Predictors of silent brain infarction on magnetic resonance imaging in patients with nonvalvular atrial fibrillation: A transesophageal echocardiographic study

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Background Silent brain infarction (SBI) is often found in patients with atrial fibrillation (AF) and may be related to cognitive decline. We investigated the predictors of SBI on brain magnetic resonance imaging (MRI) using transesophageal echocardiography (TEE) in patients with nonvalvular AF.

Methods The study population consisted of 103 neurologically asymptomatic patients with nonvalvular AF who underwent TEE before transcatheter AF ablation (76 men; mean age 63 ± 10 years). Left atrial (LA) abnormalities such as LA thrombus, spontaneous echo contrast, or abnormal LA appendage emptying velocity (<20 cm/s) and complex plaques in the aortic arch defined as large plaques ≥4 mm thickness, ulcerated plaques, or mobile plaques were evaluated by TEE. All patients were screened for SBI by brain MRI.

Results Of 103 patients, 31 (30%) showed SBI on brain MRI. Most lesions were multiple (61%) and small (<15 mm) in diameter (84%). Patients with SBI had a higher prevalence of LA abnormalities (45% vs 14%; $P < .001$) and complex arch plaques (45% vs 7%; $P < .001$) compared with those without SBI. In a multivariate logistic regression analysis including age and $CHADS_2$ score ≥2, LA abnormalities (odds ratio 4.13; 95% CI 1.34-12.72; $P = .014$) and complex arch plaques (odds ratio 4.82; 95% CI 1.23-18.92; $P = .024$) were independent predictors of SBI.

Conclusions Left atrial abnormalities and complex arch plaques detected by TEE were closely associated with the presence of SBI on brain MRI, suggesting that microembolization of small thrombi derived from the fibrillating LA or advanced aortic atherosclerotic lesions may be important causes of SBI in patients with nonvalvular AF. (Am Heart J 2015;169:783-90.)

Nonvalvular atrial fibrillation (AF) is an independent risk factor for ischemic stroke.[1] Brain infarction associated with AF is often diagnosed as cardioembolic stroke caused by left atrial (LA) thrombus, leading to major and disabling stroke with large-sized infarctions.[2-4] In contrast, several studies using brain computed tomography or magnetic resonance imaging (MRI) have shown that patients with AF have a higher prevalence of silent brain infarction (SBI) compared with those with sinus rhythm.[5-11] Although recent studies have revealed that SBI is related to cognitive decline and dementia in AF patients,[12-14] no previous studies have focused on the mechanism underlying the occurrence of SBI in patients with nonvalvular AF.

Transesophageal echocardiography (TEE) is a useful tool for detecting cardiogenic or aortogenic thromboembolic sources.[15] In high-risk patients with nonvalvular AF (age >75 years, hypertension, or previous stroke), the SPAF III study showed that LA abnormalities such as LA thrombus, spontaneous echo contrast (SEC), or abnormal LA appendage (LAA) emptying velocity (<20 cm/s) and complex aortic plaques such as large plaques ≥4 mm thickness, ulcerated plaques, or mobile plaques detected by TEE were significant risk factors for clinically symptomatic thromboembolism.[16] However, risk factors of TEE for silent ischemic stroke have never been investigated in patients with nonvalvular AF. Therefore, we aimed to evaluate SBI using brain MRI in neurologically asymptomatic patients with nonvalvular AF and the predictors of SBI using TEE in these patients.

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Methods

Study population

This study was a prospective single center study, which included 124 consecutive neurologically asymptomatic patients with nonvalvular AF who were scheduled to undergo TEE for the assessment of LA thrombus before transcatheter AF ablation between February 2012 and August 2014 in Osaka City University Hospital. Of these patients, 21 patients were excluded for the following reasons: 4 patients refused brain MRI, and 17 had a history of previous transcatheter ablation because this procedure is associated with the risk of SBI on MRI.[17] A final total of 103 patients (76 men; mean age 63 ± 10 years) were screened for SBI by brain MRI. The study protocol was approved by the hospital's ethics committee, and written informed consent was obtained from each patient.

Clinical variables

Clinical variables including risk factors such as age, hypertension, diabetes mellitus, hypercholesterolemia, and smoking status were collected for each patient. Hypertension was defined as a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg based on 2 separate occasions, a patient's self-report of hypertension history, or the use of antihypertensive medications. Diabetes mellitus was determined by the presence of an existing diagnosis, a fasting blood glucose level ≥126 mg/dL, a glycohemoglobin A1c level ≥6.5% as defined by the Japan Diabetes Society,[18] or the use of antidiabetic medications or insulin. Hypercholesterolemia was defined as a serum cholesterol value ≥220 mg/dL or a low-density lipoprotein cholesterol value ≥140 mg/dL according to the Japan Atherosclerosis Society 2007 guidelines[19] or the use of cholesterol-lowering medication. Patients were classified as nonsmokers if they had never smoked or if they had stopped smoking ≥10 years before the study. All other patients were classified as smokers. The estimated glomerular filtration rate was calculated as $0.741 \times 175 \times \text{age}^{-0.203} \times (\text{serum creatinine})^{-1.154} \times (0.742$ if female) mL/min per 1.73 m^2. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate <60 mL/min per 1.73 m^2.[20] $CHADS_2$ scores were calculated with 1 point assigned for a history of congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus and 2 points assigned for a history of stroke or transient ischemic attack.[21] Information regarding the use of medications such as anticoagulants, antiplatelet drugs, statins, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers was obtained.

Transesophageal echocardiographic analysis

Transesophageal echocardiography was performed using a commercially available ultrasound imaging system (iE33; Philips Medical Systems, Andover, MA) with a 3-dimensional matrix-array transesophageal transducer (X7-2t). Left atrial abnormalities such as LA thrombus, SEC, and LAA emptying velocity were assessed by TEE in all patients. Spontaneous echo contrast was defined as a dynamic smoke-like signal that swirled slowly in a circular pattern within the LA and appendage, with appropriate gain settings to distinguish SEC from echoes due to excessive gain.[22,23] For assessment of LAA emptying velocity, 10 consecutive pulsed-wave Doppler outflow velocity signals during diastole were measured 1 cm below the orifice of the LAA over ≥3 cardiac cycles and averaged. LA appendage emptying velocity <20 cm/s was considered abnormal.[24]

The method used to evaluate aortic arch plaques by TEE has been described in previous publications.[25,26] The aortic arch was defined as the portion of the aorta between the curve at the end of the ascending aorta and the origin of the left subclavian artery. We evaluated the presence, thickness, and characteristics of aortic plaques in the aortic arch. Plaques were defined as discrete protrusions of the intimal surface of the vessel, ≥2 mm in thickness, and different in appearance and echogenicity from the adjacent intact intimal surface.[15] In cases of multiple plaques, the most advanced lesion was considered. Ulceration was defined as a discrete indentation of the luminal surface of the plaque with a base width and maximum depth of ≥2 mm each. Complex plaques (Figure 1) were defined as large plaques (≥4mm in thickness), plaques with ulceration, or plaques with mobile components.[27] An experienced echocardiographer who was blinded to patient information (K.S.) interpreted echocardiographic studies.

Brain MRI

All participating patients underwent brain MRI that used a superconducting magnet at a field strength of 1.5 or 3.0 T on proton density, T1- and T2-weighted images, and fluid attenuated inversion recovery (FLAIR) images in axial planes at 5-mm-thick slices with an interslice gap of 1.5 mm. Silent brain infarction was defined as an area of hypointense lesions that measured >3 mm on T1-weighted images and hyperintense lesions on T2-weighted images (Figure 1).[28] Fluid attenuated inversion recovery images were used to separate dilated Virchow-Robin spaces from infarcts based on the absence or presence of a hyperintense rims around each suspected lesions. Lesions, which were absent of FLAIR hyperintense rim, were considered dilated Virchow-Robin spaces. An experienced neuroradiologist who had not been informed of the clinical information (S.S.) independently assessed brain MRI images.

Statistical analysis

The results are expressed as mean ± SD. When 2 groups were compared, the unpaired t test or Mann-Whitney U test was used as appropriate. Categorical variables were