Atrial Cardiopathy and Cryptogenic Stroke: A Cross-sectional Pilot Study

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Background: There is increasing evidence that left atrial dysfunction or cardiopathy is associated with ischemic stroke risk independently of atrial fibrillation. We aimed to determine the prevalence of atrial cardiopathy biomarkers in patients with cryptogenic stroke. *Methods:* We included consecutive patients with ischemic stroke enrolled in the New York Columbia Collaborative Specialized Program of Translational Research in Acute Stroke registry between December 1, 2008, and April 30, 2012. Medical records were reviewed and patients with a diagnosis of cryptogenic stroke were identified. Atrial cardiopathy was defined as at least one of the following: serum N-terminal probrain natriuretic peptide (NT-proBNP) level greater than 250 pg/mL, *P*-wave terminal force velocity in lead V1 (PTFV1) on electrocardiogram (ECG) greater than 5000 μV·ms, or severe left atrial enlargement (LAE) on echocardiogram. We compared clinical, echocardiographic, and radiological characteristics between patients with and without atrial cardiopathy. *Results:* Among 40 patients with cryptogenic stroke, 63% had at least one of the biomarkers of atrial cardiopathy; 49% had elevated NT-proBNP levels, 20% had evidence of increased PTFV1 on ECG, and 5% had severe LAE. Patients with atrial cardiopathy were more likely to be older (76 versus 62 years, $P = .012$); have hypertension (96% versus 33%, $P < .001$), hyperlipidemia (60% versus 27%, $P = .05$), or coronary heart disease (28% versus 0%, $P = .033$); and less likely to have a patent foramen ovale (4% versus 40%, $P = .007$). *Conclusion:* There is a high prevalence of biomarkers indicative of atrial cardiopathy in patients with cryptogenic stroke. Clinical trials are needed to determine whether these patients may benefit from anticoagulation to prevent stroke. **Key Words:** Stroke—atrial cardiopathy—cryptogenic—anticoagulant—prevention.

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Background

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is a global healthcare problem, particularly due to its rising worldwide incidence and prevalence.[1,2] To date, AF is the only marker of left atrial dysfunction for which anticoagulation has been shown to provide a greater reduction of stroke risk than antiplatelet therapy.[3] Other less established markers of left atrial dysfunction or "atrial cardiopathy" that have been associated with ischemic stroke risk in prospective studies include paroxysmal supraventricular tachycardia, elevated serum N-terminal probrain natriuretic peptide (NT-proBNP), increased *P*-wave terminal force velocity in lead V1 (PTFV1) on electrocardiogram (ECG), and moderate to severe left atrial enlargement (LAE) on echocardiogram.[4,5] Several of these biomarkers are also associated with detection of AF in prospective studies.[6,7]

Left atrial size, PTFV1, and NT-proBNP all have been linked to detection of paroxysmal AF in patients with cryptogenic stroke,[5-10] but the relationship and concordance between these 3 biomarkers is unclear. Understanding the relationship between these biomarkers and their association with cardiovascular risk factors in patients with cryptogenic stroke may shed light on the relationship between atrial cardiopathy and stroke, thereby helping to improve stroke prevention strategies.

Our aim was to determine the prevalence of biomarkers of atrial cardiopathy in patients with cryptogenic stroke and their association with cardiovascular risk factors.

Methods

Population

We included consecutive cryptogenic stroke patients enrolled in the hospital-based New York Columbia Collaborative Specialized Program of Translational Research in Acute Stroke (NYCC SPOTRIAS) registry between December 1, 2008, and April 30, 2012. These patients were enrolled in NYCC SPOTRIAS within 12 hours from symptom onset, admitted to the hospital, and had a standard stroke diagnostic evaluation based on current clinical practice guidelines. Cryptogenic stroke was defined based on the Trial of Org 10172 in Acute Stroke Treatment classification.[11] Clinical information included baseline demographics (age, sex, and race–ethnicity), risk factors (hypertension, hyperlipidemia, diabetes, coronary heart disease, congestive heart failure, renal disease, and smoking), imaging data (presence of prior embolic infarcts), ECG parameters, and echocardiographic results (ejection fraction, left ventricular hypertrophy, patent foramen ovale [PFO], and left atrial diameter).

Blood samples were drawn at enrollment and 24-48 hours after admission and were stored in the Center for Advanced Laboratory Measurement at Columbia University. We followed all patients prospectively for 30 days after their stroke as part of the registry. Two patients died during the hospitalization period and all the rest completed the 30-day follow-up. Follow-up after 30 days was retrospective and based on the availability of medical records.

The study was approved by the Columbia University Medical Center Institutional Review Board and all patients provided informed consent.

Atrial Cardiopathy Biomarkers

PTFV1 was determined, as in prior studies,[12] as the absolute value of the depth (μV) of the downward deflection (terminal portion) of the *P*-wave in ECG lead V1 multiplied by its duration (ms). Measurements were made on the admission paper ECG using digital calipers in millimeters and were then converted to microvolt and millisecond using the ECG calibration of 10 mm/mV and 25 mm/s. Elevated PTFV1 was defined as PTFV1 greater than 5000 μV·ms, a threshold that was associated with doubling of stroke risk in prior studies (H. Kamel, personal communication, 2015) and is the midpoint of thresholds used in prior studies.[13,14]

The NT-proBNP level was measured in a clinical laboratory using the Cobas e601 analyzer (Roche Diagnostics, Indianapolis, IN). The coefficient of variation for the NT-proBNP assay was 2%-5% during the testing period, and its analytic measurement range was 5-35,000 pg/mL, where 1 pg/mL equals .118 pmol/L. A threshold of 250 pg/mL was used as this threshold was also associated with a 2-fold increased risk of recurrent stroke compared to patients with a normal NT-proBNP level in the Warfarin Aspirin Recurrent Stroke Study.[15]

Left atrial diameter was obtained from the echocardiogram performed for clinical purposes and was divided by the echocardiographer into 4 groups: normal, mild, moderate, and severe LAE. We defined atrial cardiopathy as the presence of severe LAE based on prior work on the relationship between left atrial size and recurrent stroke.[16]

Statistical Analysis

The patients were divided into 2 groups based on whether or not they had atrial cardiopathy defined as having at least one of the biomarkers above. The baseline demographic characteristics (age, sex, and race–ethnicity), vascular risk factors (hypertension, hyperlipidemia, diabetes, coronary artery disease, congestive heart failure, smoking, and renal disease), echocardiographic parameters (ejection fraction, PFO, and left ventricular hypertrophy), and neuroimaging evidence of superficial cortical infarct were abstracted from the medical record and compared between the 2 groups using nonparametric tests for continuous variables and Fisher's exact tests for categorical variables. A *P* value less than .05 was considered statistically significant.