ORIGINAL ARTICLE

Elevated Free Fatty Acid is Associated with Cardioembolic Stroke Subtype

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ABSTRACT: ***Background and Objectives:*** Free fatty acids (FFAs), an important energy substrate, have an association with cardiovascular diseases, such as atherosclerosis, myocardial dysfunction and abnormal cardiac rhythm. However, limited reports are available on the association between FFAs and ischemic stroke. We hypothesized that plasma FFA concentration could be associated with an ischemic stroke, emphasizing the relationship between FFA and subtypes of ischemic stroke. ***Methods:*** A cross-sectional study examined the association between FFA concentration and subtypes of stroke and cerebral atherosclerosis from a hospital-based acute stroke registry. ***Results:*** Data of 715 stroke patients were analyzed. The concentration of FFA was highest in the cardioembolic stroke subtype compared with the other stroke subtypes. Logistic regression analysis revealed that an increase in FFA concentration was significantly associated with the cardioembolic subtype after the adjustment of covariates. FFA concentration was also higher in patients with atrial fibrillation (AF) than those without AF. According to the presence of atherosclerotic stenosis, no significantly difference of FFA concentration was found for intracranial and extracranial cerebral arterial atherosclerosis. ***Conclusion:*** Here we report a significant association between fasting FFA concentration and the cardioembolic stroke subtype. AF is suggested as the mediating factor between FFA and the cardioembolic stroke subtype.

RÉSUMÉ: Un taux élevé d'acides gras libres est associé au sous-type d'accident vasculaire cérébral cardioembolique. ***Contexte et objectifs :*** Les acides gras libres (AGL), un substrat énergétique important, sont associés aux maladies cardiovasculaires telles l'athérosclérose, la dysfonction myocardique et l'arythmie. Cependant, il existe peu de littérature portant sur l'association entre les AGL et l'accident vasculaire cérébral ischémique (AVCI). Nous avons émis l'hypothèse que la concentration plasmatique en AGL pourrait être associée à l'AVCI et nous mettons l'accent sur la relation entre les AGL et un sous-type d'AVCI. ***Méthode :*** Nous avons étudié l'association entre la concentration en AGL et le sous-type d'AVCI et l'athérosclérose cérébrale au moyen d'une étude transversale d'un registre hospitalier d'AVC aigu. ***Résultats :*** Nous avons analysé les données de 715 patients atteints d'un AVC. La concentration en AGL était plus élevée chez les patients atteints d'AVC cardioembolique par rapport aux autres sous-types d'AVC. L'analyse de régression logistique a montré qu'une augmentation de la concentration en AGL était significativement associée au sous-type d'AVC cardioembolique, après ajustement pour les covariables. La concentration en AGL était également plus élevée chez les patients atteints de fibrillation auriculaire (FA) que chez ceux qui n'avaient pas de FA. En présence d'une sténose athéroscléreuse, nous n'avons noté aucune différence significative de la concentration en AGL, que l'athérosclérose artérielle soit intra ou extra crânienne. ***Conclusion :*** Nous rapportons ici une association significative entre la concentration en AGL à jeun et un sous-type d'AVC, l'AVC cardioembolique. Nous suggérons que la FA pourrait être le lien entre les AGL et le sous-type d'AVC cardioembolique.

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Free fatty acids (FFAs), also known as non-esterified fatty acids, are important energy substrates for the body.[1] Free fatty acids are liberated from triglycerides through lipolysis from adipose tissue and circulate in plasma, bound to a form of albumin.[1] The association of FFAs with cardiovascular diseases has been reported in insulin resistance,[2] atherosclerosis,[3] myocardial dysfunction,[4] abnormal cardiac rhythm,[5,6] and sudden cardiac death.[7] Although the potential association between plasma FFAs and cardiovascular disease has been discussed for several decades,[5,8] the clinical significance of FFAs remains obscure and the routine use of FFAs as a diagnostic tool is limited because of several reasons. The high variability of FFA concentration is strongly influenced by nutrition and can partially explain the devaluation of the FFA measurement as a diagnostic tool.[1] In addition, some studies have focused on the impact of FFA concentration on atherosclerosis or myocardial infarction rather than on abnormalities of cardiac rhythm.[1,9] However, recent studies are emphasizing the role of elevated FFA on cardiac arrhythmia.[5-7]

Cardioembolic (CE) stroke is responsible for about 20% of ischemic stroke.[10] Atrial fibrillation (AF) is the most important

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CE source of ischemic stroke and is more common with increasing age.[11] About one half of patients with CE stroke have nonvalvular AF and patients with prior stroke or transient ischemic attack carry an even higher stroke risk.[10] The second most common source of cardioembolism is left ventricular thrombus that is usually associated with myocardial infarction or congestive heart failure.[10]

Theoretically, there are considerable overlapping conditions between the potential cardioembolic source of stroke and cardiac diseases that are associated with elevated plasma FFA concentration. However, the association of FFAs with ischemic stroke has not been extensively studied and the differential effect of plasma FFA concentration on stroke subtype has not been elucidated. Therefore, in this study we assessed the differential impact of FFAs on ischemic stroke subtypes, specifically on the CE stroke subtype.

Methods

Study Population

We retrospectively selected patients with ischemic stroke between July 2007 and December 2009 from a prospectively collected hospital-based stroke registry (Korea University Stroke Registry – Guro Arm; KUSR-G). All patients were ethnically Korean. Ischemic stroke was defined as having focal neurological deficits that were explained by relevant lesions on brain magnetic resonance imaging (MRI) or computed tomography (CT). Patients whose symptoms disappeared before 24 hours were included if the relevant lesion was found on brain images. During the study period, 931 patients with stroke or transient ischemic attack (TIA) were registered in KUSR-G. Of the 827 patients with ischemic stroke, 112 patients had no data on FFAs. Finally, data from 715 patients were analyzed. The study was approved by the Institutional Review Boards of the Korea University Guro Hospital.

Clinical and Radiological Assessment

Detailed demographic and clinical parameters were measured as previously described.[12] Hypertension was defined as the combination of a self-reported high blood pressure diagnosis and use of antihypertensive medications, or blood pressure recordings that continued to exceed 140/90 mm Hg beyond the second week after stroke. Diabetes was defined as a fasting glucose ≥126 mg/dl or a self-reported use of insulin or oral hypoglycemic agents. Concentrations for total cholesterol, triglycerides, low density lipoprotein (LDL), high density lipoprotein (HDL), glucose, and FFAs were analyzed from fasting blood on admission day. Colorimetric analysis was performed to measure FFAs (ADIVA 1650; Siemens, Erlangen, Germany). Smoking status was assigned as the patient being either a current/past smoker or a non-smoker. A history of previous strokes was recorded separately. The body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. The stroke classification was divided into five groups based on previously published guidelines: large artery atherosclerosis (LAA), CE, small vessel occlusion (SVO), undetermined etiology (UDE), and other-determined etiology (ODE).[13] We classified patients into the CE subtype and the non-CE subtype to compare differences. Arterial stenosis of intracranial cerebral arteries and extracranial arteries was assessed using magnetic resonance angiography (MRA), computed tomogram angiography (CTA) or conventional angiography. Intracranial cerebral arterial stenosis (ICAS) was diagnosed when significant stenosis (>50%) was found on at least one segment of the middle cerebral artery, anterior cerebral artery, posterior cerebral artery, intracranial internal carotid artery or basilar artery. Extracranial cerebral arterial stenosis (ECAS) was diagnosed when significant stenosis (>50%) was found on at least one segment of the extracranial carotid artery or extracranial vertebral artery.

Statistical Analysis

Statistical analysis was performed using SPSS (version 10.0; SPSS Inc., Chicago, IL, USA), and p values <0.05 were regarded as significant. Descriptive statistics are presented as mean ± SD for continuous variables or as a proportion for categorical variables. Differences between groups were tested with an independent t-test or Mann-Whitney U test according to the distribution of the value of the variables. To test the independent association of the concentration of FFAs with ICAS, ECAS and CE stroke subtypes, a logistic regression analysis was performed using the backward method for covariates selection. Covariates included in the initial model were age, sex, total-cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, fasting glucose, BMI, hypertension, diabetes mellitus, smoking status, previous statin medication, and FFA. The results are presented as an odds ratio (OR) with a 95 percent confidence interval (CI). Odds ratios for continuous variables were values per one standard deviation increment.

Results

Details of the demographic and clinical data are presented in Table 1. The distribution of patients according to the subtype of stroke was 216 (30.2%) for LAA, 107 (15.0%) for CE, 182 (25.5%) for SVO, 184 (25.7%) for UDE, and 26 (3.6%) for ODE. The list of the potential source of cardioembolism (PSCE) is presented in Table 2. AF was the most common PSCE (77 patients, 72.6%). The concentration of FFAs was different according to smoking status (884.39 ± 673.53 for non-smoker and 783.37 ± 622.94 for current smoker, p = 0.032), initial National Institutes of Health Stroke Scale (NIHSS) score (Correlation coefficient 0.176, p < 0.001) and the stroke subtype. The FFA concentration was highest in the CE (1194.68 ± 806.45) group followed by UDE (907.49 ± 685.60), ODE (843.96 ± 645.50), LAA (801.60 ± 600.30) and SVO (662.20 ± 513.54) according to the subtype of stroke. The difference of FFAs between the CE and non-CE groups was significant (p < 0.001; Table 1). Patients with the CE subtype showed lower LDL-cholesterol and triglycerides and higher HDL-cholesterol than those with the non-CE subtype. Patients with CE subtype visited the hospital earlier than those with non-CE subtype. Smoking was more prevalent in patients with non-CE than those with the CE subtype. According to the presence of atherosclerotic stenosis, patients with ICAS showed significantly higher FFA concentration (896.48 ± 662.94) than those without ICAS (830.18 ± 657.58, p = 0.017). However, no significant difference was found for ECAS (p = 0.139). The association between ICAS and FFA disappeared on the logistic regression analysis.

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Table 1: Clinical and laboratory data of the population

	Stroke			p
	All stroke (n = 715)	CE (n = 107)	Non-CE (n = 608)	
Age, years	65.83 ± 12.65	67.48 ± 11.91	65.54 ± 12.77	0.092
Sex – male	449 (62.9)	63 (58.9)	386 (63.6)	0.352
Hypertension	426 (59.6)	63 (58.9)	363 (59.7)	0.873
Diabetes	198 (27.7)	24 (22.4)	174 (28.6)	0.187
Smoking	217 (30.3)	20 (18.7)	197 (32.4)	0.004
BMI, kg/m^2	24.20 ± 3.19	24.43 ± 2.63	24.17 ± 3.27	0.463
Statin therapy	71 (9.9)	10 (9.3)	61 (10.0)	0.827
Initial NIHSS	4.89 ± 5.22	8.39 ± 7.51	4.28 ± 4.43	<0.001
Time from onset to visit, hours	38.56 ± 50.97	24.41 ± 46.58	41.13 ± 51.34	<0.001
Laboratory findings				
FFA, Eq/L	853.73 ± 659.79	1194.68 ± 806.45	793.73 ± 611.87	<0.001
TC, mg/dl	176.57 ± 39.38	171.58 ± 40.42	177.45 ± 39.16	0.115
LDL, mg/dl	114.74 ± 34.25	109.93 ± 36.17	115.58 ± 33.87	0.024
HDL, mg/dl	44.12 ± 11.85	46.85 ± 13.91	43.64 ± 11.39	0.033
TG, mg/dl	135.18 ± 86.52	104.40 ± 58.13	140.62 ± 89.56	<0.001
FBS, mg/dl	140.29 ± 63.02	140.64 ± 47.93	140.23 ± 65.36	0.061
Subtypes of stroke				
LAA	216 (30.2)			
CE	107 (15.0)			
SVO	182 (25.5)			
UDE	184 (25.7)			
ODE	26 (3.6)			

Values are mean ± standard deviation or number (%). CE = cardioembolism; FFA = free fatty acid; TC = total cholesterol; LDL = low density lipoprotein; HDL = high density lipoprotein; TG = triglycerides; FBS = fasting blood glucose; BMI = body mass index; NIHSS = National Institute of Health Stroke Scale; LAA = large artery atherosclerosis; SVO = small vessel occlusion; UDE = undetermined etiology; ODE = other-determined etiology.

Logistic regression analysis between the CE and non-CE subtype revealed that an increase in FFA concentration (OR: 1.584; 95% CI: 1.306–1.922; $p < 0.001$) was significantly associated with the CE subtype (Table 3). An increase in triglycerides and a decrease in NIHSS score at admission were significantly associated with the non-CE subtype.

Because patients with CE showed significantly higher FFA concentration than those with the non-CE subtype, further analysis was performed to investigate the association between the potential source of cardioembolism and FFA concentration. Among the 715 stroke patients, 106 patients had AF. Patients with AF (1297.48 ± 818.48) showed significantly higher FFA concentrations than those without AF (776.50 ± 596.00, $p < 0.001$; Figure). This difference was also verified in patients with the CE subtype (1311.53 ± 830.61 for AF positive, 894.77 ± 663.20 for AF negative, $p < 0.001$). FFA concentration of non-CE subtype stroke patients with AF was 1260.17 ± 798.47.

The receiver operating characteristic (ROC) curve showed moderate power for discriminating the CE stroke subtype (area under curve 0.664, 95% CI: 0.602–0.725) and AF (area under curve 0.717, 95% CI: 0.657–0.774). Using a reference range of FFAs where the center was 1000 μEq/L and was applied as the

Table 2: Causes of cardioembolic stroke

Causes	Number (%)
Atrial fibrillation	77 (72.0)
Myocardial infarction	10 (9.3)
Akinetic wall or congestive heart failure with low ejection fraction	9 (8.4)
Valvular heart disease	6 (5.6)
Patent foramen ovale	9 (8.4)
Mural thrombi in left atrial appendage	1 (0.9)
Atrial septal defect	1 (0.9)

Total number included in the table was 113 patients because 2 with myocardial infarction, 1 with akinetic wall or congestive heart failure with low ejection fraction, and 3 in valvular heart disease had concomitant atrial fibrillation.

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Table 3: Logistic regression analysis to predict cardioembolic subtype

	OR	95% CI	p
FFA	1.584	1.306–1.922	<0.001
TG	0.351	0.199–0.619	<0.001
NIHSS	1.693	1.365–2.098	<0.001
BMI	1.226	0.969–1.550	0.090

The backward selection method was adopted for the selection of covariates (probability for removal of variable was 0.10). Covariates included in the initial model were age, sex, total-cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, fasting glucose, BMI, hypertension, diabetes mellitus, smoking status, previous statin medication, initial NIHSS, time from onset to visit, and FFA. Odds ratio (OR) for continuous variables were values per one standard deviation (SD) increment. NIHSS = National Institute of Health Stroke Scale.

cut-off value, the specificity of FFA for discriminating the CE stroke subtype was 80.60% and of AF was 82.10%.

Discussion

In this study, we found a significant association of CE stroke subtype with plasma FFA concentration among ischemic stroke patients. The mean FFA concentration for CE stroke subtype was about 1.5 fold higher than that of the non-CE subtype. Among patients with the CE stroke subtype, FFA concentration was also higher for patients with AF than those without AF. From these findings we deduced that the association between the CE subtype and elevated FFA concentration was caused by a heart rate abnormality such as AF. Our data also revealed an association with intracranial atherosclerosis and FFA concentration. However, the association did not reach statistical significance after logistic regression analysis.

The results of this study may be interpreted in several ways. Elevated FFA concentration may cause AF or other cardiac diseases which can provoke ischemic stroke. Cardioembolic stroke per se may elevate plasma FFA concentration. Or, the elevated FFA concentration may be an epiphenomenon of ischemic stroke.

A growing body of evidence has accumulated about the association of FFAs with arrhythmia. Oliver et al have consistently addressed the relationship between FFAs and arrhythmia since the 1970s.[5,7,8] Cardiomyocytes generate about 70% of their energy needs through the β-oxidation of fatty acids.[1] Paradoxically, an increase in β-oxidation caused by the elevation of FFAs can have an adverse effect on the heart. The arrythmogenic effect of FFAs could be explained in several different ways. First, if the molar ratio of FFAs to albumin is sufficiently high, cytosolic Ca^{2+} influx is increased which promotes Ca^{2+}-dependent reperfusion arrhythmias.[5] The arrhythmogenic effect of increased FFAs can be partially explained by the relationship of FFAs with ion channels. Second, a regional excess of fatty acids may lead to a membrane detergent effect by peroxidation of the membranes resulting in dispersion of membrane potentials.[7] Third, an elevated FFA concentration is also associated with an increase in catecholamine activity in acute coronary syndrome.[7] Although there is no clear evidence that stroke-induced catecholamine activity induces FFA increase, a similar situation could take place in acute stroke.

These theoretical relationships have been verified by several clinical studies. Cocco and Chu reported two cases of rimonabant associated AF, emphasizing the role of FFAs on arrhythmia generation.[14] Rimonabant is an endocannabinoid antagonist that selectively decreases the intake of savory drink and food by altering the pleasure response.[15] Although rimonabant has no direct effect on the cardiovascular system, it increases the serum concentration of FFAs.[16] Therefore, it was speculated that the increased FFAs induced microcirculatory dysfunction and an impairment of myocardial electromechanical properties that produced arrhythmia.[15] The pro-arrhythmic property of an increased FFA concentration was also observed in patients with acute myocardial ischemia.[17] An epidemiologic study verified the pro-arrhythmic property of an increased FFA concentration.[6,18,19] Elevated FFA levels were associated with an increased heart rate in patients with metabolic derangement such as diabetes and obesity.[6] For diabetic patients, the concentration of FFAs was associated with the frequency of ventricular premature complexes.[19] The Paris Prospective Study I, an epidemiologic study, provided further indirect evidence about the relationship between FFAs and arrhythmia.[18] Among the 5250 men included in the study, the risk of sudden cardiac death was sequentially increased according to circulating FFA level, whereas no relationship existed for fatal myocardial infarction. The authors deduced that an increased circulating FFA concentration induced arrhythmia resulting in sudden cardiac death. Similar results were also verified in another cohort study that showed that FFA concentration was associated with cardiac mortality and sudden cardiac death.[20,21]

The elevated FFA concentration was evident not only in patients with CE stroke subtype but also in patients with AF. The association between FFA and AF was consistent in all patients and in patients with CE stroke subtype group. There is a limitation to explain the causal relationship between FFA elevation and AF in this study. However, it is noteworthy that non-CE subtype patients with AF had also higher FFA concentration than CE subtype patients without AF. From the

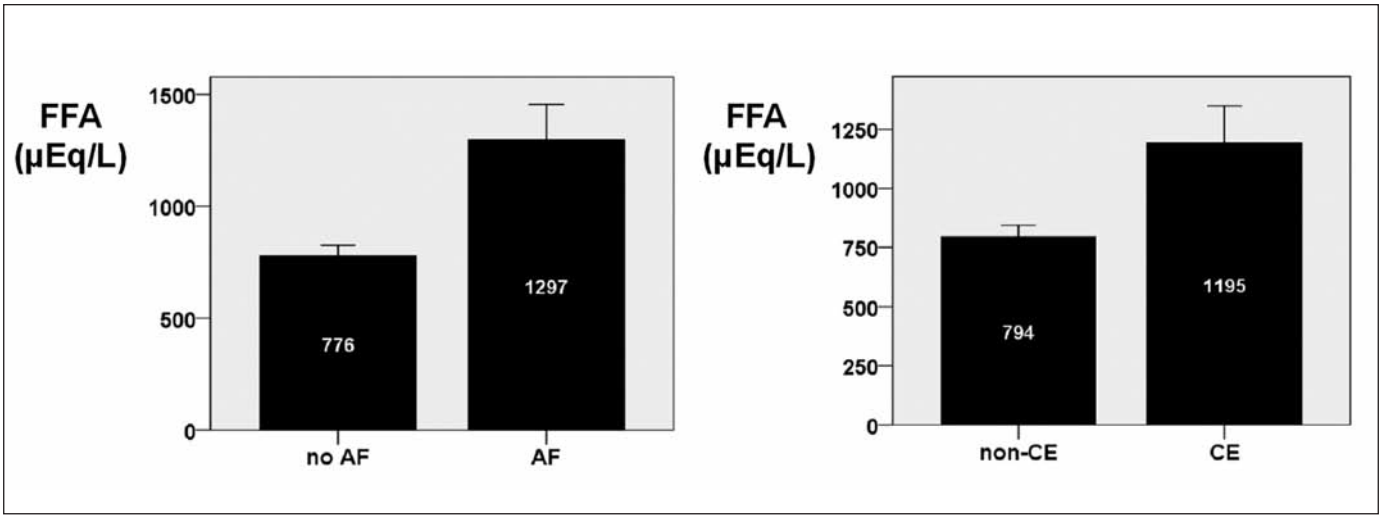

Figure: *Difference of serum free fatty acid (FFA) concentrations in patients with and without atrial fibrillation (AF). (A) Patients with AF showed significantly higher FFA concentrations than those without AF. (B) This difference was also verified in patients with the cardioembolic stroke subtype.*

results, we can deduce that elevated FFA was associated with AF rather than CE subtype itself. For the clarification of the causal relationship between elevated FFA concentration and CE subtype (or AF), a prospective study is needed to compare the influence of FFA concentration on stroke occurrence between patients with AF and those without AF.

Another possible explanation of an association between FFA and subtype of stroke is that the elevated FFA concentration may be an epiphenomenon related to cortical damage after stroke. The positive correlation between initial NIHSS score and FFA concentration makes the hypothesis more plausible. However, the association between FFA concentration and CE subtype was independent of initial NIHSS score in logistic regression analysis. Furthermore, unlike cardiac disease, the impact of an increased FFA concentration on ischemic stroke has not been well documented. The association of ischemic stroke and FFA concentration has been studied in terms of neuroprotection. An increased concentration of FFAs in brain ischemia was associated with brain edema due to mitochondrial uncoupling.[22,23] Citicholine, a precursor essential for the synthesis of phosphatidylcholine, lowers the plasma concentration of FFA. In a clinical trial of acute ischemic stroke patients, citicholine showed modest efficacy.[24] Paik et al found that plasma FFAs were elevated after transplantation of human mesenchymal stem cells in the middle cerebral artery occlusion rat model and concluded that the elevated FFAs in plasma was an epiphenomenon for compensating for depleted polyunsaturated fatty acid.[25]

Currently, the most promising way to prevent recurrent ischemic stroke in patients with AF is with a regular dosing of warfarin.[26] Nonetheless, variable bioeffects and the need for frequent blood sampling are major short comings of warfarin use in clinical practice.[27] Therefore, the high risk of future stroke and clinical inconvenience have prompted new treatment strategies other than warfarin,[28] and several novel antiarrhythmic drugs are under development or are in ongoing clinical trials.[29] The significant association between FFAs and AF could add another treatment strategy to the current treatment of patients with AF.

Several limitations of this study require further investigation. First, the cross-sectional design limits a causal relationship between elevated FFAs and the CE subtype. Second, the measurement of the FFAs was performed after the onset of stroke. Elevation of FFAs can be induced by cerebral infarction and may be a non-specific response to stress or a catecholamine-induced response.[7] However, because all of our patients were under the influence of cerebral infarction, the possibility that the CE stroke subtype was differently influenced by stress is low. Third, myocardial injury, such as acute myocardial infarction, may act as a confounder. Acute myocardial infarction causes both ischemic stroke and AF and is also associated with elevated FFA concentration. However, patients with AF-induced CE stroke had significantly higher FFA concentration than the other CE stroke patients which included acute myocardial infarction. Fourth, colorimetric measurement used in this study remained the possibility of measuring the unbound FFA. However, the concentration of the unbound form of FFAs in plasma is very low and is highly significantly correlated with the concentration of total FFAs.[30] Fifth, measurement of plasma FFA is influenced by metabolic conditions such as homocysteine or drugs such as heparin. Elevated homocysteine is associated with elevated FFA concentration and thus can affect stroke occurrence.[31] The administration of heparin increases plasma FFA.[32] However, we speculate that the effect of heparin on FFA concentration was smaller than expected because blood sampling for laboratory tests had been performed before starting administration of heparin in most cases. Finally, the population of this study is ethnically Korean. Therefore, the results should be confirmed in other ethnic populations.

In contrast, there are several strong points of this study. First, this is the first report to study the association of FFAs and stroke

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subtype. Second, the number of patients included in this study was large enough to compare between the CE and non-CE subgroups. Third, the association between AF and the concentration of FFAs was consistently observed in all stroke patients or was confined to the CE stroke group. Fourth, this high degree of specificity may be helpful for discriminating the CE stroke subtype in patients with a cryptogenic stroke subtype.

In conclusion, this study showed that the plasma concentration of FFAs at admission was significantly higher in patients with the CE stroke subtype. AF is thought to be a mediator between FFAs and the CE stroke subtype. Whether the increment of FFAs in the CE subtype has a causal relationship needs to be assessed in future studies.

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