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Characteristic lesion pattern and echocardiographic findings in extra-cardiac shunt-related stroke

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ABSTRACT

Among embolic strokes of undetermined source, under-recognized etiology such as extra-cardiac shunt could be a potential risk factor. We sought to characterize infarction patterns on diffusion-weighted imaging (DWI) and transesophageal echocardiography (TEE) findings in extra-cardiac shunt-related stroke. We enrolled 96 consecutive patients with cryptogenic stroke who had an extra- or intra-cardiac shunt. Diagnosis of the shunt was performed using TEE with agitated saline contrast and pulmonary vein isolation. Infarction patterns on DWI and total lesion volume were analyzed. Bubble amounts through the shunt were classified via the International Consensus Criteria (ICC). Short-term prognosis, patterns and size of DWI lesions, and involved vascular territories were not significantly different between two groups. Multivariate analysis revealed that extra-cardiac shunt group has a smaller total infarct volume (odds ratio [OR] = 0.427, 95% confidence interval [95% CI] 0.228–0.799, $p = 0.008$), and significantly higher bubble grade during resting state and lower grade during the Valsalva maneuver (OR = 0.539, 95% CI 0.438–0.663, $p < 0.001$). Stroke related to an extra-cardiac shunt presented smaller infarct volume, favorable clinical outcomes and characteristic finding on TEE with agitated saline contrast. Further study is needed to confirm whether the extra-cardiac shunt is an independent risk factor.

1. Introduction

Cryptogenic stroke is defined by the presence of a transient or permanent neurological deficit with MRI evidence of an ischemic lesion in the absence of a clear etiology. Cryptogenic stroke accounts for 30 to 40% of ischemic stroke in most modern stroke registries [1,2]. After a complete evaluation, atrial fibrillation (AF) was detected in 20–30% [3,4] and patent foramen ovale (PFO) was present in 25–30% of cryptogenic strokes [5,6]. Whether PFO is a risk factor for stroke has been controversial. Several studies reported the PFO was associated with increased risk of stroke [7,8]. Whereas, other studies could not confirm the results [9,10]. Causes in the remaining 40–50% of cryptogenic stroke are still unclear. In several cases, pulmonary arteriovenous fistula (AVF) and arteriovenous malformation (AVM) have been suggested as potential facilitators of stroke [11–14]. About 40 to 50% of patients with pulmonary AVF were at risk of TIAs (37%) and strokes (18%) [13,15].

Patterns of ischemic lesions found on diffusion-weighted imaging (DWI) are different depending on the etiologic stroke mechanisms [16]. In a recent study, an intra-cardiac shunt related stroke usually appeared as a single cortical or multiple small ischemic lesions in the vertebrobasilar circulation [17]. Therefore, we presumed that a stroke associated with extra-cardiac shunt could present less severe ischemic lesion and better clinical outcome which may be related to smaller thrombus burden than those with intra-cardiac shunt. We also hypothesized that patients with extra-cardiac shunt show positive bubble test on TEE during the resting state and Valsalva maneuver does not increase bubble amounts. These results could help to differentiate extra-cardiac shunt from intra-cardiac shunt.

2. Methods

2.1. Patients

This is a retrospective analysis of the natural history of patients with acute ischemic stroke who were admitted to the Samsung Medical Center, Seoul, Korea between January 1, 2011 and May 31, 2015. We defined cryptogenic stroke as patients with a final diagnosis of cryptogenic embolism who had an acute ischemic stroke, which corresponded to the Stop Stroke Study Trial of Org 10,172 in Acute Stroke Treatment (SSS-TOAST) classification [18].

All the included patients were admitted within 7 days of stroke symptoms. We reviewed the stroke registry of Samsung medical center

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to classify patients. Those who received DWI, magnetic resonance angiography (MRA) and TEE with agitated saline contrast were enrolled. Extra-cardiac shunt related stroke was defined as cryptogenic stroke with documented extra-cardiac shunt by TEE with agitated saline contrast. Intra-cardiac shunt related stroke was defined as the same way. However, stroke from other embolic sources, such as (1) significant atherosclerosis in corresponding arteries evaluated by MRA; (2) significant atherosclerosis in the aortic arch or ascending aorta evaluated by MRA or TEE; (3) high risk factors for cardiogenic embolism; (4) evidence of other causes of ischemic stroke such as arterial dissection, vasculitis, and cancer-related stroke, were excluded. Hypercoagulability work-up was also performed.

Our institutional review board approved this study.

2.2. Clinical data

Demographics, conventional stroke risk factors (hypertension, DM, hyperlipidemia, smoking, and previous stroke history), current antithrombotic medication, baseline laboratory results (complete blood count, fasting glucose, lipid profile, blood urea nitrogen, creatinine, and C-reactive protein) and thrombotic profile data (platelet count, fibrinogen, prothrombin time-international normalization ratio [PT-INR], protein C, S Ag, homocysteine, *anti*-phospholipid antibody profile [lupus anticoagulant, anti-cardiolipin antibody, and anti-beta 2 glycoprotein I antibody]) were acquired on admission day. Prognostic factors (National Institutes of Health Stroke Scale [NIHSS] score and modified Rankin score [mRS]) were evaluated on the day of admission and discharge.

2.3. MRI (diffusion-weighted imaging assessment)

The DWI was performed using a 3-Tesla magnetic resonance system. DWI lesions were analyzed by pattern, location and volume [16]. Lesion patterns were evaluated by lesion number, distribution and size. Number and distribution of ischemic lesions was divided into single (cortical, subcortical) or multiple (small scattered in 1 vessel territory, confluent lesion with additional lesions, multiple vascular territories). Single cortical lesion include small cortical or large corticosubcortical lesion. The vascular territory of ischemic lesions was classified as anterior circulation, posterior circulation or multiple vascular territories. DWI were processed using MATLAB R2007b (The MathWorks, MA). Volumes of interest (VOI) of DWI lesions were calculated using MIPAV 7.2.0 (http://mipav.cit.nih.gov/). Regions of interest (ROI) were visually inspected and manually drawn by 2 neurologists.

2.4. Transesophageal echocardiography

TEE with agitated saline contrast was used for the diagnosis of extra-cardiac shunt. This evaluation was done within 14 days of the onset of stroke. The detection of extra-cardiac shunt was performed by the following methods. Patients lying in the left lateral decubitus position got an injection of the saline contrast agent mixed with air through an antecubital vein at rest and during the Valsalva maneuver. 1 cm^3 of air and 9 cm^3 of saline were mixed and manually agitated between two syringes connected by 3-way stopcock. The agitated saline contrast was injected manually as a bolus. Simultaneously, a well-trained sonographer acquired an apical 4 chamber view. If agitated saline bubbles appear in the left atrium after 3-to-5 cardiac cycles after opacification of the right atrium, then an extra-cardiac shunt is suggested. We also did pulmonary vein isolation during the study. This procedure was performed to exclude intra-cardiac shunting that resulted from a PFO or atrial septal defect (ASD). A specialist in cardiology reviewed the echocardiography data independently.

The International Consensus Criteria (ICC) was used to classify bubble grade. Absence of bubbles was classified as grade 0. A positive study was classified as 1 to 9 bubbles (grade I), 10 to 20 bubbles (grade II), and >20 bubbles (grade III) appearing in the left atrium.

Intra-cardiac shunt was defined as the passage of >3 microbubbles from the right to the left atrium through the gap within 3 cardiac cycles after complete opacification of the right atrium. Size of intra-cardiac shunt and the coexistence of an atrial septal aneurysm or hypermobile septum were measured. The size was measured at multiple planes, and the maximal length between the septum primum and secundum at resting or during Valsalva was measured.

2.5. Statistical analysis

Continuous data are presented as mean ± standard deviation or median and interquartile range according to normality values of the Kolmogorov-Smirnov test. We compared demographics, risk factors, and laboratory results between extra-cardiac shunt and intra-cardiac shunt groups.

DWI lesion patterns, total volume of infarction, involved vascular territories, bubble quantities on TEE, and prognostic factors (National Institutes of Health Stroke Scale, modified Rankin score) were also compared. Pearson χ^2 test, Fisher's exact test, Student *t*-test, Mann–Whitney *U* test and Logistic regression analysis were used appropriately. Generalized Estimating Equation was applied to repeated measurements of parameters. Analysis was conducted using SPSS version 18.0 (SPSS Inc.; Chicago, IL), and a $p < 0.05$ was considered statistically significant.

3. Results

From a review of the clinical stroke registry of our hospital, 3318 patients were diagnosed with ischemic stroke. Of those, 331 patients (10.0%) were classified with cryptogenic embolism. There were 132 patients who met the inclusion criteria. Among the patients, shunt was found in 113 patients. Extra-cardiac shunt was observed in 21 patients (21.9%), and intra-cardiac shunt was found in 75 patients (78.1%). 36 patients were excluded from this study; 19 patients did not have intra- or extra-cardiac shunt on TEE and 17 patients had both intra- and extra-cardiac shunts (Fig. 1, see Supplementary data online, Fig. S1, Table S1).

3.1. Clinical characteristics

Age, sex and risk factors for stroke (hypertension, diabetes, smoking and previous stroke history) were not significantly different between the two groups (Table 1). Laboratory data including complete blood count, LDL cholesterol, and chemistry data were not different between the groups. The stroke severities on admission NIHSS were low but not significantly different in both groups (mean ± SD 3.2 ± 4.4 vs 1.7 ± 2.2, $p = 0.426$). Prognostic factors such as admission and discharge National Institutes of Health Stroke Scale (NIHSS), modified Rankin score (mRS) and modified Barthel index (mBI) also were not significantly different (Table 2).

3.2. Characteristic findings on DWI

Comparing distribution of DWI lesions, no patterns were statistically different between the groups. However, analyzing the volume of lesions on DWI, stroke with extra-cardiac shunt presented significantly smaller than intra-cardiac shunt group (0.9 ml [IQR 0.3–6.3] vs 3.9 ml [IQR 0.9–19.7]; $p = 0.017$) (Table 3).

3.3. Transesophageal echocardiography findings

Using TEE with agitated saline contrast, we checked bubble numbers during the resting state and Valsalva maneuver. Using a binary logistic regression and generalized estimating equation (GEE) analysis, probability of extra-cardiac shunt increased according to bubble grade on