Increased Left Ventricular Filling Pressure and Arterial Occlusion in Stroke Related to Atrial Fibrillation

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Background: We investigated whether left ventricular filling pressure is associated with arterial occlusion in patients with ischemic stroke related to atrial fibrillation (AF). *Methods:* Ninety-nine patients with AF-related stroke were included. Left ventricular filling pressure was assessed by E (early mitral inflow velocity)/e' (early diastolic velocity of the mitral valve annulus velocity) ratio based on tissue Doppler echocardiography. Arterial occlusion was evaluated by computed tomography or magnetic resonance angiography. In addition, the presence of a hyperdense middle cerebral artery sign (HMCAS) on noncontrast brain computed tomography, a marker of acute thrombus burden, was assessed. Multiple logistic regression was used to evaluate the association of E/e' with arterial occlusion and the HMCAS. *Results:* The mean age was 73.2 (±10.2), and 56% were men. Thirty-six (36.4%) patients had arterial occlusion on imaging. E/e' ratios were independently associated with arterial occlusion with an odds ratio of 1.24 (per 1 increase, 95% confidence interval 1.11-1.38). The receiver operating characteristics curve demonstrated that E/e' ratios have an excellent discriminatory capacity in predicting arterial occlusion with an area under the curve of .77 ($P < .001$). In addition, E/e' ratios were higher in patients with HMCAS than in those without (19.1 versus 14.0, $P < .001$). *Conclusion:* E/e' ratios were associated with arterial occlusion in AF-related stroke and may play a role in identifying patients at high risk of severe stroke. **Key Words:** Heart failure—cerebral infarction—atrial fibrillation—magnetic resonance imaging.

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Introduction

Ischemic strokes caused by atrial fibrillation (AF) are likely to have a larger infarct volume and unfavorable outcomes than other stroke subtypes.[1] However, the severity of AF-related strokes varies considerably, from being clinically silent to catastrophic, with the presence of major arterial occlusion being the main predictor of outcome. The burden of thrombus that embolizes may depend upon the amount of thrombus at the source in the left atrium.[2]

Diastolic dysfunction is one of the main causes of heart failure in subjects with normal left ventricular ejection fraction.[3] Diastolic dysfunction increases the risk of stroke and left atrial appendage thrombus formation in AF.[4,5] Moreover, diastolic dysfunctions are found in up to 25% of patients with cryptogenic stroke in whom undetected paroxysmal AF is the causal agent.[6] Increased left ventricular filling pressure, the key feature of diastolic

dysfunction, gives rise to left atrial stasis,[7] which may increase the risk of in situ thrombosis in the atrium, as well as the size of embolism resulting from clot migration.[5] We, therefore, hypothesized that increased left ventricular filling pressure is related to arterial occlusion and infarct volume in AF-related strokes,[8] reflecting embolic burden. The early diastolic velocity of the mitral valve annulus (e') reflects the rate of myocardial relaxation. When combined with the early mitral inflow velocity (E), the resultant ratio (E/e') correlates well with left ventricular filling pressure.[9-12] We investigated the association of the E/e' ratio with major cerebral artery occlusion and infarct volume in ischemic stroke attributable to AF.

Methods

Study Population

We analyzed a prospectively recruited stroke cohort comprising a consecutive series of patients with ischemic stroke who visited our stroke center within 7 days of symptom onset from March 2013 to December 2015. During the study period, 868 patients with ischemic stroke were admitted to our center, and 131 were categorized as having had cardioembolism by the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.[13] We excluded patients who had other causes of cardioembolism, such as a mechanical prosthetic valve (n = 5), akinetic or hypokinetic left ventricular segment (n = 4), infective endocarditis (n = 1), left atrial thrombus without AF (n = 1), ejection fraction of less than 50% (n = 2), and patent foramen ovale (n = 8). We further excluded patients with unavailable arterial imaging of the brain (n = 4) and echocardiography (n = 7) due to devastating stroke or poor cooperation. After exclusions, 99 patients remained in the analyses. All experiments followed the tenets of the Declaration of Helsinki. The Institutional Review Board of Dongguk University Ilsan Hospital approved the present study and waived the requirement for informed consent for study inclusion, based on the retrospective study design.

Clinical Data

Variables that potentially influence arterial occlusion were derived from a stroke database that has been curated with a standardized protocol since 2011.[14] These include age, gender, smoking status, history of hypertension, diabetes, dyslipidemia, coronary artery disease and stroke, time from symptom onset to arterial imaging, and prior use of medications. The ictus of the index stroke was defined as the last time when the patient was known to be free of neurological symptoms. AF chronicity was classified as paroxysmal, persistent, and permanent.[15] We calculated the CHA_2DS_2-VASc score by assigning 1 point for age 65-74, congestive heart failure, hypertension, diabetes mellitus, vascular disease, and female gender, and 2 points for a history of stroke or transient ischemic attack and age 75 years or older.[16]

Imaging Analysis

Arterial occlusion was determined using 3-dimensional time-of-flight magnetic resonance (MR) angiography (n = 65), contrast-enhanced MR angiography (n = 10), or computed tomography (CT) angiography (n = 24). Arterial occlusion relevant to cerebral infarct was determined by an experienced neurologist blinded to patients' characteristics. "Proximal arterial occlusion" was defined when extracranial or intracranial carotid artery, vertebral artery, basilar artery, and the first segment of anterior cerebral artery, posterior cerebral artery, and middle cerebral artery were occluded. Other visible arterial occlusions on imaging relevant to the index stroke were defined as "distal arterial occlusion." The time of either first MR or CT angiography was defined as the arterial imaging time.

Acute infarct volume was assessed using diffusion-weighted magnetic resonance imaging (MRI) performed on 1.5 T (n = 62) or 3.0 T (n = 35). Two patients did not undergo diffusion-weighted MRI. Diffusion-weighted MRI protocols were b-values of 0 and 1000 s/mm^2, repetition time of 5400 ms, echo time of 77 ms, field of view of 220×220, slice thickness of 3.0 mm, and interslice gap of .3 mm. All scans were transferred to the Korean Brain MRI Data Center for central data storage and quantitative analysis. As previously reported,[17,18] diffusion-weighted MRI was converted into a patient-independent quantitative visual format. Brain template images ($1 \times 1 \times 1$ mm^3 voxels) were chosen from the Montreal Neurological Institute template within the range of –63.5 to 74.5 mm in the Z-axis of Talairach space. After normalization of images, each patient's high signal intensity lesions on diffusion-weighted MRI were semiautomatically segmented and registered onto the brain templates under close supervision by vascular neurologists. During the process of quantification for acute infarct volume, the inter-rater variability was minimal, and the intraobserver correlation coefficient was high, ranging from .84 to .98.[18] The infarct volume on diffusion-weighted imaging (DWI) was calculated as a percentage of brain volume by dividing the number of voxels in the lesions over the total number of brain voxels.

Because intravenous recombinant tissue plasminogen activator is given to patients based on noncontrast brain CT before arterial imaging, we investigated the association between E/e' ratios and the imaging marker of thrombus burden on noncontrast brain CT, which is the hyperdense middle cerebral artery sign (HMCAS), in the patients who had infarct at the territory of the middle cerebral artery (n = 69).[19] HMCAS was diagnosed by 2 experienced neurologists (W.S.R. and S.H.P.) blinded to patients' characteristics when the first segment (M1) of the middle cerebral artery was denser than the contra-