Plasma free fatty acid is associated with ischemic cardiomyopathy and cardiac dysfunction severity in systolic heart failure patients with diabetes

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Heart failure (HF) is a worldwide problem due to the substantial morbidity and mortality of patients with cardiovascular diseases. Recently, the PARADIGM-HF trial (the Prospective comparison of angiotensin receptor-neprilysin inhibitor [ARNI] with angiotensin-converting enzyme inhibitor [ACEI] to Determine Impact on Global Mortality and morbidity in Heart Failure trial) showed that ischemic heart disease is the most common etiology of HF, which accounts for 60% of HF with reduced ejection fraction (HFrEF).[1] However, effective predictors are still in urgent need to predict ischemic cardiomyopathy (ICM) in HF patients.

Diabetes mellitus (DM) could be found in over 40% of HF patients. Cardiac events are more frequently encountered in HF patients with DM.[2] Recently, plasma free fatty acid (FFA) was detected highly in DM patients and was associated with HF and cardiovascular mortality.[3] However, it remains unclear whether FFA is associated with ICM and cardiac dysfunction severity in systolic HF patients with DM. In the present study, we investigated the role of plasma FFA in systolic HF patients with DM. We also tried to uncover the effects of plasma FFA on ICM and cardiac dysfunction severity in systolic HF patients with DM.

This study retrospectively enrolled 229 HF patients with type 2 DM from the Department of Cardiology of Ruijin Hospital from January 2016 to June 2019. Finally, the data of 155 HF patients with DM were analyzed after data screening. In addition, HFrEF patients (EF <40%) were also selected to confirm the association of FFA with ICM and cardiac dysfunction severity as the subgroup of systolic HF patients with DM ($n = 100$). This study was approved by the Institutional Review Board of Ruijin Hospital (No. NCT02998788). The procedures were conducted following the *Helsinki Declaration* of 1975. The patients enrolled in the study provided signed informed consent.

HF patients enrolled in the present study were those who had symptoms and signs of HF for at least 3 months or hospitalized for HF at least once (age >18 years). The patients were confirmed with elevated levels of the N-terminal pro-brain natriuretic peptide (NT-proBNP), anomalies in echocardiographic indicators, reduced left ventricular ejection fraction (LVEF <50%), and left atrial enlargement or left ventricular hypertrophy. Type 2 DM was diagnosed according to fasting plasma glucose levels (≥7.0 mmol/L), 2 h postprandial blood glucose (≥11.1 mmol/L), and the use of antidiabetic drugs. ICM patients were those with previously documented myocardial infarction proved by an imaging study demonstrating coronary artery disease with the corresponding areas of akinesis, dyskinesis, or severe hypokinesis on maximal appropriate medical therapy with a confirmed decreased ejection fraction (<50%). Patients with primary valvular heart disease, known malignant tumor, acute infection, acute coronary syndrome, or LVEF ≥50% were excluded from the present study.

Statistical analyses were performed on Stata 15.0 (StataCorp LLC, College Station, TX, USA). Multivariate logistic regression and linear regression analysis were performed to evaluate the predictive value of FFA for ICM, LVEF <35%, and NT-proBNP among HF patients with DM. Odds ratio (OR) values, 95% confidence interval (95% CI), and β values were presented as adjusted for confounding factors. Statistical significance was defined as $P < 0.05$.

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In the present study, the data of 155 HF patients with DM were retrospectively analyzed after data screening. All patients were divided into three tertiles, namely, patients with low FFA (≤0.46 mmol/L, First tertile, T1), median FFA (0.46–0.69 mmol/L, Second tertile, T2), and high FFA (≥0.69 mmol/L, Third tertile, T3). In the present study, the level of NT-proBNP was significantly higher in the higher FFA group compared with the lower group (T1: 1700 pg/mL *vs*. T2: 1506 pg/mL *vs*. T3: 2144 pg/mL, $Z = 3.151$, $P = 0.036$). However, the percentages of coronary artery disease (T1: 76.5% *vs*. T2: 60.8% *vs*. T3: 43.4%, $\chi^2 = 11.866$, $P = 0.003$) and ICM (T1: 64.7% *vs*. T2: 51.0% *vs*. T3: 34.0%, $\chi^2 = 9.878$, $P = 0.007$) were significantly higher in the lower FFA group compared with the higher FFA group.

Univariate logistic regression analysis showed that FFA was negatively associated with ICM in systolic HF patients with DM (OR = 0.133; 95% CI: 0.032–0.559; $P = 0.006$) and HFrEF patients with DM (OR = 0.162; 95% CI: 0.031–0.852; $P = 0.032$). The negative association remains significant in multivariate logistic regression analysis after being adjusted for relevant confounders (OR = 0.145; 95% CI: 0.026–0.817; $P = 0.029$). The results were also confirmed by dividing FFA into three tertiles, which showed that the patients in the second FFA tertile had a greater risk of ICM than those in the third FFA tertile, both in systolic HF patients with DM (OR = 2.939; 95% CI: 1.036–8.336; $P = 0.043$) and HFrEF patients with DM (OR = 4.466; 95% CI: 1.038–19.224; $P = 0.044$). The difference was much greater in the first FFA tertile in systolic HF patients with DM (OR = 3.093; 95% CI: 1.109–8.630; $P = 0.031$) [Table 1]. The effect of FFA was adjusted for age, gender, body mass index, hypertension, triglyceride, total cholesterol, low-density lipoprotein-cholesterol, high sensitivity C reactive protein, glycosylated hemoglobin, Sacubitril-Valsartan taken, ACEI/angiotensin receptor blockers taken, β-receptor blockers taken, and Spironolactone taken.

The FFA level was much higher in the LVEF <35% group than that in the LVEF ≥35% group (0.654 ± 0.302 *vs*. 0.532 ± 0.183 mmol/L, $P = 0.002$). Multivariate logistic regression analysis showed that FFA is an independent risk factor for LVEF <35% in systolic HF patients with DM (OR = 5.248, 95% CI: 1.088–31.932; $P = 0.046$) and HFrEF patients with DM (OR = 9.687; 95% CI: 1.109–84.615; $P = 0.040$). The results by dividing FFA into three tertiles showed that the patients in the second FFA tertile had less risk of LVEF <35% than those in the third FFA tertile in systolic HF patients with DM (OR = 0.201; 95% CI: 0.074–0.548; $P = 0.002$) and HFrEF patients with DM (OR = 0.085; 95% CI: 0.018–0.404; $P = 0.002$). The difference was also observed in the first FFA tertile in systolic HF patients with DM (OR = 0.408; 95% CI: 0.154–1.081; $P = 0.071$) and HFrEF patients with DM (OR = 0.179; 95% CI: 0.039–0.833; $P = 0.028$).

Moreover, multivariate linear regression analyses showed that FFA is an independent risk factor for NT-proBNP in systolic HF patients with DM ($\beta = 3781.27$ $P = 0.078$) and HFrEF patients with DM ($\beta = 7837.637$, $P = 0.008$). In

Table 1: Multivariable regression models for ICM, LVEF <35%, and NT-proBNP in systolic HF patients with DM and HFrEF patients with DM.

	ICM		LVEF<35%		NT-proBNP	
Variables	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**β (95% CI)**	***P***
Systolic heart failure (EF <50%, $n = 155$)						
FFA	0.145 (0.026, 0.817)	0.029	5.248 (1.088, 31.932)	0.046	3781.270 (−493.432, 8055.971)	0.078
FFA tertiles						
1st tertile	3.093 (1.109, 8.630)	0.031	0.408 (0.154, 1.081)	0.071	−3598.513 (−6188.287, −1008.739)	0.007
2nd tertile	2.939 (1.036, 8.336)	0.043	0.201 (0.074, 0.548)	0.002	−3022.741 (−5598.177, −447.306)	0.022
3rd tertile	Reference		Reference		Reference	
Heart failure with reduced ejection fraction (EF <40%, $n = 100$)						
FFA	0.241 (0.026, 2.257)	0.213	9.687 (1.109, 84.615)	0.040	7837.637 (2070.014, 13605.260)	0.008
FFA tertiles						
1st tertile	2.256 (0.483, 10.537)	0.301	0.179 (0.039, 0.833)	0.028	−6108.677 (−10051.910, −2165.440)	0.003
2nd tertile	4.466 (1.038, 19.224)	0.044	0.085 (0.018, 0.404)	0.002	−2491.622 (−6311.996, 1328.752)	0.198
3rd tertile	Reference		Reference		Reference	

Multivariable logistic regression models were performed for ICM and LVEF <35% in systolic HF patients with DM and HFrEF patients with DM. Multivariable linear regression models were performed for NT-proBNP in systolic HF patients with DM and HFrEF patients with DM. All the results were adjusted for age, gender, body mass index, hypertension, triglyceride, total cholesterol, LDL-c, hsCRP, HbA1c, taking Entresto, taking ACEI/ARB, taking β-receptor blockers, and taking Spironolactone. ICM: Ischemic cardiomyopathy; LVEF: Left ventricular ejection fraction; NT-proBNP: Pro-brain natriuretic peptide; HF: heart failure; DM: Diabetes mellitus; HFrEF: Heart failure with reduced ejection fraction; OR: Odds ratio; 95% CI: 95% Confidence interval; FFA: Free fatty acid; LDL-c: Low-density lipoprotein-cholesterol; hsCRP: High sensitivity C reactive protein; HbA1c: Glycosylated hemoglobin; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blockers.

addition, the patients in the second FFA tertile had less risk of high NT-proBNP than those in the third FFA tertile in systolic HF patients with DM ($\beta = -3022.741$, $P = 0.022$). The difference was also observed in the first FFA tertile in systolic HF patients with DM ($\beta = -3598.513$, $P = 0.007$) and HFrEF patients with DM ($\beta = -6108.677$, $P = 0.003$).

FFA could steadily provide an estimated 50% to 70% of the consumed adenosine triphosphate (ATP) during cardiac contraction. Recently, FFA was found to be a risk factor for major adverse cardiovascular events in acute coronary syndrome patients with DM.[4] However, the present study showed that FFA is negatively associated with ICM in HF patients with DM. This discrepancy could be due to the differences in the enrolled population. All the subjects in the study were HF patients with DM, of whom the FFA levels were already higher than those of the people without HF. To put it another way, the FFA levels of DM patients with ICM were higher than those of people without HF but lower than those of DM patients without ICM.

The study showed that FFA is an independent risk factor for cardiac dysfunction severity in systolic HF patients with DM. This is consistent with previous studies, which could be explained by the effects of accumulated FFA on enhancing lipid accumulation and lipotoxicity in cardiomyocytes, resulting in cardiomyocyte apoptosis and contractile dysfunction eventually. Furthermore, switching myocardial fuel utilization into fatty acid oxidation is one of the mechanisms of empagliflozin in protecting left ventricular systolic function.[5] This suggests that enhancing the use of FFA might be a promising way to reduce the adverse left ventricular remodeling in HF patients with DM.

In conclusion, this study provides evidence that plasma FFA is negatively associated with ICM in HF patients with DM. In addition, plasma FFA is also an independent risk factor for cardiac dysfunction severity in systolic HF patients with DM and HFrEF patients with DM.

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Conflicts of interest

None.

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