Biomarkers of Atrial Cardiopathy and Atrial Fibrillation Detection on Mobile Outpatient Continuous Telemetry After Embolic Stroke of Undetermined Source

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Background: Biomarkers of atrial dysfunction or "cardiopathy" are associated with embolic stroke risk. However, it is unclear if this risk is mediated by undiagnosed paroxysmal atrial fibrillation or flutter (AF). We aim to determine whether atrial cardiopathy biomarkers predict AF on continuous heart-rhythm monitoring after embolic stroke of undetermined source (ESUS). *Methods:* This was a single-center retrospective study including all patients with ESUS undergoing 30 days of ambulatory heart-rhythm monitoring to look for AF between January 1, 2013 and December 31, 2015. We reviewed medical records for clinical, radiographic, and cardiac variables. The primary outcome was a new diagnosis of AF detected during heart-rhythm monitoring. The primary predictors were atrial biomarkers: left atrial diameter on echocardiography, P-wave terminal force in electrocardiogram (ECG) lead V1, and P wave - R wave (PR) interval on ECG. A multiple logistic regression model was used to assess the relationship between atrial biomarkers and AF detection. *Results:* Among 196 eligible patients, 23 (11.7%) were diagnosed with AF. In unadjusted analyses, patients with AF were older (72.4 years versus 61.4 years, $P < .001$) and had larger left atrial diameter (39.2 mm versus 35.7 mm, $P = .03$). In a multivariable model, the only predictor of AF was age ≥ 60 years (odds ratio, 3.0; 95% CI, 1.06-8.5; $P = .04$). *Conclusion:* Atrial biomarkers were weakly associated with AF after ESUS. This suggests that previously reported associations between these markers and stroke may reflect independent cardiac

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pathways leading to stroke. Prospective studies are needed to investigate these mechanisms. **Key Words:** Cryptogenic stroke—embolic stroke of undetermined source—ischemic stroke—atrial fibrillation—atrial cardiopathy.

Introduction

Embolic stroke of undetermined source (ESUS) accounts for approximately 20% of all ischemic strokes.[1] Following ESUS, atrial fibrillation or flutter (AF) is detected in 16% of patients on 30-day cardiac monitoring[2] and 30% after 3 years on implantable cardiac monitors.[3]

Recently, "atrial cardiopathy," a condition characterized by structural, functional, and biochemical abnormalities, including serum N-terminal pro b-type natriuretic peptide (NT-proBNP), left atrial enlargement on echocardiography, and increased P-wave terminal force in ECG lead V1 (PTFV1) on ECG, has been shown to be associated with ischemic stroke risk, even in the absence of atrial fibrillation.[4,5] Atrial cardiopathy is particularly associated with embolic stroke subtypes.[6,7] Although biomarkers of atrial cardiopathy are associated with incident AF in epidemiological cohorts,[8-11] the association between these biomarkers and AF detection after ESUS is unclear. Identification of biomarkers measurable at time of stroke is strongly associated with future detection of AF and would provide an opportunity to focus cardiac monitoring on those at highest risk of AF, or potentially even avoid it altogether. In this study, we aim to determine the association between biomarkers of atrial cardiopathy and AF detection after ESUS.

Methods

Study Population

We retrospectively analyzed data from our prospective ischemic stroke inpatient database and included all consecutive patients who met consensus criteria for ESUS[12] and who underwent 30 days of ambulatory heart-rhythm monitoring as screening for AF between January 1, 2013 and December 31, 2015. All patients in our institution with ESUS were referred for outpatient cardiac telemetry. We reviewed medical records for demographic (age and sex) and clinical (history of hypertension, diabetes, hyperlipidemia, prior stroke, coronary artery disease, active smoking) risk factors, and admission National Institutes of Health Stroke Scale (NIHSS) score. Brain imaging (computed tomography or magnetic resonance imaging) was reviewed for the following radiographic variables: presence of superficial infarct(s), presence of subcortical infarct(s), and presence of old superficial infarct(s). Cardiac evaluation included an electrocardiogram (ECG), two-dimensional transthoracic echocardiogram, and at least 24 hours of inpatient cardiac telemetry on all patients.

Primary Predictors

The following biomarkers of atrial cardiopathy were used as predictors of AF detection:

1) P wave - R wave (PR) interval measured digitally on the ECG.
2) PTFV1 measured on admission ECG using the method previously described[13] (by Y.G.; interrater reliability between Y.G. and S.Y. was K = .833).
3) Left atrial anterior-posterior diameter on two-dimensional transthoracic echocardiogram.

Outcome

Auto-triggered and patient-triggered events on the 30-day monitor were recorded and reviewed by a cardiologist subspecializing in electrophysiology (A.C.). The primary outcome was a new diagnosis of atrial fibrillation or atrial flutter of duration 30 seconds or more detected during heart-rhythm monitoring. We also recorded whether or not anticoagulation therapy was started when atrial fibrillation or atrial flutter was detected.

Statistical Analysis

Patients were divided into 2 groups based on whether AF was detected on the outpatient cardiac monitor (AF and non-AF). Demographic, clinical, and radiological variables were compared between the two using Fisher's exact test for categorical variables and independent sample *t*-test for continuous variables. A multivariable logistic regression model was built including variables significant in the univariate model ($P < .05$) to identify predictors of AF on the 30-day cardiac monitor. Analysis was performed using SPSS version 16.0 (Chicago, IL) and $P < .05$ was considered statistically significant.

Results

Study Sample, Baseline Characteristics, and Neuroimaging Data

We identified 196 patients with ESUS who underwent 30-day cardiac monitoring. The mean age was 62.7 ± 15.0 years and 86 (43.9%) were men. AF was detected in 23 patients (11.7%), all of whom were started on anticoagulation therapy. The baseline clinical risk factors