

Original Article



Epicardial Fat Thickness and Free Fatty Acid Level are Predictors of Acute Ischemic Stroke with Atrial Fibrillation

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Conflict of Interest

The authors have no financial conflicts of
interest.

ABSTRACT

BACKGROUND: Increased epicardial fat is known to be associated with the presence and chronicity of atrial fibrillation (AF). Free fatty acids (FFAs) are major components of epicardial fat; however, their potential association with AF in ischemic stroke has not been investigated. We aimed to assess the performance of echocardiographic epicardial fat thickness (EFT) and plasma FFA level in identifying patients with ischemic stroke and AF.

METHODS: We enrolled a total of 214 consecutive patients (mean age, 66.8 ± 12.3 years; 39.7% women) diagnosed with acute ischemic stroke between March 2011 and June 2014. The patients were divided into two groups: ischemic stroke with AF ($n = 35$, 16.4%) and ischemic stroke without AF ($n = 179$, 83.6%).

RESULTS: The ischemic stroke with AF group showed significantly higher serum FFA level (1379.7 ± 717.5 vs. 757.8 ± 520.5 uEq/L, $p < 0.0001$) and EFT (6.5 ± 1.2 vs. 5.3 ± 1.2 mm, $p < 0.001$) than the group without AF. Multivariable logistic regression analysis demonstrated that age (odds ratio [OR], 1.112), serum FFA level (OR, 1.002), and EFT (OR, 1.740) were independently associated with the ischemic stroke group with AF. EFT and FFA significantly improved the goodness-of-fit and discriminability of the simple regression model including age as a covariate (log likelihood difference, 21.35; $p < 0.001$; c-index difference, 17.9%; $p < 0.001$).

CONCLUSIONS: High EFT and serum FFA level were associated with ischemic stroke in patients with AF. Echocardiographic EFT and serum FFA level can play a significant role in identifying ischemic stroke with AF.

Keywords: Stroke; Epicardial fat thickness; Free fatty acids; Atrial fibrillation

INTRODUCTION

Accurate classification of stroke etiology is crucial for optimizing stroke management.¹⁾ Cardio-embolic stroke is the most frequently predicted cause of cryptogenic stroke; the most frequent cause of cerebral cardio-embolism is atrial fibrillation (AF), including paroxysmal AF.²⁾ AF is the most common etiology of ischemic stroke; the incidence of stroke in individuals with non-valvular AF is estimated to be 5 times higher than in individuals without AF.³⁾ The prevalence of AF in the whole stroke population has been reported to range

from 17%–25.6%.⁴⁾⁵⁾ The risk for stroke and thromboembolism in patients with AF has been shown to escalate proportionally with combined vascular risk factors.⁶⁾⁷⁾ However, by routine arrhythmia screening methods, it is difficult to detect the short and usually asymptomatic presentations of paroxysmal AF (also called occult AF).

There is evidence that abnormal levels of plasma free fatty acids (FFAs) are associated with an increased risk of myocardial disease, including AF and heart failure.⁸⁾⁹⁾ Adipose tissue covers a significant portion of the epicardial surface,¹⁰⁾ and myocyte-adipocyte cross linking is known to be important in the physiological function of the normal myocardium.¹¹⁾ Myocardial injury and ischemia are followed by changes in the levels of adipocyte-derived biomarkers (FFAs and adipokines) and adipose deposition.¹²⁾¹³⁾ Fat can accumulate around the heart in epicardial adipose tissue or inside the heart as lipid droplets.¹⁴⁾ The mechanism by which fatty infiltration promotes arrhythmogenicity is not well characterized.¹⁵⁾ Recent studies have shown that increased epicardial adiposity can directly modulate the electrophysiological properties of the heart and ion currents, causing higher arrhythmogenesis in left atrial myocytes, which contributes to an increased risk of AF.¹⁶⁾¹⁷⁾

Epicardial fat is a metabolically active tissue; echocardiography is a useful technique for measuring epicardial fat thickness (EFT).¹⁸⁾ Previous studies have demonstrated associations between EFT and coronary artery disease, carotid atherosclerosis, metabolic syndrome, and obesity.¹⁹⁻²²⁾ In addition, increased EFT has been shown to be associated with the presence and chronicity of AF.²³⁾

However, the potential association between EFT and FFA plasma level in ischemic stroke with or without AF has not been previously investigated. The objective of this study was to assess the performance of EFT and plasma FFA level in identifying patients with ischemic stroke and AF.

METHODS

We retrospectively included patients with acute ischemic stroke who were admitted within 3 days of symptom onset to a single university hospital between March 2011 and June 2014. We defined acute ischemic stroke as new focal or global neurological deficits with evidence of acute cerebral infarction on magnetic resonance imaging (MRI). Patients with chronic congestive heart failure, surgery within 60 days, infection, malignancy, rheumatologic disorder, immunological disorder, chronic renal insufficiency, acute coronary syndrome within 30 days before admission, mitral valve disease, and patent foramen ovale were excluded. In addition to the epidemiologic variables age and sex, classic cardiovascular risk factors were also considered. Old age was defined as > 65 years; hypertension was defined as systolic blood pressure (BP) > 140 mmHg and diastolic BP > 90 mmHg by repeated BP measurement or previous diagnosis; and diabetes mellitus (DM) was defined as a fasting plasma glucose level \geq 126 mg/dL in 2 consecutive assessments or current treatment for DM. The presence of dyslipidemia was assumed if subjects were taking lipid-lowering drugs or had a high total cholesterol level (> 200 mg/dL). This study complies with the Declaration of Helsinki and was approved by the Institutional Review Board of our institution.

Laboratory measurements

Venous blood was drawn the morning after an overnight fast on the first hospitalized day. The following parameters were obtained by standard techniques on the examination day: total

cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), triglycerides, high sensitivity C-reactive protein (hs-CRP), and fibrinogen. Plasma FFA was measured by the enzymatic colorimetric method. Specifically, the NEFA-HR (2) reagent kit (Wako Pure Chemical Industries, Osaka, Japan) was used to quantitatively determine FFA level (Hitachi 7600 Automatic Analyzer, Hitachi-High-Technologies Corporation, Nishi-Shimbashi 1-chome, Minato-ku, Tokyo, Japan). Height and weight were measured and used to calculate body mass index (BMI, kg/m²).

Identification of AF

Electrocardiographs (ECGs) of all selected patients were reviewed. Patients with a sinus rhythm were placed on 24-48 hour Holter monitoring to monitor for paroxysmal AF. Subjects with 12-lead ECGs demonstrating AF or arrhythmia > 30 seconds in duration on Holter monitoring or telemetry recordings were considered to have AF.

Neurologic assessment

All patients with stroke underwent computerized tomography (CT) scans of the brain followed by MRI. CT angiography or magnetic resonance angiography of the brain and neck was also performed for all patients with stroke. Ischemic stroke was classified as large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology, or stroke of undetermined etiology, according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.²⁴⁾ Stroke severity on admission was assessed by a stroke neurologist using the Korean version of the National Institutes of Health Stroke Scale (NIHSS).²⁵⁾ Functional outcomes were measured at 3 months after stroke onset using the modified Rankin Scale (mRS).²⁶⁾

Echocardiographic measurement

Standard two-dimensional and strain echocardiography scans were performed on all patients using a 3.5-MHz transducer (Philips iE33, Philips Medical Systems, Bothell, WA, USA). The scans were acquired with the patient in the left lateral decubitus position. All echocardiography examiners were blinded to patient information. Measurements of the thickness of the interventricular septum and posterior wall, the diameter of the left atrium (LA), left ventricular (LV) cavity, and the LV mass index (LVMI) were performed according to the American Society of Echocardiography criteria.²⁷⁾ Pulsed wave Doppler of the transmitral LV inflow was performed in an apical 4-chamber view with the sample volume placed at the level of the mitral valve tips. The following measurements of global LV diastolic function were determined: peak early (E) and late (A) diastolic mitral flow velocity, ratio of E and A, E/A; early (Ea) diastolic mitral annular velocity; deceleration time of the E wave; and LV isovolumetric relaxation time (IVRT).

EFT was measured perpendicular from the free wall of the right ventricle at end-systole in three cardiac cycles according to a method we previously described.²⁸⁾ Epicardial fat was defined as the echo-free space between the outer wall of the myocardium and the visceral layer of the pericardium. The maximum EFT was measured from the point on the free wall of the right ventricle along the midline of the ultrasound beam perpendicular to the aortic annulus as the anatomic landmark. Since a critical issue in EFT measurement is inconsistency of the measurement location, the mean EFT was averaged from the parasternal long axis and parasternal short axis view images. Offline measurement of EFT was performed by two cardiologists who were blinded to the clinical data. Measurement of EFT was performed at least twice to ensure high reliability. The intra-observer and inter-observer variability values of EFT were 3.2% and 5.6%, respectively.

Statistical analysis

Statistical analyses were performed using SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA) and R (<http://www.r-project.org>). Observed values of continuous and discrete variables were summarized as mean \pm standard deviation or as frequency with percentage (%), respectively. The normality assumption was validated using the Kolmogorov–Smirnov test. For continuous variables, mean differences between patient groups (without and with AF) were compared using Student's t-test; differences between categorical variables were compared using the Chi-square test. Multivariable logistic regression models were employed to identify variables independently associated with ischemic stroke with AF. To avoid potential multi-collinearity issues, we performed variable selection in a stepwise fashion. The Hosmer-Lemeshow test and C-index were utilized to evaluate the calibration and discriminability of logistic regression models, respectively.²⁹⁾ Utilizing likelihood ratio tests and Delong's tests,³⁰⁾ we compared the goodness-of-fit and discriminability of four different logistic regression models: Model 1, which includes age; Model 2, which extends Model 1 with EFT; Model 3, which extends Model 1 with FFA; and Model 4, which extends Model 1 with EFT and FFA. *p*-values less than 0.05 were considered statistically significant.

RESULTS

Comparison of clinical and echocardiographic characteristics in the ischemic stroke groups with or without AF

The baseline characteristics between patients with stroke with or without AF are shown in **Table 1**. Patients with ischemic stroke with AF (*n* = 35) were older, more likely to be female, and had higher prevalence of coronary artery disease and heart failure. In the patients with AF, the mean AF duration was 13.5 months, and the subtypes included paroxysmal

Table 1. Baseline clinical characteristics between stroke patients with AF and without AF

	Ischemic stroke without AF (<i>n</i> = 179)	Ischemic stroke with AF (<i>n</i> = 35)	<i>p</i> -value
Age, years	65.4 \pm 12.1	75.0 \pm 10.6	< 0.001
Age \geq 65 years, <i>n</i> (%)	92 (51.4)	28 (80)	< 0.001
Male gender, <i>n</i> (%)	114 (63.7)	15 (42.9)	0.018
Body mass index, kg/m ²	24.2 \pm 3.2	24.3 \pm 3.3	0.859
Systolic BP, mmHg	160.6 \pm 28.4	155.9 \pm 25.0	0.322
Diastolic BP, mmHg	88.2 \pm 16.5	90.1 \pm 16.1	0.534
Heart rate, bpm	78.8 \pm 15.0	89.0 \pm 25.3	0.027
Body temperature, °C	36.5 \pm 0.4	36.4 \pm 0.5	0.265
Alcohol, <i>n</i> (%)	72 (40.4)	10 (28.6)	0.128
Current smoking, <i>n</i> (%)	83 (46.4)	13 (37.1)	0.199
Hypertension, <i>n</i> (%)	137 (76.5)	30 (85.7)	0.165
Diabetes, <i>n</i> (%)	75 (41.9)	9 (25.7)	0.052
Dyslipidemia, <i>n</i> (%)	56 (31.3)	8 (22.9)	0.216
Coronary artery disease, <i>n</i> (%)	12 (6.7)	7 (20.0)	0.020
Heart failure, <i>n</i> (%)	4 (2.2)	5 (14.3)	0.007
Previous stroke, <i>n</i> (%)	28 (15.6)	4 (11.4)	0.366
Previous medication, <i>n</i> (%)			
Antiplatelets	34 (19.0)	8 (22.9)	0.374
Anticoagulant	3 (1.7)	3 (8.6)	0.057
Statin	14 (7.8)	7 (20.0)	0.036
Atrial fibrillation			
Mean duration (month)		13.46	
Paroxysmal, <i>n</i> (%)		12 (34.3)	
Persistent or chronic, <i>n</i> (%)		23 (65.7)	

All values are presented as mean \pm SD.

AF: atrial fibrillation, BP: blood pressure.

Table 2. Baseline laboratory characteristics between stroke patients with AF and without AF

	Ischemic stroke without AF (n = 179)	Ischemic stroke with AF (n = 35)	p-value
White blood cells, 10 ³ /μL	8.2 ± 3.2	9.1 ± 3.1	0.112
Neutrophil, %	63.4 ± 13.8	69.9 ± 12.0	0.006
Monocyte, %	6.7 ± 2.5	6.1 ± 2.8	0.223
Lymphocyte, %	27.3 ± 12.1	22.1 ± 10.0	0.011
Eosinophil, %	1.6 ± 1.8	1.2 ± 1.5	0.117
Hemoglobin, g/dL	13.5 ± 1.8	13.9 ± 1.9	0.293
Hematocrit, %	40.5 ± 5.0	41.8 ± 5.5	0.212
Platelets, 10 ³ /μL	207.2 ± 55.5	222.2 ± 62.3	0.158
Uric acid, mg/L	5.3 ± 4.6	5.2 ± 2.3	0.863
eGFR MDRD	92.2 ± 28.6	80.4 ± 26.8	0.022
Creatinine, mg/dL	0.87 ± 0.35	0.91 ± 0.34	0.491
Fasting glucose, mg/dL	113.4 ± 51.8	127.3 ± 36.4	0.087
Total cholesterol, mg/dL	192.5 ± 48.2	178.7 ± 40.6	0.081
LDLcholesterol, mg/dL	112.9 ± 40.6	98.9 ± 36.7	0.317
HDL cholesterol, mg/dL	47.5 ± 13.3	53.0 ± 17.6	0.085
Triglycerides, mg/dL	148.5 ± 89.3	121.6 ± 66.8	0.045
ESR	17.9 ± 16.1	19.5 ± 13.9	0.559
Homocystein	12.7 ± 4.3	15.5 ± 13.1	0.049
Free fatty acid, uEq/L	757.8 ± 520.5	1379.7 ± 717.5	< 0.001
hs-CRP, mg/dL	2.48 ± 6.01	5.27 ± 7.60	0.050
Fibrinogen	335.6 ± 106.6	346.3 ± 74.0	0.504

All values are presented as mean ± SD.

AF: atrial fibrillation, eGFR: estimated glomerular filtration rate, ESR: erythrocyte sedimentation rate, HDL: high density lipoprotein, hs-CRP: high sensitivity C-reactive protein, LDL: low density lipoprotein, MDRD: modification of diet in renal disease.

AF (34.3%) and non-paroxysmal AF (persistent and chronic AF, 65.7%). Regarding the laboratory data, patients with ischemic stroke with AF showed significantly higher serum FFA level (1379.7 ± 717.5 vs. 757.8 ± 520.5 uEq/L, $p < 0.001$) (**Table 2**).

Comparison of echocardiographic parameters showed that the stroke with AF group had significantly greater EFT (6.5 ± 1.2 vs. 5.3 ± 1.2 mm, $p < 0.001$), LA diameter, and LA volume compared with the stroke without AF group (**Table 3**). In subgroup analysis, there were no significant differences in EFT (paroxysmal vs persistent or permanent: 6.36 ± 1.06 vs 6.50 ± 1.28 mm, $p = 0.769$) and FFA (paroxysmal vs persistent/permanent: 1060.2 ± 557.6 vs 1546.4 ± 745.3 uEq/L, $p = 0.056$).

Table 3. Comparison of echocardiographic parameters between stroke patients with AF and without AF

	Ischemic stroke without AF (n = 179)	Ischemic stroke with AF (n = 35)	p-value
EFT, short axis view, mm	5.4 ± 1.3	6.5 ± 1.4	< 0.001
EFT, long axis view, mm	5.2 ± 1.3	6.5 ± 1.1	< 0.001
EFT, mean, mm	5.3 ± 1.2	6.5 ± 1.2	< 0.001
LVEDD, mm	47.8 ± 6.4	45.7 ± 5.1	0.092
LVESD, mm	30.9 ± 6.1	29.3 ± 4.8	0.186
IVSTd, mm	12.4 ± 2.1	12.6 ± 2.2	0.614
PWTd, mm	10.8 ± 1.7	10.6 ± 1.8	0.716
LVMI, g/m ²	125.4 ± 42.3	115.8 ± 25.8	0.128
EF, %	64.7 ± 8.5	64.8 ± 9.5	0.962
LA diameter, mm	36.4 ± 5.8	42.4 ± 9.4	0.003
LA volume, mL	19.6 ± 7.2	31.2 ± 13.1	0.002
Aorta diameter, mm	34.2 ± 3.7	34.6 ± 4.6	0.675
E velocity, cm/sec	0.67 ± 0.17	0.81 ± 0.21	0.003
E/Ea	10.9 ± 4.2	11.6 ± 5.3	0.531

All values are presented as the mean ± SD.

E: peak early diastolic mitral filling velocity, Ea: mitral annular velocity, EF: ejection fraction, EFT: epicardial fat thickness, IVSTd: diastolic interventricular septal wall thickness, LA: left atrial diameter, LVEDD: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter, LVMI: left ventricular mass index, PWTd: diastolic posterior wall thickness.

Table 4. Clinical characteristics between stroke patients with AF and without AF

	Ischemic stroke without AF (n = 179)	Ischemic stroke with AF (n = 35)	p-value
In hospital death, n (%)	12 (6.7)	8 (22.9)	0.007
NIHSS admission	3.4 ± 4.2	7.4 ± 5.4	< 0.001
mRS discharge	1.6 ± 1.5	2.8 ± 2.1	0.004

All values are presented as the mean ± SD.

AF: atrial fibrillation, mRS: modified Rankin Scale, NIHSS: National Institutes of Health Stroke Scale.

Comparison of neurologic clinical characteristics showed that the stroke with AF group had significantly higher hospital mortality (22.9% vs. 6.7%, $p = 0.007$), mRS discharge (2.8 ± 2.1 vs. 1.6 ± 1.5 , $p < 0.004$), and NIHSS admission (7.4 ± 5.4 vs. 3.4 ± 4.2 , $p < 0.001$) (**Table 4**) than the stroke without AF group.

Association of serum FFA and EFT with ischemic stroke with AF

According to simple logistic regression analysis, marginally significant baseline covariates of age, gender, heart rate, eGFR, LA size, presence of coronary artery disease, heart failure, FFA, and EFT were entered into a multivariable logistic regression model (**Table 5**). According to the final model, which was selected in stepwise fashion, both EFT (adjusted odds ratio [OR], 2.031; 95% confidence interval [CI], 1.454–2.938; $p < 0.001$) and FFA [adjusted OR, 1.002; 95% CI, 1.001–1.002; $p < 0.001$] were independent prognostic factors associated with ischemic stroke with AF after adjusting for age (**Table 5**). There was no evidence against the goodness-of-fit of the fitted model (Hosmer-Lemeshow test statistic = 5.16; df = 8; $p = 0.741$).

As shown in **Table 6**, the incremental effect of EFT and FFA on ischemic stroke with AF was investigated by comparing four different logistic regression models. Comparison of these models showed that EFT and FFA significantly improved the goodness-of-fit and

Table 5. Risk factors significantly associated with the ischemic stroke patients having AF according to logistic regression models

Risk factors	Simple		Multivariable	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Age	1.083 (1.040–1.133)	< 0.001	1.096 (1.029–1.168)	0.004
Male gender	2.623 (1.149–6.189)	0.023		
Heart rate	1.032 (1.010–1.057)	0.005		
Left atrial size	1.156 (1.075–1.243)	< 0.001	1.109 (1.029–1.168)	0.024
Coronary artery disease	3.479 (1.262–9.595)	0.016		
Heart failure	7.292 (1.852–28.714)	0.004		
eGFR	0.982 (0.966–0.996)	0.017		
Free fatty acid	1.002 (1.001–1.002)	< 0.001	1.002 (1.001–1.003)	< 0.001
Epicardial fat thickness	2.031 (1.454–2.938)	< 0.001	1.968 (1.190–3.254)	0.008

AF: atrial fibrillation, eGFR: estimated glomerular filtration rate.

Table 6. Incremental values of free fatty acid and epicardial fat thickness assessed by the goodness-of-fit and discriminability

	Likelihood ratio test			Discriminability		
	LogLik	Diff.	p-value*	c-index (%)	Diff.(%)	p-value†
Model 1	–68.51			73.21		
Model 2	–59.48			83.27		
Model 3	–50.80			88.49		
Model 4	–47.15			91.06		
Model 1 vs. Model 2		9.03	< 0.001		10.06	0.011
Model 1 vs. Model 3		17.70	< 0.001		15.27	0.001
Model 1 vs. Model 4		21.35	< 0.001		17.85	< 0.001

c-index: Harrell's concordance index, Diff: difference, LogLik: loglikelihood, Model 1: age, Model 2: Model 1 + EFT, Model 3: Model 1 + FFA, Model 4: Model 1 + EFT + FFA.

*p-value is based on the loglikelihood ratio test.

†p-value is based on the Delong's test.

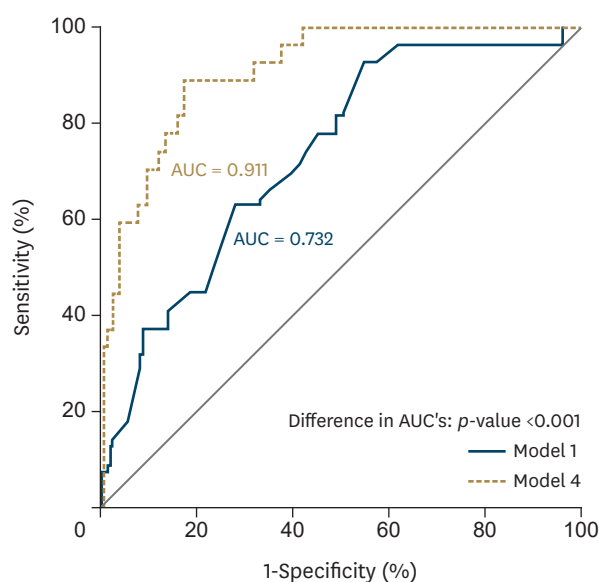


Figure 1. Comparison of four different logistic regression models of the incremental effect of EFT and FFA on ischemic stroke with AF. Comparison of these models showed that EFT and FFA significantly improved the goodness-of-fit and discriminability of Model 1 (log likelihood difference, 21.35; $p < 0.001$; c-index difference, 17.9%; $p < 0.001$).

AF: atrial fibrillation, AUC: area under curve, EFT: epicardial fat thickness, FFA: free fatty acid.

discriminability of Model 1 (log likelihood difference, 21.35; $p < 0.001$; c-index difference, 17.9%; $p < 0.001$) (Figure 1).

DISCUSSION

It is critically important to detect AF in patients with stroke to predict prognosis and determine the optimal treatment direction. We found that, among patients with ischemic stroke, those with AF had poorer prognosis, significantly higher serum FFA level, and a significantly higher mean EFT than those without AF. In addition, serum FFA level was significantly correlated with EFT and serum FFA level and EFT were independently associated with stroke with AF.

Some previous studies have concluded that EFT performs well in predicting the risk of AF.^{31,32} Also, there is evidence supporting that abnormal levels of plasma FFAs are associated with an increased risk of AF,⁸ and that FFAs can predict the prognosis of AF.^{33,34} Seo et al.³⁵ reported that FFA was highest in cardioembolic stroke compared with other stroke subtypes, and also that FFA was higher in patients with AF than in those without AF. We recently demonstrated that FFA is a promising biomarker for predicting outcome events in stroke with AF, in addition to the CHADS2 and CHA2DS2-VASc scoring systems.³⁶ The present study is the first to report that both EFT and FFA are independent prognostic factors of ischemic stroke with AF.

We suggest two possible mechanisms that can explain our results. First, since FFA is involved in the formation of visceral fat such as epicardial fat, increased FFA levels can cause thicker EFT, which can contribute to the occurrence of AF. An increase in FFA tracer storage per adipocyte is associated with AF.³⁷ In obesity, increased numbers of adipocytes in epicardial fat tissue can cause high arrhythmogenesis in LA myocytes. This arrhythmogenesis might play an important role in the pathophysiology of AF.¹⁶ Abed et al.¹⁷ demonstrated that obesity

progression changes LA size, conduction, histology, and expression of profibrotic mediators; moreover, these changes were associated with more persistent AF. Second, increased levels of FFAs might result in ion channel changes due to their properties, which could increase arrhythmogenesis in LA myocytes. A recent study demonstrated that the FFA stearic acid in sheep atrial myocytes disrupts their t-tubular architecture and remodels properties of membrane ionic currents, with potential implications for arrhythmogenesis.³⁸⁾

Similar to a previous study reporting that ischemic stroke due to cardioembolism had poorer prognosis than ischemic stroke, due to macro- or microangiopathy,⁵⁾ we also report a higher rate of in-hospital death and significantly higher mRS and NIHSS values in the ischemic stroke with AF group. Since a cardioembolism source can cause major stroke without atherosclerosis of the cerebral vessel, it is difficult to predict stroke occurrence. In cardioembolic stroke, structural diseases such as mitral valve disease or patent foramen ovale can be detected by echocardiography. However, patients with paroxysmal AF, which is not always detected by 24-hour Holter monitoring, could be missed. An ongoing prospective study is testing possible correlations between detection of AF by an implantable ECG recorder and gene mutations in patients with cryptogenic stroke/TIA; results will be available in 2018.³⁹⁾ Additive biomarkers or clinical variables that have the power to discriminate between ischemic stroke with or without AF would be helpful for outlining future directions, specifically how to best determine whether AF is present and/or whether to start anticoagulant therapy. The results from our study will be useful for identifying undetected AF in patients with ischemic stroke.

Our study has several limitations. First, the studied population with AF was relatively small (n = 35), limiting generalization of our results. Second, we assessed AF by documented ECG or Holter monitoring, meaning that patients with paroxysmal AF without documented ECG could have been missed. Third, with respect to baseline characteristics, the ischemic stroke with AF group showed higher prevalence of old age, heart failure, coronary artery disease, and statin use; these characteristics might have influenced the development of stroke or prognosis. Fourth, the retrospective design could have led to selection bias. Fifth, we did not analyze abdominal circumference; thus, an effect of central obesity cannot be ruled out. Finally, serum FFA levels were based on a single measurement. Future studies are needed to test whether serum FFA levels change over time and whether FFA levels on subsequent tests remain a predictor of the severity of stroke with AF.

CONCLUSION

To the best of our knowledge, this is the first work to demonstrate associations of EFT and serum FFA with ischemic stroke with AF. Echocardiographic EFT and serum FFA levels could facilitate the identification of patients with ischemic stroke with AF.

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