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Atrial Myopathy and Ischemic Stroke in Heart Failure with Preserved Ejection Fraction

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Abstract

Recent studies suggested an association between atrial myopathy and stroke independent of atrial fibrillation (AF). We examined the hypothesis that atrial myopathy may be associated with ischemic stroke in patients with heart failure with preserved ejection fraction (HFpEF). This is an exploratory, post-hoc analysis of the TOPCAT trial. Patients with sinus rhythm documented at baseline ECG and without known AF were included in this analysis. Atrial myopathy was defined by echocardiographic evidence of left atrial enlargement (left atrial diameter > 46mm or left atrial volume index > 36 mL/m2) or elevated natriuretic peptides (BNP > 100 pg/mL or NT-Pro-BNP > 400 pg/mL). We used Cox regression to investigate the effect of atrial myopathy on incident ischemic stroke over the study period. Among 3445 patients in the TOPCAT trial, 2225 (mean age 67.5±4.9 years; female 54.8%) had normal sinus rhythm at baseline and no history of AF. Atrial myopathy was present in 756 (34.0%) patients. During a median follow-up of 2 years, 56 (2.5%) patients developed ischemic stroke, including 25 with atrial myopathy. Atrial myopathy was associated with increased risk of stroke (HR=1.74, 95% CI 1.01 – 2.98, p=0.04) in multivariate analysis. Diabetes (HR=2.02, 95% CI 1.19 – 3.43 p=0.01) was the only other independent predictor of stroke. Among patients with HFpEF, atrial myopathy increases the risk of ischemic stroke, in the absence of AF. Further investigations are needed to better characterize this association and implement stroke prevention strategies.

Keywords

atrial fibrillation; stroke; heart failure with preserved ejection fraction; atrial myopathy

Over the last decade, the prevalence of heart failure with preserved ejection fraction (HFpEF) has increased, reaching approximately 50% of all heart failure cases[1]. Atrial

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fibrillation (AF) and HFpEF are closely associated, and progressive left atrial (LA) remodeling has been demonstrated to correlate with increasing AF burden in patients with HFpEF[2]. However, it has been shown that atrial structural and electrical changes, collectively referred to as atrial myopathy, occur even in the absence of AF[3,4]. While AF increases stroke risk by 5-fold, the lack of temporal association between AF and stroke events has led to the description of a new paradigm, where AF would be considered a marker of atrial myopathy rather than the cause of stroke[4–6]. At present however, there are no standard diagnostic criteria for atrial myopathy, even though biochemical, electrocardiographic, and echocardiographic markers have been used to screen for atrial myopathy in selected populations, including those with embolic stroke of unknown significance (ESUS)[6]. Recent studies demonstrated a correlation of markers of atrial myopathy with stroke events[7,8]. Importantly, LA enlargement and pro–B-type natriuretic peptide (NT-proBNP) were found to predict ischemic stroke in patients without known AF[7,8]. In light of the strong association of HFpEF with atrial myopathy[3], we conducted a post hoc analysis of the TOPCAT trial, to investigate the predisposing role of atrial myopathy in developing ischemic stroke in a subpopulation of patients with HFpEF without known AF.

Methods

The study design, inclusion criteria, and primary findings of TOPCAT have been previously described[9]. The data and study materials were made available through the National Institutes of Health. TOPCAT was a multicenter, randomized, double-blind, placebo-controlled trial that evaluated the effects of spironolactone in patients with symptomatic HFpEF. Briefly, the trial included patients older than 50 years with signs and symptoms of heart failure, left ventricular ejection fraction >45%, controlled systolic blood pressure, serum potassium levels <5 mmol/L, serum creatinine <2.5 mg/dL, and who fulfilled at least 1 of the following inclusion criteria: (1) history of hospitalization for HF within the past 12 months; or (2) brain natriuretic peptide (BNP) ≥100 pg/mL or an N-terminal-pro-BNP (NT-pro-BNP) ≥360 pg/mL within 60 days before randomization. The study included 3445 participants from 233 sites across the Americas and Europe. The mean duration of follow-up was 3.4 ± 1.7 years. The primary end point was time to first of cardiovascular death, HF hospitalization, or aborted cardiac arrest. All end-points after randomization were adjudicated by a central adjudication committee blinded to treatment assignment. The Institutional Review Board at the University of Oklahoma Health Sciences Center approved the present analysis.

For this analysis, the primary end point was incident ischemic stroke over the study period. Among 3445 patients in the TOPCAT trial, we included 2225 patients with sinus rhythm documented at baseline ECG and not known to have a history of AF. Patients were screened for atrial myopathy with available echocardiographic and/ or laboratory data at baseline, defined as left atrial enlargement (left atrial diameter > 46mm or left atrial volume index > 36 mL/m2) or elevated natriuretic peptides (BNP > 100 pg/mL or NT-Pro-BNP > 400 pg/mL)[10]. Using this definition, atrial myopathy was present in 756 (34.0%) patients. Echocardiographic variables were available for 575 (25.8%) patients and 840 (37.8 %) patients had baseline natriuretic peptide values available for this analysis.

Baseline characteristics including age, race, body mass index (BMI), waist circumference, hypertension, dyslipidemia, diabetes, asthma, chronic obstructive pulmonary disease (COPD), thyroid disease, peripheral artery disease, history of stroke, pacemaker, and smoking were compared using the chi-square test and Student's t-test test for categorical and continuous variables, respectively. Stroke-free survival was calculated using the Kaplan-Meier method. Patients were censored if they were lost to follow up or died during the follow up period before a stroke event occurred. Subgroups were compared using the log-rank method. Associations between atrial myopathy, other variables and endpoints were determined using Cox proportional hazards models. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated. Variables that were significant by univariate analysis were entered into a multivariate Cox proportional hazard model with backwards elimination to identify the most parsimonious model. Interaction between atrial myopathy and other clinical variables were also considered, and were dropped from the model when not statistically significant. P values <0.05 were considered statistically significant for main and interaction effects. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

Results

A total of 2225 patients with HFpEF without known history of AF at baseline were included in this analysis. The mean age was 67.5± 4.9 years, and 54.8% were female. Atrial myopathy was present in 756 (34.0%) patients. Of those, 58 had left atrial enlargement, 622 had elevated BNP and 74 had both. Over a median follow-up of 2 years, 56 (2.5%) patients developed ischemic strokes, including 25 with atrial myopathy. During the follow up period, 96 (4.3%) patients developed AF [49 (6.5%) and 47 (3.2%) with and without atrial myopathy, respectively; p=0.0004]. Three (3.1%) of these patients who developed AF during follow up, also developed stroke, including 2 patients with atrial myopathy. The baseline characteristics of patients with and without atrial myopathy are summarized in Table 1. Patients with atrial myopathy had more comorbidities, including diabetes (42.6%), dyslipidemia (70.4%), peripheral arterial disease (13.3%), history of pacemaker implantation (7.9%) and history of prior strokes (8.9%) compared to those without atrial myopathy. More patients with atrial myopathy were on aspirin and warfarin, compared to those without atrial myopathy (31.5% vs. 18.7%; p<0.001 and 4.8% vs. 1.3%; p<0.001, respectively), likely reflecting the higher burden of comorbidities. In addition, atrial myopathy patients had larger left atria and higher left ventricular filling pressures, as estimated by the ratio of the mitral inflow velocity to the mitral annular velocity (E/e').

Incident stroke during follow up occurred in 25 (3.3%) patients with atrial myopathy and 31 (2.1%) patients without atrial myopathy (HR=1.94, 95% CI 1.14 – 3.31, p=0.01, Figure 1). By univariate analysis, other variables associated with incident stroke included diabetes (p=0.003), dyslipidemia (p=0.04) and aspirin use (p=0.001); Table 2). By multivariate analysis, the only independent predictors of incident stroke were atrial myopathy (HR=1.74, 95% CI 1.01 – 2.98, p=0.04) and diabetes (HR=2.02, 95% CI 1.19 – 3.44, p=0.01; Table 2). There was no interaction of atrial myopathy with age or diabetes.

Furthermore, since the definition of atrial myopathy is still not well defined[4–6], we performed a sensitivity analysis by defining atrial myopathy using echocardiographic parameters only (LA diameter >4.6cm and/or LA volume index >36ml/m2). Using this definition, atrial myopathy was still associated with incident stroke (HR=2.43, 95% CI 1.02 – 5.99, p=0.03, Figure 2). We further divided the LA diameter into tertiles and assessed the association of incident stroke by tertiles. Compared with those in the lowest tertile, those in the highest tertile had a nearly 5-fold increase in the risk of incident stroke (HR=4.82, 95% CI 1.04 – 22.35, p=0.04), whereas there was a numerical, albeit non-significant increase in the risk of stroke in those in the middle tertile (HR=2.39, 95% CI 0.51–11.23, p=0.27).

Discussion

The current secondary analysis of the TOPCAT trial assessed the hypothesis that atrial myopathy would increase the risk of incident stroke in patients with HFpEF independent of the presence of AF. Our results, which support this hypothesis, are consistent with recent evidence linking impaired left atrial function in HFpEF with adverse outcomes[11]. Importantly, our results highlight the notion that structural and cellular changes in the left atrium may be the final common pathway of multiple comorbidities, including AF, predisposing to thrombogenesis, and eventually leading to thromboembolic stroke[6]. This notion is being prospectively tested in the ARCADIA trial (Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke), in which patients with ESUS and either left atrial enlargement, abnormally high P-wave terminal force in ECG lead V1, or elevated N-terminal pro B-type natriuretic peptide are randomly assigned to either apixaban or aspirin for secondary stroke prevention[12]. It should be noted that a universal definition of atrial myopathy is lacking at present[6,10]. In our analysis, we used acceptable markers for atrial myopathy, including LA dilation and elevated natriuretic peptides, based on evidence from previous studies showing that these values are associated with elevated thromboembolic risk[6,10].

The “atrial myopathy” concept reframes our understanding of the relationship between AF and thromboembolism. Atrial myopathy refers to adverse atrial structural, electrical, and functional abnormalities that can present irrespective of AF, but may lead to AF[4–6]. Importantly, although AF may lead to the initiation and/or progression of atrial myopathy, the presence of AF is not essential to the development and/or maintenance of the atrial myopathic state[6]. Atrial myopathy is caused by comorbid conditions, including aging, obesity, inflammation, oxidative stress, and stretching of the atria, which are prevalent in patients with HFpEF[3]. At the cellular level, atrial myopathy is associated with alterations in calcium cycling, ion channels, and gap junctions, as well as structural changes, manifesting as fibrosis[6]. These changes, coupled with endothelial dysfunction and stasis, induce a prothrombotic state, leading to thrombogenesis, independent of AF[6]. Clinical studies corroborate these experimental findings. The ASSERT trial, that enrolled 2,580 patients with cardiac implantable electronic devices demonstrated a lack of temporal association between AF episodes and ischemic stroke, with only 8% of patients having AF episodes within 30 days of stroke events[13]. In addition, rhythm control trials such as RACE (Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation Study) and AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) failed to

demonstrate improvement in stroke prevention by maintaining sinus rhythm, suggesting that local stasis during AF is not the primary cause of stroke[14,15]. Our results support this concept and highlight the role of atrial myopathy and diabetes in the development of stroke in patients with HFpEF. Taking this concept a step forward, it has been proposed that cardiac inflammation, fibrosis and microvascular dysfunction represent the final common pathway leading to both HFpEF and thromboembolism through atrial and ventricular myopathy, while AF is a marker of atrial myopathy, rather than the cause of thromboembolism[3]. Further studies are required to elucidate the complex association between HFpEF, atrial myopathy and thromboembolism.

A major hurdle in our understanding of the association of atrial myopathy with thromboembolism is that a clear definition of atrial myopathy is not currently available. Methods to identify atrial myopathy include atrial electrograms showing fractionation, indicative of fibrosis, tissue biopsy showing fibrosis, cardiac imaging, including echocardiography and cardiac magnetic resonance imaging, and serum biomarkers[5]. Development of molecular imaging probes for detection of atrial myopathy might enable early diagnosis, ultimately leading to improved treatment outcomes[16]. Meanwhile, the most commonly diagnostic criteria of atrial myopathy include LA size, N-terminal pro–B-type natriuretic peptide levels (NT-proBNP), and P-wave terminal force in V1[6,10]. These parameters are being used to define atrial myopathy in the ongoing ARCADIA trial[12]. In our study, we used LA enlargement and elevated natriuretic peptides to define atrial myopathy. Notably, a systematic review including 67,875 patients underlined the predisposing role of LA enlargement for stroke development in patients with sinus rhythm[17]. Moreover, a post hoc analysis of the NAVIGATE ESUS, which failed to show a superiority of rivaroxaban compared to aspirin in secondary stroke prevention in the overall study population with ESUS, demonstrated that patients with enlarged left atrium (estimated as left atrial diameter >4.6 cm, ≈10% of trial patients) had a significant reduction of recurrent strokes with rivaroxaban than aspirin[18]. A recent prospective cohort study emphasized the association between high NT-proBNP levels and increased risk of cardioembolic stroke in the general population[19]. Another post-hoc analysis of the WARSS trial suggested a significant decrease in secondary stroke risk in patients with elevated NT-proBNP (>750 pg/ml), who were treated with warfarin rather than aspirin[20]. Our results are in line with the findings of these two secondary analyses; however, this evidence should be regarded as hypothesis-generating and will require confirmation in a prospective trial. It also remains unclear whether initiation of oral anticoagulation therapy in patients with markers of atrial myopathy or with cryptogenic stroke or ESUS will decrease recurrent stroke events.

There are several limitations of this analysis. This is a post-hoc exploratory analysis that stratified patients according to the presence or absence of atrial myopathy and should thus be regarded as hypothesis-generating only. Our findings may not be generalizable to the general population since we included a specific population with HFpEF. Echocardiographic data were available in a fraction of the total population, therefore, we elected to include elevated natriuretic peptide values in the definition of atrial myopathy, acknowledging that some patients may have such elevation due to heart failure rather than atrial myopathy. However, in our sensitivity analysis including patients with atrial myopathy according to echocardiographic left atrial dilation, corroborated our initial findings. These issues

highlight the need for a more accurate biomarker indicative of atrial myopathy, which is lacking at present. AF may be underdiagnosed due to its intermittent nature; therefore, the risk for misclassification bias cannot be excluded. Finally, due to a probable incomplete ischemic stroke workup during the TOPCAT trial, it is possible that some patients with new-onset stroke in this study did not have ESUS, but a different etiology for stroke.

Atrial myopathy in patients with HFpEF patients without AF is associated with a high risk of stroke. Further studies are warranted to confirm these findings and evaluate whether early identification of atrial myopathy based on novel biomarkers may identify a subpopulation at higher risk of stroke who might benefit from oral anticoagulation therapy.

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Declaration of interests

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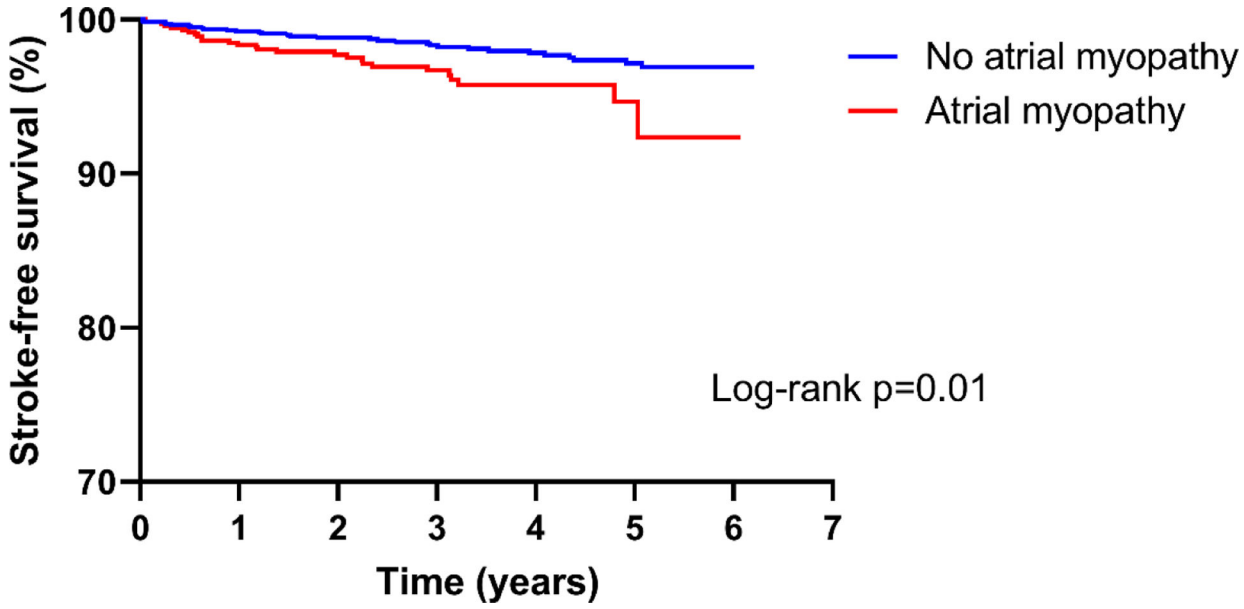

Figure 1.
Cumulative event rates of recurrent ischemic stroke for those with and without atrial myopathy over the study period.

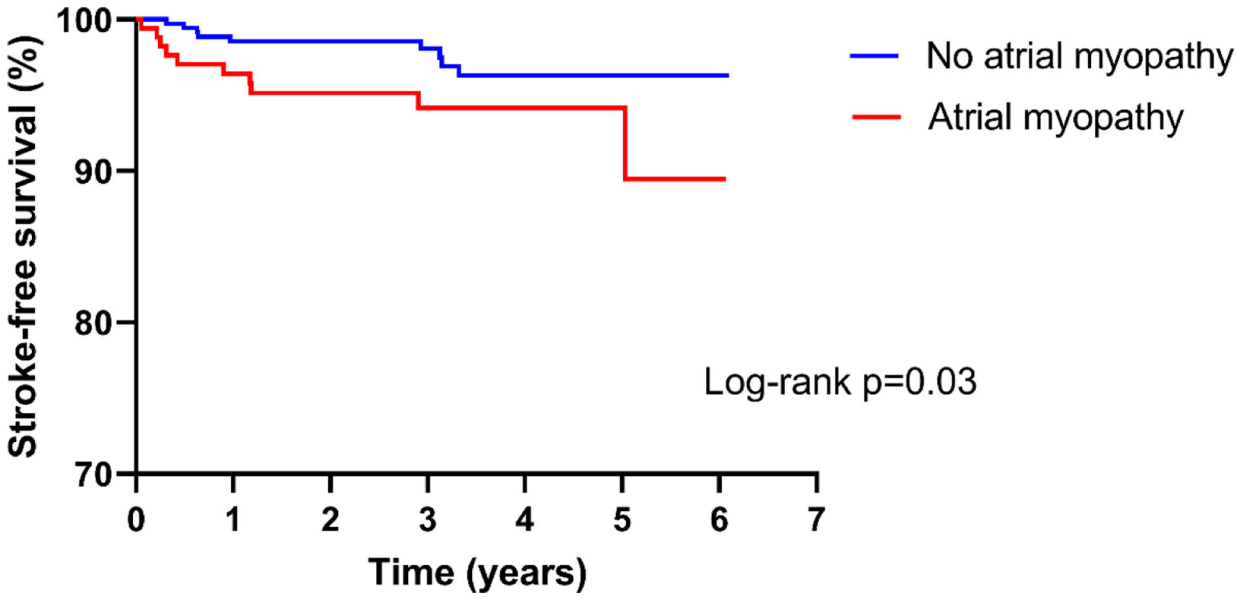

Figure 2.

Cumulative event rates of recurrent ischemic stroke for those with and without atrial myopathy, defined as left atrial enlargement by echocardiography, over the study period.

Table 1.

Baseline characteristics according to the presence or absence of atrial myopathy.

Characteristic		Atrial myopathy (n=756)	No atrial myopathy (n=1469)	P value
Age, years		69.5 ± 10.0	65.8 ± 8.9	**<0.001**
Female (%)		387 (51.2%)	832 (56.6%)	**0.01**
Race	White	607 (80.3%)	1340 (91.2%)	**< 0.001**
	Non-white	149 (19.7%)	129 (8.8%)	
Body mass index (kg/m2)		32.3 ± 7.7	31.9 ± 6.9	0.29
Waist circumference (cm)		105.8 ± 17.0	103.4 ± 16.7	**0.002**
Chronic obstructive pulmonary disease		107 (14.1%)	126 (8.6%)	**< 0.001**
Hypertension		684 (90.5%)	1361 (92.7%)	0.08
Diabetes		323 (42.7%)	435 (29.6%)	**< 0.001**
Dyslipidemia		534 (70.6 %)	776 (52.8%)	**< 0.001**
Peripheral arterial disease		99 (13.1%)	120 (8.2%)	**< 0.001**
Thyroid disease		103 (13.6%)	172 (11.7%)	0.18
Current smoker		81 (10.7%)	200 (13.6%)	**0.05**
Pacemaker		60 (7.9%)	33 (2.2%)	**< 0.001**
History of stroke		67 (8.9%)	82 (5.6%)	**0.003**
Aspirin use		238 (31.5%)	275 (18.7%)	**< 0.001**
Warfarin use		36 (4.8%)	19 (1.3%)	**< 0.001**
Left ventricular ejection fraction		59.4 ± 8.3	60.1 ± 7.4	0.27
Left atrial diameter		4.4 ± 0.6	3.8 ± 0.4	**< 0.001**
Left atrial volume index		29.1 ± 10.3	22.4 ± 6.4	**< 0.001**
E/e’		14.7 ± 5.6	12.6 ± 5.1	**0.002**

E/e’ = ratio of the early mitral inflow Doppler velocity to the early diastolic mitral annulus velocity

Table 2.

Univariate analysis and multivariate regression analysis of the influence of baseline characteristics on the stroke event rates.

Univariate Analysis			
Parameter	**Hazard ratio**	**95% Confidence interval**	**P-value**
Age	1.01	0.98 – 1.04	0.43
Gender	0.94	0.56 – 1.59	0.82
Race	1.24	0.66 – 2.30	0.50
Body mass index	1.01	0.97 – 1.05	0.68
Waist circumference	1.01	0.99 – 1.03	0.21
Chronic obstructive pulmonary disease	1.60	0.76 – 3.38	0.25
Hypertension	2.37	0.58 – 9.73	0.23
Diabetes	2.19	1.30 – 3.71	**0.003**
Dyslipidemia	1.85	1.04 – 3.31	**0.04**
Peripheral arterial disease	1.43	0.65 – 3.15	0.38
Current smoker	1.33	0.65 – 2.71	0.44
History of Stroke	2.19	1.00 – 4.84	**0.05**
Aspirin use	1.25	1.13 – 1.38	**0.001**
Warfarin use	1.22	0.94 – 1.60	0.14
Atrial myopathy	1.94	1.14 – 3.31	**0.01**
Multivariate Analysis			
Parameter	**Hazard ratio**	**95% Confidence Interval**	**P-value**
Diabetes	2.02	1.19 – 3.44	**0.01**
Atrial myopathy	1.74	1.01 – 2.98	**0.04**