Volume and morphology of left atrial appendage as determinants of stroke subtype in patients with atrial fibrillation

Woo Kyo Jeong, MD,[*] Jin-Ho Choi, MD,[†] Jeong Pyo Son, MS,[‡] Suyeon Lee, MS,[‡] Mi Ji Lee, MD,[*] Yeon Hyeon Choe, MD,[§] Oh Young Bang, MD[*‡]

From the [*]Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, [†]Department Cardiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, [‡]Department of Health Sciences and Technology, Samsung Advanced Institute for Health Sciences and Technology, Sungkyunkwan University, Seoul, Korea, and [§]Department of Radiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

BACKGROUND Atrial fibrillation (AF) is a leading cause of stroke, but not all cases of stroke in patients with AF are due to AF.

OBJECTIVE The purpose of this study was to determine whether morphometric or volumetric parameters of left atrial appendage (LAA) would be related to the development of cardioembolism in subjects with AF.

METHODS A total of 433 consecutive patients with acute ischemic stroke underwent multidetector cardiac computed tomography (MDCT). Of these patients, 88 with AF were divided into cardioembolic stroke (CES; n = 57) and non-CES (n = 31) groups, and 95 age- and sex-matched patients with non-CES without AF served as controls. Clinical factors, echocardiographic findings, and MDCT parameters were evaluated.

RESULTS Brain infarct volume, LAA orifice diameter, and LAA volume were larger in patients with CES with AF than in those with non-CES with AF ($P < .05$ in all cases), but no difference was observed between patients with non-CES with AF and those with non-CES without AF. MDCT and echocardiographic parameters of left atrial (LA) dysfunction were different depending on the presence of AF but not between patients with CES with AF vs non-CES with AF. After adjusting for covariates, LAA orifice diameter (odds ratio 1.19, 95% confidence interval 1.06–1.33, $P = .004$) and LAA volume (odds ratio 12.20, 95% confidence interval 2.58–57.79, $P = .002$) were independently associated with CES with AF, as was infarct volume.

CONCLUSION In patients with AF, LAA orifice diameter and LAA volume, but not left atrial dysfunction, were determinants of CES and were useful for stratifying noncardioembolic risk in patients with AF.

KEYWORDS Atrial fibrillation; Coronary computed tomography; Embolism; Cardiac anatomy; Stroke

(Heart Rhythm 2016;13:820–827)

Introduction

Atrial fibrillation (AF) is a leading cause of stroke. Adequate anticoagulation is the mainstay for thromboembolic prophylaxis in patients with AF. Paroxysmal AF is one of the most underdiagnosed mechanisms of apparent cryptogenic stroke. The yield of cardiac rhythm monitoring for documenting AF varies greatly depending on the duration of monitoring and the choice of monitoring devices.[1]

On the contrary, AF is not always a culprit of stroke in patients with AF plus stroke. Because most of the risk factors for thromboembolism in AF (eg, $CHADS_2$ score) also enhance the risk of other stroke subtypes such as large artery atherosclerosis or small artery occlusion, one can assume that ischemic stroke in AF patients can be caused by noncardioembolic mechanisms rather than cardioembolism.[2–4] The stroke in approximately one-sixth of patients with AF plus stroke is noncardioembolic in nature and often occurs despite adequate anticoagulation.[5] Therefore, differentiating between these two mechanisms in AF patients may have therapeutic implications.

Efforts have been made to demonstrate possible biomarkers predicting risk of stroke in patients with AF, including risk schemes[6] and serologic[7] and genetic[8] biomarkers. Cardiac imaging biomarker is another approach that can be used to differentiate between cardiogenic and noncardiogenic stroke.[9] Such an approach has several advantages, including no need for prolonged monitoring, direct visualization of thrombus or other source of cardioembolism,

This study was supported by A grant from the Heart Vascular and Stroke Institute, Samsung Medical Center, and the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (HI14C16240000). **Address reprint requests and correspondence:** Dr. Oh Young Bang, Department of Neurology, Samsung Medical Center, Sungkyunkwan University. 81, Irwon-Ro, Gangnam-gu, Seoul 135-710, South Korea. E-mail address: ohyoung.bang@samsung.com.

and detection of asymptomatic coronary artery disease.[10] However, in most studies, echocardiographic and multidetector cardiac computed tomography (MDCT) findings were compared between patients with isolated AF and patients with stroke plus AF without consideration of the duration of AF and related mechanical abnormalities or stroke subtype (eg, lacunar stroke).

We hypothesized that morphometric or volumetric parameters of left atrial appendage (LAA) are related to the mechanisms of stroke (cardioembolic vs noncardioembolic) in subjects with AF. Thus, we compared the MDCT and echocardiographic findings of stroke patients with cardioembolic stroke (CES) plus AF, incidental AF (other documented etiologies such as carotid stenosis or lacunar stroke), and no AF.

Methods

Patient selection

We analyzed prospectively collected MDCT data of 433 consecutive patients who were admitted for acute cerebral ischemia within 7 days after symptom onset and participated in the institutional heart and brain program (Comprehensive Brain and Heart Health [CBHH] program) at a university medical center between January 2011 and July 2014. The CBHH is a program operated by an integrated team of specialized neurologists, neuroradiologists, neurosurgeons, and cardiologists providing comprehensive evaluation and management of acute ischemic stroke patients who were willing to participate. Patients were included in this study if (1) they underwent MDCT, (2) they had AF, (3) acute ischemic lesion was documented on diffusion-weighted imaging (DWI); and (4) they underwent complete etiologic workups for ischemic stroke, including neuroimaging and cardiologic studies. From this initial population, patients with poor-quality MDCT images were excluded. The causes of poor quality were severe arrhythmia, which may cause motion artifacts on the MDCT images, and patients' poor cooperation due to unstable medical conditions or severe neurologic deficits. Patients with valvular heart disease or prosthetic valve also were excluded. The enrolled patients were divided into CES with AF and non-CES with AF groups according to presumed stroke subtypes based on the published criteria by the Stroke Prevention in Atrial Fibrillation investigators with some modifications (Supplementary Table 1).[4,5] In addition, age- and sex-matched subjects with non-CES without AF who were randomly selected from the same database served as controls (Figure 1). Typical examples of patients in each group are shown in Figure 2. The study was approved by the local institutional review board, and each participant provided informed consent.

Diagnostic evaluation

Patients were assessed according to a protocol based on demographic data, medical history, vascular risk factors, routine blood test, brain magnetic resonance imaging including DWI and magnetic resonance angiography, and cardiologic evaluation including electrocardiography (ECG), cardiac telemetry for at least 24 hours, and echocardiography. Medical history and vascular risk factors consisted of hypertension, diabetes, hyperlipidemia, congestive heart failure, coronary heart disease, smoking, previous history of stroke or transient ischemic attack, previous use of antiplatelet or warfarin medications, and National Institutes of Health Stroke Scale score. Blood tests were performed within 24 hours of admission and analyzed for glucose, lipid panel, and a standard battery of biochemical and hematologic tests, including prothrombin time. AF was diagnosed by 12-lead ECG and/or 24-hour Holter monitoring during hospitalization or based on medical history of ECG-documented AF. Persistent AF was defined as AF lasting at least 7 days and requiring pharmacologic therapy or electrical cardioversion for termination.

Infarct patterns were classified into three groups based on the observed DWI patterns: (1) large cortical/cortical-deep patterns including territorial infarcts, cortical infarcts involving one subdivision, mixed cortical-deep infarcts, or deep lesions with concomitant small DWI lesions outside the territory of penetrating arteries; (2) small cortical pattern, infarcts with small single or multiple ischemic lesions <1 cm in diameter on DWI; and (3) deep-only pattern defined as deep infarcts restricted to the territory of the basal or brainstem-penetrating arteries. DWI infarct volume measurements were performed by an investigator (JPS) who was blinded to the clinical information. For each patient, DWI lesions were outlined automatically with subsequent manual correction, and volumes were calculated with a computer-assisted volumetric analysis program (Medical Image Processing, Analysis and Visualization, version 2.1, Center for Information Technology, National Institutes of Health).

Computed tomography

MDCT imaging of the heart was performed using a 128-slice dual-source computed tomography (CT) system (SOMATOM Definition Flash, Siemens Healthcare, Erlangen, Germany) with 2- $\times$ 64- $\times$ 0.6-mm detector collimation and the z-axis flying focal spot technique resulting in 2 $\times$ 128 sections. An antecubital intravenous catheter was placed for contrast injection, and ECG leads were placed on the patient's chest. No beta-blocker was administered. The CT scan was obtained 1 minute after the sublingual administration of nitroglycerin 0.4 mg.

The retrospective ECG-gated helical mode was used with the full radiation dose window set at 68% to 78% of the R-R interval in patients with heart rates $\leq$65 bpm and 200–400 ms after the R peak in patients with heart rate $>$65 bpm. A reduced dose (4% of the dose during the acquisition window) was used for the rest of the R-R interval to minimize the radiation dose. The typical contrast dose for this portion of the examination was 60–70 mL of iomeprol 400 (Iomeron 400 mg/mL, Bracco, Milan, Italy) , followed by 20 mL of a saline mixture (30% contrast/70% saline) injected at 4 mL/s. Acquisition was craniocaudal from above the origin of the