney

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transplant or hemodialysis, were excluded. Chronic AF was defined as AF that was documented electrocardiographically on at least 2 separate occasions (4 weeks apart).

2.2. Study methods

Baseline characteristics including the CHA_2DS_2-VASc score (Congestive heart failure, Hypertension, Age $\geq$75 years [2 points], Diabetes mellitus, Stroke [2 points], Vascular disease, Age 65 to 74 years, Sex category [female]) [1] for each patient were obtained from medical records. Smoking status was categorized as non-smoker, environmental smoker, or current smoker based on self-reporting and urinary cotinine levels [16], as follows: a current smoker was defined as a patient that answered "yes" to the question "Do you currently smoke?" at the time of TEE [13]. Since non-smokers included environmental smokers, non-smokers were considered to be environmental smokers if their urinary cotinine levels were greater than 1.3 ng/mg creatinine (limit of detection). The study was approved by our institutional ethics committee, and informed consent was obtained from each patient.

2.2.1. Urine cotinine levels

The spot urine sample was collected in a 10-mL sterile specimen tube at the time of TEE examination for each patient and was immediately frozen at −20 °C for later analyses. Cotinine direct ELISA kits (Cosmic Co., Japan) were used to measure each patient's urine cotinine concentration [17]. Urine creatinine levels were also measured using enzymatic methods. We used creatinine-adjusted urine cotinine levels in the following analysis.

2.2.1.1. Echocardiography. All patients underwent transthoracic echocardiography and TEE studies. Transthoracic echocardiography was performed with a broadband 3.5-MHz phased-array transducer connected to an ultrasound system (Vivid E9; GE Healthcare, Buckinghamshire, England). LA dimension (LAD), left ventricular end-diastolic dimension (LVDd), and left ventricular ejection fraction (LVEF) were determined from M-mode images.

TEE was performed using a 5-MHz multiplane transducer as previously reported [18]. Briefly, patients were examined in a fasting state with topical anesthesia of the pharynx. LAA flow velocity, LASEC, presence of LA thrombi, and aortic plaque were determined. Subsequently, the severities of LASEC and LAA peak flow velocity were determined. LASEC was diagnosed in the presence of dynamic smoke-like echoes within the LA or LAA with a characteristic swirling motion that was distinct from the white noise artifact. The severity of LASEC was defined using the criteria established by Fatkin et al. [14]; 0=none (absence of echogenicity); 1+=mild (minimal echogenicity detectable only transiently during the cardiac cycle with optimal gain settings); 2+=mild to moderate (transient spontaneous echocardiographic contrast without increased gain settings and a more dense pattern than 1+); 3+=moderate (dense swirling pattern during the entire cardiac cycle); and 4+=severe (intense echo density and very slow swirling patterns in the LAA, usually with a similar density in the main left atrial cavity). Peak LAA flow velocity was determined by pulse-wave Doppler echocardiographic interrogation at the orifice of the appendage.

Intima-media thickness of the thoracic aorta was measured on the B-mode image after freezing the optimal image on the R-wave of the ECG. In addition, the severity of aortic atherosclerosis was evaluated using the grading system of Montgomery et al. [19]: grade I=no disease or intimal thickening; grade II=intimal thickening; grade III=atheroma $<$ 5 mm; grade IV=atheroma $\geq$ 5 mm; and grade V=any mobile atheroma. Two independent observers determined the severity of LASEC and aortic atherosclerosis. Any difference in the determination was resolved by a third independent observer. LA abnormality was defined as thrombi in the LA/LAA, dense LASEC (grade 3 or 4), or peak LAA flow velocity $<$20 cm/s. Severe aortic atherosclerosis with complex aortic plaque was defined as mobile, ulcerated, pedunculated, or wall thickness $\geq$ 5 mm [19].

2.3. Statistical analyses

Data are expressed as the mean $\pm$ SD. All analyses were performed using JMP® 10 (SAS Institute Inc., Cary, NC, USA). Comparison of continuous variables was performed with a one-way analysis of variance, followed by Newman-Keuls multiple comparisons. The proportions of categorical variables, including smoking status and TEE findings, were compared using a chi-square test. Multiple logistic regression analysis was used to determine the independent predictors of the TEE findings. Explanatory variables were selected from clinical variables that had a p value $<$0.1 on univariate analysis, and included the presence of chronic AF, smoking status, and components of the CHA_2DS_2-VASc score. A p value $<$0.05 was considered to be significant.

3. Results

3.1. Baseline characteristics

Table 1 summarizes the baseline characteristics and transthoracic echocardiographic variables according to smoking status. The mean age of the study patients was 63.3 $\pm$ 9.7 years, and 101 patients (82.7%) were men.

Based on urinary cotinine levels, 23 of 88 non-smokers were classified as environmental smokers. Current smokers and environmental smokers tended to be male and about half of each group of patients had paroxysmal AF. Hypertension was the most common comorbidity, followed by paroxysmal AF and heart failure. The frequency of warfarin use was higher in non-smokers than in current smokers and environmental smokers, while the mean prothrombin time-international normalized ratio (PT-INR) level of non-smokers receiving warfarin was comparable to that of the other 2 groups. The frequency of direct oral anticoagulant administration and the mean CHA_2DS_2-VASc scores did not differ significantly among the 3 groups. None of the patients had a CHA_2DS_2-VASc score of more than 8 in this study. In terms of LAD, LVDd normalized by body surface area, and LVEF, there were no significant differences among the 3 groups, whereas the BMI of the environmental smokers was incidentally the highest among the 3 groups.

3.2. Smoking status and aortic wall thickness

Fig. 1 shows the relationship between smoking status and the wall thickness of the thoracic aorta. As expected, the aortic wall thickness was increased to a greater extent in current smokers than in non-smokers. This was also true for environmental smokers versus current smokers ($p < 0.05$). However, the wall thickness did not differ between non-smokers and environmental smokers. Additionally, there was no significant difference in the wall thickness according to paroxysmal and chronic AF in all study patients (2.6 $\pm$ 1.4 mm vs. 2.5 $\pm$ 1.4 mm), while current smokers who had paroxysmal AF had increased aortic wall thickness compared with non-smokers (3.5 $\pm$ 2.0 mm vs. 2.1 $\pm$ 1.0 mm, $p < 0.05$). Severe aortic atherosclerosis with mobile plaque was more frequently observed in current smokers than in environmental and non-smokers (current smokers; 26%, environmental smokers; 17%, non-smokers; 9%, $p < 0.05$).

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