Associations of Mitral and Aortic Valve Calcifications with Complex Aortic Atheroma in Patients with Embolic Stroke of Undetermined Source

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Background: This study investigated the associations of mitral and aortic valve calcification with complex aortic atheroma among patients with embolic stroke of undetermined source. *Methods:* We included 52 consecutive patients (mean age 58.1 years; 75.0% male) with embolic stroke of undetermined source. Mitral annular calcification, aortic annular calcification, and aortic valve sclerosis were assessed by transthoracic echocardiography. Complex aortic atheroma was assessed by transesophageal echocardiography and was defined as plaque protruding greater than or equal to 4 mm into the lumen or with ulcerated or mobile components. *Results:* Ten patients (19.2%) had complex aortic atheroma. Patients with and without complex aortic atheroma showed significant differences in terms of hypertension (80.0% versus 38.1%, $P = .017$), dyslipidemia (90.0% versus 31.0%, $P < .01$), chronic kidney disease (60.0% versus 14.3%, $P < .01$), previous coronary artery disease (30.0% versus 4.8%, $P = .013$), prior stroke (40.0% versus 7.1%, $P < .01$), left atrial dimension (4.0 cm versus 3.6 cm, $P = .023$), aortic valve sclerosis (80.0% versus 26.2%, $P < .01$), aortic valve calcification (aortic annular calcification or aortic valve sclerosis) (80.0% versus 26.0%, $P < .01$), and left-sided valve calcification (mitral annular calcification or aortic annular calcification or aortic valve sclerosis) (80.0% versus 28.6%, $P < .01$). In multivariate analysis, left-sided valve calcification was independently associated with complex aortic atheroma (odds ratio 4.1, 95% confidence interval 1.3-26.1, $P = .049$). *Conclusions:* Mitral or aortic valve calcification detected by transthoracic echocardiography can be a useful marker for predicting complex aortic atheroma in patients with embolic stroke of undetermined source.
Key Words: Embolic stroke of undetermined source—transesophageal echocardiography—valve calcification—aortic atheroma.

Introduction

A clinical entity termed embolic stroke of undetermined source (ESUS) designates cryptogenic strokes presumably due to embolism with no evidence of lacunar stroke, ipsilateral stenosis in intra- and extracranial arteries, or major cardioembolic sources.[1] Severe atherosclerosis of the aortic arch is one of the most frequent etiologies of ESUS.[1] Complex aortic atheroma (CAA), including atherosclerotic plaques greater than or equal to 4 mm, ulcerated plaques, and mobile plaques, can be reliably detected by transesophageal echocardiography

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(TEE),[2,3] whereas TEE is not a mandatory standard assessment to diagnose ESUS.[1] Given the high risk of recurrent vascular events (as high as 26% per year[4]) in patients with stroke and CAA, the detection of CAA in patients with ESUS is of great importance from the perspectives of treatment, follow-up, and prognosis.

Calcification of cardiac valves, including mitral annular calcification (MAC), aortic annular calcification (AAC), and aortic valve sclerosis (AVS), is considered to be a manifestation of generalized atherosclerosis.[5] Indeed, several previous studies reported that these left-sided valve calcifications were associated with atherosclerosis in coronary arteries,[6,7] carotid arteries,[8] and aortic arch.[9,10] Therefore, we hypothesized that mitral and aortic valve calcifications, both of which can be noninvasively assessed by transthoracic echocardiography (TTE), are good markers for predicting the presence of CAA among patients with ESUS. Identification of patients who are likely to have CAA would be informative for the efficient performance of poststroke workup. The aim of this study was to determine the associations of MAC, AAC, and AVS detected by TTE with CAA among patients with ESUS.

Materials and Methods

Study Protocol

The ethics committee of our institution approved the study protocol. We conducted a hospital-based retrospective study involving 148 consecutive patients who were admitted to our center and diagnosed with ESUS within 1 week of onset, between October 2007 and September 2016. After excluding 96 patients (90, incomplete evaluation; 5, prosthetic valves; and 1, rheumatic valvular heart disease), 52 patients who had a complete poststroke workup, including brain imaging, vessel imaging, and extensive cardiac assessments (12-lead electrocardiography [ECG], Holter ECG, TTE, and TEE), were included in the current analysis. ESUS was defined according to the Cryptogenic Stroke/ESUS International Working Group criteria (i.e., stroke detected by computed tomography or magnetic resonance imaging that is not lacunar; absence of extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischemia; no major-risk cardioembolic source of embolism or no other specific cause of stroke identified [e.g., arteritis, dissection, migraine or vasospasm, drug misuse]).[1] The severity of the event was assessed using the National Institutes of Health Stroke Scale (NIHSS) score; NIHSS scores range from 0 to 42, with higher values reflecting more severe neurologic deficits.

Risk Factors

Patients were diagnosed with hypertension if they had evidence of systolic blood pressure higher than or equal to 140 mm Hg or diastolic blood pressure higher than or equal to 90 mm Hg or if they had received any antihypertensive medication. Diabetes mellitus was specified as a fasting serum glucose greater than or equal to 126 mg/dL, serum glucose greater than or equal to 200 mg/dL on 2 random measurements, glycated hemoglobin greater than or equal to 6.5%, or use of antidiabetic therapy (oral hypoglycemic agents or insulin). Dyslipidemia was diagnosed if the patient had low-density lipoprotein cholesterol greater than or equal to 140 mg/dL or total cholesterol greater than or equal to 220 mg/dL, or if the patient had been treated with lipid-lowering agents. The estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease formula with the Japanese coefficient. Chronic kidney disease was defined as an estimated glomerular filtration rate less than 60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$. Smoking status was defined based on current use. Intracranial arterial stenosis greater than or equal to 50% on magnetic resonance angiography, 3-dimensional computed tomography angiography, or digital subtraction angiography was considered a significant finding. Findings of carotid artery ultrasonography were evaluated by trained neurologists, and stenosis greater than or equal to 50% was defined as significant extracranial arterial stenosis.

Echocardiography Examination

Transthoracic 2-dimensional and Doppler echocardiography was performed using the iE33 ultrasound system (Philips Healthcare, Bothell, WA) with an S5 transducer. Left atrial dimension was measured at end-systole, when the left atrial chamber is at its greatest dimension. MAC was defined as an intense echocardiographic-producing structure that was located at the junction of the atrio-ventricular groove and posterior mitral leaflet on the parasternal long-axis, apical 4-chamber, or parasternal short-axis view.[11] AAC and AVS were defined as increased echocardiographic density of the aortic root and whenever aortic cusp thickening with normal aortic cusp excursion and a peak transaortic valve velocity 2.0 m/s were identified, respectively.[11] In this study, aortic valve calcification was defined as the presence of AAC or AVS, and left-sided valve calcification was defined as the presence of MAC or AAC or AVS, respectively. Left ventricular hypertrophy was defined as left ventricular mass greater than 116 g/m^2 for men and greater than 96 g/m^2 for women. The left ventricular ejection fraction was calculated using the biplane Simpson formula.

TEE was performed using the iE33 ultrasound system (Philips Healthcare) using a multiplane probe. Before performing TEE, intraoral xylocaine spray and intravenous propofol were administered to all patients. The heart rhythm was monitored by ECG during the examination. Patients were placed in the left lateral decubitus position during probe insertion. The probe was advanced to the distal esophagus and withdrawn slowly