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

Kyoung-Im Cho, MD, PhD1,*, Bong-Joon Kim, MD1,*, Sang-Hoon Cho, MD, PhD2, Jin-Hyung Lee, MD2, Meyung-Kug Kim, MD2, and Bong-Goo Yoo, MD, PhD3

1Department of Cardiology, Kosin University College of Medicine, Busan, Korea
2Department of Statistics and Actuarial Science, Soongsil University, Seoul, Korea
3Department of Neurology, Kosin University College of Medicine, Busan, Korea

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. 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. 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. The prevalence of AF in the whole stroke population has been reported to range...
from 17%–25.6%, The risk for stroke and thromboembolism in patients with AF has been shown to escalate proportionally with combined vascular risk factors. 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. Adipose tissue covers a significant portion of the epicardial surface, and myocyte-adipocyte cross linking is known to be important in the physiological function of the normal myocardium. Myocardial injury and ischemia are followed by changes in the levels of adipocyte-derived biomarkers (FFAs and adipokines) and adipose deposition. Fat can accumulate around the heart in epicardial adipose tissue or inside the heart as lipid droplets. The mechanism by which fatty infiltration promotes arrhythmogenicity is not well characterized. 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.

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

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 ≥ 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. Stroke severity on admission was assessed by a stroke neurologist using the Korean version of the National Institutes of Health Stroke Scale (NIHSS). Functional outcomes were measured at 3 months after stroke onset using the modified Rankin Scale (mRS).

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. 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. 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 ± 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.\(^\text{29}\) Utilizing likelihood ratio tests and Delong’s tests,\(^\text{30}\) 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 (\(n = 179\)) | Ischemic stroke with AF (\(n = 35\)) | \(p\)-value |
|--------------------------------|----------------------------------------|-------------------------------------|-------------|
| Age, years                     | 65.4 ± 12.1                            | 75.0 ± 10.6                         | < 0.001     |
| Age ≥ 65 years, n (%)          | 92 (51.4)                              | 28 (80)                             | < 0.001     |
| Male gender, n (%)             | 114 (63.7)                             | 15 (42.9)                           | 0.018       |
| Body mass index, kg/m\(^2\)    | 24.2 ± 3.2                             | 24.3 ± 3.3                          | 0.859       |
| Systolic BP, mmHg              | 160.6 ± 28.4                           | 155.9 ± 25.0                        | 0.322       |
| Diastolic BP, mmHg             | 88.2 ± 16.5                            | 90.1 ± 16.1                         | 0.534       |
| Heart rate, bpm                | 78.8 ± 15.0                            | 89.0 ± 25.3                         | 0.027       |
| Body temperature, °C           | 36.5 ± 0.4                             | 36.4 ± 0.5                          | 0.265       |
| Alcohol, n (%)                 | 72 (40.4)                              | 10 (28.6)                           | 0.128       |
| Current smoking, n (%)         | 83 (46.4)                              | 13 (37.1)                           | 0.199       |
| Hypertension, n (%)            | 137 (76.5)                             | 30 (85.7)                           | 0.165       |
| Diabetes, n (%)                | 75 (41.9)                              | 9 (25.7)                            | 0.052       |
| Dyslipidemia, n (%)            | 56 (31.3)                              | 8 (22.9)                            | 0.216       |
| Coronary artery disease, n (%) | 12 (6.7)                               | 7 (20.0)                            | 0.020       |
| Heart failure, n (%)           | 4 (2.2)                                | 5 (14.3)                            | 0.007       |
| Previous stroke, n (%)         | 28 (15.6)                              | 4 (11.4)                            | 0.366       |
| Previous medication, n (%)     |                                       |                                     |             |
| 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            |                                       | 13.46                               |             |
| Mean duration (month)          |                                       |                                     |             |
| Paroxysmal, n (%)              | 12 (34.3)                              | 23 (65.7)                           |             |
| Persistent or chronic, n (%)   |                                       |                                     |             |

All values are presented as mean± SD.

AF: atrial fibrillation, BP: blood pressure.
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).

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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| 192.9 ± 48.2                      | 178.7 ± 40.6                    | 0.081   |
| LDL cholesterol, mg/dL| 112.9 ± 40.6                         | 98.9 ± 36.7                     | 0.377   |
| 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 ± 6.0                           | 5.27 ± 7.60                     | 0.050   |
| Fibronogen            | 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.

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 interventricularseptal 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.
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, 1.001–1.003; \( p < 0.001 \)) 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

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**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.

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

| Risk factors                     | Simple Odds ratio (95% CI) | \( p \)-value | Multivariable 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.

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**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 + FFA, Model 3: Model 1 + EFT, Model 4: Model 1 + FFA + EFT.

*\( p \)-value is based on the loglikelihood ratio test.
†\( p \)-value is based on the Delong’s test.
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,\(^3\) 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.\(^38\) Abed et al.\(^37\) 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.

REFERENCES

1. Kim BJ, Kim JS. Ischemic stroke subtype classification: an asian viewpoint. J Stroke 2014;16:8-47.
2. Sanak D, Hutrya M, Kral M, et al. Paroxysmal atrial fibrillation in young cryptogenic ischemic stroke: A 3-week ECG Holter monitoring study. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2015;159:283-7.
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3. Mozaffarian D, Benjamin EJ, Go AS, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation 2015;131:e29-322. 
PUBMED | CROSSREF

4. Tsang TS, Petty GW, Barnes ME, et al. The prevalence of atrial fibrillation in incident stroke cases and matched population controls in Rochester, Minnesota: changes over three decades. J Am Coll Cardiol 2003;42:99-100. 
PUBMED | CROSSREF

5. Grau AJ, Weimar C, Buggle F, et al. Risk factors, outcome, and treatment in subtypes of ischemic stroke: the German stroke data bank. Stroke 2001;32:2559-66. 
PUBMED | CROSSREF

6. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864-70. 
PUBMED | CROSSREF

7. European Heart Rhythm AssociationEuropean Association for Cardio-Thoracic SurgeryCamm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010;31:2369-429. 
PUBMED | CROSSREF

8. Khawaja O, Bartz TM, Is JH, et al. Plasma free fatty acids and risk of atrial fibrillation (from the Cardiovascular Health Study). Am J Cardiol 2012;110:212-6. 
PUBMED | CROSSREF

9. Djoussé L, Benkeser D, Arnold A, et al. Plasma free fatty acids and risk of heart failure: the Cardiovascular Health Study. Circ Heart Fail 2013;6:964-9. 
PUBMED | CROSSREF

10. Al Chekakie MO, Welles CC, Metoyer R, et al. Pericardial fat is independently associated with human atrial fibrillation. J Am Coll Cardiol 2010;56:784-8. 
PUBMED | CROSSREF

11. Ouchi N. Obesity: Progress in diagnosis and treatment; Topics, IV. Recent topics; 3. Obesity and new secretory factors; 2) Sfrp 5 acts as a novel adipocytokine that affects metabolic function. Nihon Naika Gakkai Zasshi 2011;100:1002-7. 
PUBMED | CROSSREF

12. Chhabra L, Spodick DH. Role of epicardial fat in atrial fibrillation after coronary artery bypass surgery. Am J Cardiol 2014;113:2090. 
PUBMED | CROSSREF

13. Hendrickson SC, St Louis JD, Lowe JE, Abdel-aleem S. Free fatty acid metabolism during myocardial ischemia and reperfusion. Mol Cell Biochem 1997;166:85-94. 
PUBMED | CROSSREF

14. Mazzali G, Fantin F, Zoico E, et al. Heart fat infiltration in subjects with and without coronary artery disease. J Clin Endocrinol Metab 2015;100:3364-71. 
PUBMED | CROSSREF

15. Pantanowitz L. Fat infiltration in the heart. Heart 2001;85:253. 
PUBMED | CROSSREF

16. Lin YK, Chen YC, Chen JH, Chen SA, Chen YJ. Adipocytes modulate the electrophysiology of atrial myocytes: implications in obesity-induced atrial fibrillation. Basic Res Cardiol 2012;107:293. 
PUBMED | CROSSREF

17. Abed HS, Samuel CS, Lau DH, et al. Obesity results in progressive atrial structural and electrical remodeling: implications for atrial fibrillation. Heart Rhythm 2013;10:90-100. 
PUBMED | CROSSREF

18. Hirata Y, Yamada H, Kusunose K, et al. Clinical utility of measuring epicardial adipose tissue thickness with echocardiography using a high-frequency linear probe in patients with coronary artery disease. J Am Soc Echocardiogr 2015;28:1240-1246.e1. 
PUBMED | CROSSREF

19. Tok D, Çagli K, Kadife I, et al. Impaired coronary flow reserve is associated with increased echocardiographic epicardial fat thickness in metabolic syndrome patients. Coron Artery Dis 2013;24:191-5. 
PUBMED | CROSSREF

20. Kim BJ, Kim BS, Kang JH. Echocardiographic epicardial fat thickness is associated with arterial stiffness. Int J Cardiol 2013;167:2234-8. 
PUBMED | CROSSREF
21. Kim BI, Kim BS, Kang JH. Echocardiographic epicardial fat thickness is associated with coronary artery calcification - results from the CAESAR study. *Circ J* 2015;79:818-24. [PUBMED](https://doi.org/10.1253/circj.CJ-14-1822) [CROSSREF](https://e-jcvi.org/)

22. Sengul C, Cevik C, Ozveren O, et al. Echocardiographic epicardial fat thickness is associated with carotid intima-media thickness in patients with metabolic syndrome. *Echocardiography* 2011;28:853-8. [PUBMED](https://doi.org/10.1111/j.1540-8175.2010.01061.x) [CROSSREF](https://e-jcvi.org/)

23. Stojanovska J, Kazerooni EA, Sinno M, et al. Increased epicardial fat is independently associated with the presence and chronicity of atrial fibrillation and radiofrequency ablation outcome. *Eur Radiol* 2015;25:2298-309. [PUBMED](https://doi.org/10.1007/s00330-014-3298-8) [CROSSREF](https://e-jcvi.org/)

24. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. *Trial of Org 10172 in Acute Stroke Treatment. Stroke* 1993;24:35-41. [PUBMED](https://doi.org/10.1161/01.STR.24.1.35) [CROSSREF](https://e-jcvi.org/)

25. Oh MS, Yu KH, Lee JH, et al. Validity and reliability of a Korean version of the national institutes of health stroke scale. *J Clin Neurol* 2012;8:177-83. [PUBMED](https://doi.org/10.3988/jcn.2012.8.3.177) [CROSSREF](https://e-jcvi.org/)

26. Bonita R, Beaglehole R. Recovery of motor function after stroke. *Stroke* 1988;19:1497-500. [PUBMED](https://doi.org/10.1161/01.STR.19.6.1497) [CROSSREF](https://e-jcvi.org/)

27. Levy D, Savage DD, Garrison RJ, Anderson KM, Kannel WB, Castelli WP. Echocardiographic criteria for left ventricular hypertrophy: the Framingham Heart Study. *Am J Cardiol* 1987;59:956-60. [PUBMED](https://doi.org/10.1016/0002-9149(87)90277-0) [CROSSREF](https://e-jcvi.org/)

28. Shim IK, Cho KI, Kim HS, Heo JH, Cha TJ. Impact of Gender on the Association of Epicardial Fat Thickness, Obesity, and Circadian Blood Pressure Pattern in Hypertensive Patients. *J Diabetes Res* 2015;2015:924539. [PUBMED](https://doi.org/10.1155/2015/924539) [CROSSREF](https://e-jcvi.org/)

29. Harrell FE Jr, Califf RM, Pryor DB, Lee KL, Rosati RA. Evaluating the yield of medical tests. *JAMA* 1982;247:2543-6. [PUBMED](https://doi.org/10.1001/jama.1982.03350150063013) [CROSSREF](https://e-jcvi.org/)

30. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;44:837-45. [PUBMED](https://doi.org/10.2307/2531595) [CROSSREF](https://e-jcvi.org/)

31. Acet H, Ertaş F, Akıl MA, et al. New inflammatory predictors for non-valvular atrial fibrillation: echocardiographic epicardial fat thickness and neutrophil to lymphocyte ratio. *Int J Cardiovasc Imaging* 2014;30:81-9. [PUBMED](https://doi.org/10.1007/s10554-013-9997-8) [CROSSREF](https://e-jcvi.org/)

32. Soeki T, Sata M. Role of epicardial adipose tissue in atrial fibrillation. *Circ J* 2012;76:2738-9. [PUBMED](https://doi.org/10.1253/circj.CJ-11-1278) [CROSSREF](https://e-jcvi.org/)

33. Spence JD. Free fatty acids and stroke from atrial fibrillation. *Can J Neurol Sci* 2011;38:803. [PUBMED](https://doi.org/10.1017/S0317167111000731) [CROSSREF](https://e-jcvi.org/)

34. Jickling GC, Spence JD. Free fatty acids to predict recurrent ischemic stroke. *Neurology* 2014;82:1104-1. [PUBMED](https://doi.org/10.1212/WNL.0000000000000428) [CROSSREF](https://e-jcvi.org/)

35. Seo WK, Kim J, Kim YH, et al. Elevated free fatty acid is associated with cardioembolic stroke subtype. *Can J Neurol Sci* 2011;38:874-9. [PUBMED](https://doi.org/10.1017/S0317167111001423) [CROSSREF](https://e-jcvi.org/)

36. Choi JY, Jung JM, Kwon DY, et al. Free fatty acid as an outcome predictor of atrial fibrillation-associated stroke. *Ann Neurol* 2016;79:317-25. [PUBMED](https://doi.org/10.1002/ana.24860) [CROSSREF](https://e-jcvi.org/)

37. Koutsari C, Dumesic DA, Patterson BW, Votruba SB, Jensen MD. Plasma free fatty acid storage in subcutaneous and visceral adipose tissue in postabsorptive women. *Diabetes* 2008;57:1186-94. [PUBMED](https://doi.org/10.2337/diabetes.57.6.1186) [CROSSREF](https://e-jcvi.org/)

38. O’Connell RP, Musa H, Gomez MS, et al. Free fatty acid effects on the atrial myocardium: membrane ionic currents are remodeled by the disruption of T-tubular architecture. *PLoS One* 2015;10:e0133052. [PUBMED](https://doi.org/10.1371/journal.pone.0133052) [CROSSREF](https://e-jcvi.org/)

39. Petrovičová A, Kurča E, Broznan M, et al. Detection of occult paroxysmal atrial fibrillation by implantable long-term electrocardiographic monitoring in cryptogenic stroke and transient ischemic attack population: a study protocol for prospective matched cohort study. *BMC Cardiovasc Disord* 2015;15:160. [PUBMED](https://doi.org/10.1186/s12954-015-0047-8) [CROSSREF](https://e-jcvi.org/)