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Complement C1q/Tumor Necrosis Factor-Related Protein-3 (CTRP3) is Significantly Decreased in Patients with Heart Failure and Closely Related with Ventricular Tachycardia

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Background: The relationship between serum complement C1q/tumor necrosis factor (TNF)-related protein-3 (CTRP3) levels and ventricular tachycardia (VT) in heart failure patients with reduced ejection-fraction (HFrEF) is unclear. The aim of this study was to investigate changes in serum CTRP3 level and the relationship with VT in HFrEF.

Methods: The study included 88 patients with HFrEF with and without VT and 30 age- and sex-matched healthy controls. Serum CTRP3 levels were measured in addition to routine anamnesis, physical, laboratory and echocardiography examinations. The patients were divided into groups with and without HFrEF and HFrEF patients with and without VT.

Results: Serum CTRP3 levels were significantly lower in the patients with HFrEF than in the control group (206 ± 16 ng/mL and 427 ± 49 ng/mL, $p < 0.001$). Similarly, CTRP3 levels were lower in the patients with VT (194 ± 10 ng/mL and 216 ± 15 ng/mL, $p < 0.001$). Left ventricular (LV) volume and tricuspid regurgitation pressure gradient were significantly higher and LV ejection-fraction was significantly lower in the patients with VT (all $p < 0.05$). Serum CTRP3 and LV end-systolic volume values independently determined the patients with VT (all $p < 0.01$). Every 10 ng/mL decrease in CTRP3 level increased the odds ratio of VT by 79%. In the receiver operating characteristic curve (ROC) analysis, the area under the ROC curve for CTRP3 was 0.884 ($p < 0.001$). A CTRP3 cut-off value of 200 ng/mL could predict VT with 88.1% sensitivity and 80.2% specificity.

Conclusions: Serum CTRP3 levels were significantly decreased in the patients with HFrEF, and decreased CTRP3 levels were very closely related to the presence of VT in these patients.

Key Words: CTRP3 level • Heart failure • Ventricular tachycardia

INTRODUCTION

Adipokines are polypeptides that are secreted from adipose tissue and play a critical role in regulating energy metabolism.[1] Complement C1q/tumor necrosis factor (TNF)-related protein-3 (CTRP3) is a new member of the adipokine family. The main effects of CTRP3 are inhibiting high glucose-induced oxidative stress, inhibiting apoptosis, anti-inflammation, promoting angiogenesis, inhibiting fibrosis and inhibiting gluconeogenesis.[2-5] CTRP3 has been investigated for its metabolic effects, and it has been shown to reduce the incidence of cardiovascular (CV) diseases.[6-9]

In a recent study, serum levels of CTRP3 were investigated in patients with heart failure with reduced ejec-

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tion fraction (HFrEF). The authors reported that serum CTRP3 levels were decreased in patients with HFrEF, and that this was closely related to mortality and morbidity in these patients.[10] The most important cause of mortality in patients with HFrEF is ventricular tachycardia (VT). The pathophysiology and mechanism of VT in patients with HFrEF is complex and multifactorial. However, increased inflammation, fibrosis, apoptosis and oxidative stress are closely related to the presence and occurrence of VT in patients with HFrEF.[11-13] Due to the fact that decreased CTRP3 levels are closely related to inflammation, fibrosis, apoptosis and oxidative stress, we hypothesized that VT, which is the most common cause of mortality in patients with HFrEF, may be associated with decreased CTRP3 levels. To the best of our knowledge, no previous studies have investigated serum CTRP3 levels in patients with VT. Therefore, the aim of this study was to investigate the changes in serum CTRP3 levels and the relationship between CTRP3 levels and VT in patients with HFrEF.

MATERIALS AND METHODS

Study population

Patients with HFrEF who were indicated for implantable cardioverter defibrillator (ICD) according to the current European Society of Cardiology (ESC) Heart Failure guidelines and those who had an ICD implanted for primary and secondary protection were screened between January 2019 and January 2020.[14,15] Gao et al.[10] compared mean CTRP3 levels between patients with HFrEF (173.3 ± 49.8 ng/mL) and controls (236.4 ± 62.9 ng/mL) using a two-sample t test at a 5% significance level with 80% power, and found that 14 patients for each groups were needed. Based on the knowledge that 28-31% of HFrEF patients have VT,[11,12] we planned to enroll 100 HFrEF patients in order to include at least 30 HFrEF patients with VT. However, the number of HFrEF patients with VT was much higher than expected, so 88 HFrEF patients were finally enrolled in this prospective study.

The 88 patients (58 male, 30 female, mean age 64.5 ± 13.1 years) were admitted to the arrhythmia clinic of our hospital and all had an ICD device for primary and secondary prevention. All 88 patients had HFrEF [ejection fraction ≤ 40%] and New York Heart Association (NYHA) class I-II-III with medical treatment according to the stage. In addition, 30 and age- and sex-matched healthy controls (20 males, 10 females, mean age 64.1 ± 6.3 years) were also included.

All patients included in the study had ICD implantation for at least 6 months. In all patients, whether or not they had VT, all electrogram (EGM) records in the device were examined. All EGM recordings considered to indicate VT were evaluated by two electrophysiology specialists with experience in ICD implantation and VT ablation. In the EGM recordings, VT was considered if the heart rate was ≥ 171 bpm and the RR interval was equal. If the two electrophysiology specialists could not make a clear decision about the diagnosis of VT, the opinion of the chief of the electrophysiology department was sought. At the same time, all patients underwent similar NYHA staging. Patients with acute coronary syndrome, patients with a history of liver disease, severe renal insufficiency, moderate-severe heart valve disease, active thyroid disease, suspected cancer and/or pregnancy, left ventricule ejection fraction (LVEF) ≥ 40%, and those who did not wish to be included in the study were excluded. The study was conducted according to the recommendations of the Helsinki Declaration of Human Subjects Biomedical Research and the protocol was approved by our institutional ethics committee. Voluntary consent forms were explained in detail to all patients and the patients were included in the study after obtaining written consent.

A detailed history was taken and physical examination was performed in all patients. Subsequently, the demographic characteristics including age, gender, hypertension (HT), diabetes mellitus (DM), active smoking and hyperlipidemia (HPL) history were recorded. The patients with HFrEF were evaluated for coronary artery disease. Patients with a history of myocardial infarction, revascularization procedure or patients with critical coronary artery disease were classified as having ischemic HF. Body mass index (BMI) was calculated by measuring their weight and height. High sensitive C reactive protein (hs-CRP) and high sensitive cardiac troponin I (hs-cTnI) were measured in addition to routine laboratory parameters (glucose, renal and liver functions, lipid parameters and NT-proBNP) in all patients with HFrEF included in the study.

Blood samples for CTRP3 levels were taken from the patient and control groups at 08:00 am following a fasting period of at least 12 hours. The venous blood samples were taken and centrifuged at 4000 rpm for at least 10 minutes. Serum samples were kept frozen at -80 °C until analysis. For measuring the serum CTRP3 levels, CTRP3 (human) competitive enzyme-linked immunosorbent assay (ELISA) kit (Adipogen, South Korea, Cat# AG-45A0042EK-KI01) were used. CTRP3 sensitivity was assay range: 1 ng/mL-1000 ng/mL, and the results were given as ng/mL.

Echocardiography examinations were performed on an EPIQ 7 system (Philips Healthcare, Andover, Massachusetts, USA). American Echocardiography Society guidelines were followed to obtain images. The patients were monitorized and placed on their left side, then standard parasternal long and short axis views were obtained, as well as apical 5, 4 and 2 space chambers and at least 3 consecutive cycles.[16] LV diastolic and systolic (LVd and LVs) volumes and LVEF were calculated during echocardiography using the modified Simpson method from apical 4 and 2 space chambers.[17] Tricuspid regurgitation pressure gradient (TRPG) was calculated using the Bernoulli equation over the peak flow rate of tricuspid regurgitation.

Statistical analysis

All analyses were done using SPSS 22.0 (Chicago, IL, USA) statistical software package. Whether the distribution of continuous variables was normal or not was evaluated using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as numbers and percentages. Continuous variables that showed normal distribution were compared using the Student t test, whereas the Mann-Whitney U test was used to compare differences between two independent groups when the dependent variable was either ordinal or continuous, but not normally distributed. The chi-square ($\chi 2$) test was used to compare categorical variables. Logistic regression analysis was performed to determine the independent markers among the HFrEF patients with VT. Receiver operating characteristic curve (ROC) curve analysis was performed to re-evaluate the CTRP3 level to detect the HFrEF patients with VT and to determine the cutoff value of CTRP3. The value of the area under the curve was used as a measure of the accuracy of the test. Statistical significance was accepted if $p < 0.05$.

RESULTS

CTRP3 measurements were successfully performed in all patients with HFrEF and the control patients included in the study. The study data were compared in two groups as patients with HFrEF and control group. In addition, patients with HFrEF were grouped and compared as patients with and without VT. Parameters that could independently determine the patients with VT were determined.

Serum CTRP3 levels were significantly lower in the patients with HFrEF than in the control group (206 ± 16 ng/mL and 427 ± 49 ng/mL, $p < 0.001$, power = 100%). Similarly, CTRP3 levels were lower in the patients with VT (194 ± 10 ng/mL and 216 ± 15 ng/mL, $p < 0.001$, power = 100%).

Demographic, clinical and laboratory data of the patients with HFrEF and the control group

When the demographic data of the patients with and without HF were compared, age and gender were found to be similar. For the laboratory parameters, glucose, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, uric acid, triglycerides, hs-cTnI, hs-CRP and NT-proBNP levels were higher in the patients with HFrEF (Table 1). Serum albumin, total protein, all cholesterols and CTRP3 levels were lower in the patients with HFrEF (Table 1). Other laboratory data were similar between the two groups. For echocardiography parameters, LVd and LVs volumes and TRPG values were higher and LVEF was significantly lower in the patients with HFrEF (Table 1).

Demographic, clinical and laboratory data of the patients with HFrEF with and without VT

When the demographic data of the patients with and without VT were compared, age and gender were similar, and the frequencies of HT, DM, smoking and HPL were higher in the patients without VT. For the laboratory parameters, hs-cTnI, hs-CRP and NT-proBNP levels were higher in the patients with VT (Table 2). CTRP3 levels were lower in the patients with VT (Table 2). Other

Table 1. Demographic and laboratory findings of patients with HFrEF and healthy controls

Variable	HFrEF (*n* = 88)	Healthy controls (*n* = 30)	p value
Age (year)	64.5 ± 13.1	64.1 ± 6.3	0.873
Gender (female), n (%)	30 (34.0)	10 (33.3)	0.905
Hypertension, n (%)	47 (53.4)	–	
Diabetes mellitus, n (%)	33 (37.5)	–	
Current smoker, n (%)	31 (35.2)	–	
Hyperlipidemia, n (%)	35 (39.8)	–	
NYHA class I-II-III, n	29-45-14	–	
BMI (kg/m^2)	28.89 ± 2.31	28.2 ± 2.24	0.658
Glucose (mg/dL)	152 ± 59	91.6 ± 7.6	< 0.001
BUN (mg/dL)	58.2 ± 27.5	28.7 ± 6.3	< 0.001
Creatinine (mg/dL)	1.13 ± 0.38	0.61 ± 0.15	< 0.001
Total protein (gr/dL)	6.48 ± 0.55	6.98 ± 0.27	< 0.001
Serum albumin (gr/dL)	3.67 ± 0.47	4.19 ± 0.17	< 0.001
Aspartate aminotransferase (u/L)	38.2 ± 26.5	20.9 ± 7.5	< 0.001
Alanine aminotransferase (u/L)	33.9 ± 23	18.2 ± 6.31	< 0.001
Uric acid (mg/dL)	7.23 ± 1.24	4.36 ± 0.84	< 0.001
Total cholesterol (mg/dL)	175 ± 35	199 ± 34	< 0.001
LDL cholesterol (mg/dL)	110 ± 25	124 ± 27	0.007
HDL cholesterol (mg/dL)	35.5 ± 7.4	52.7 ± 12.3	< 0.001
Triglycerides (mg/dL)	148 ± 89	108 ± 41	0.020
hs-cTnI (ng/L)	0.31 ± 0.16	0.15 ± 0.19	< 0.001
hs-CRP (mg/dL)	15.4 ± 5.3	5.53 ± 1.77	< 0.001
NT-proBNP (pg/mL)	2977 ± 1234	35.7 ± 15.02	< 0.001
CTRP3 (ng/mL)	206 ± 16	427 ± 49	< 0.001
LVd volume (mL)	112 ± 13	78.1 ± 9.6	< 0.001
LVs volume (mL)	78.6 ± 12	31.2 ± 5.2	< 0.001
LVEF (%)	30.1 ± 4.5	60.4 ± 3.5	< 0.001
TRPG (mmHg)	35.2 ± 5.54	18.5 ± 3.4	< 0.001

The values were shown as mean ± standard deviation or n (%).
BMI, body mass index; BUN, blood urea nitrogen; CTRP3, complement C1q/tumor necrosis factor (TNF)-related protein-3; HDL, high density lipoprotein; HFrEF, heart failure with reduced ejection fraction; hs-CRP, high sensitive C reactive protein; hs-cTnI, high sensitive cardiac troponin I; LDL, low density lipoprotein; LVd, left ventricular diastolic; LVEF, left ventricular ejection fraction; LVs, left ventricular systolic; NYHA, New York Heart Association; TRPG, tricuspid regurgitation pressure gradient.

laboratory data were similar between the two groups. For the echocardiography parameters, LVd and LVs volumes and TRPG values were higher and LVEF was significantly lower in the patients with VT (Table 2).

Regression analysis to determine patients with ventricular tachycardia

Demographic, clinical and laboratory parameters associated with VT in Table 2 were evaluated using multivariate logistic regression analysis. Serum CTRP3 level and LVs volume could independently determine the patients with VT (Table 3). In this analysis, every 10 ng/mL decrease in CTRP3 level was found to increase the probability of the patient's having VT by 79%. In the same analysis, LVd volume, LVEF, TRPG, and serum values of high sensitive cardiac troponin I (hs-TnI), NT-proBNP and hs-CRP did not independently determine the presence of VT.

ROC analysis for CTRP3 level in determining the patients with VT

In the ROC analysis performed to determine the CTRP3 values for HFrEF patients with VT, the area under the ROC curve for CTRP3 was found to be 0.884 (0.812-957) and it was statistically significant (p < 0.001). A CTRP3 cutoff value of 200 ng/mL could predict the pa-

Table 2. Demographic and laboratory findings of HFrEF patients according to presence of ventricular tachycardia

Variable	Ventricular tachycardia (+) (*n* = 46)	Ventricular tachycardia (-) (*n* = 42)	p value
Age (year)	63.2 ± 12.7	65.9 ± 13.5	0.315
Gender (female)	17	13	0.357
Hypertension, n (%)	19 (41.3)	28 (66.7)	0.015
Diabetes mellitus, n (%)	11 (23.29)	22 (52.4)	0.005
Current smoker, n (%)	6 (13.0)	25 (59.5)	0.001
Hyperlipidemia, n (%)	12 (26.1)	23 (54.8)	0.006
NYHA class I-II-III, n	12-26-8	17-19-6	0.210
BMI (kg/m^2)	28.9 ± 2.5	28.9 ± 2.1	0.971
Glucose (mg/dL)	146 ± 61	160 ± 56	0.267
BUN (mg/dL)	55 ± 27	62 ± 28	0.258
Creatinine (mg/dL)	1.09 ± 0.33	1.19 ± 0.42	0.224
Total protein (gr/dL)	6.51 ± 0.65	6.46 ± 0.42	0.684
Serum albumin (gr/dL)	3.71 ± 0.60	3.63 ± 0.29	0.442
Aspartate aminotransferase (u/L)	34.1 ± 11.7	42.7 ± 36	0.127
Alanine aminotransferase (u/L)	30.8 ± 9.7	37.4 ± 43.6	0.321
Uric acid (mg/dL)	7.06 ± 1.30	7.43 ± 1.16	0.165
Total cholesterol (mg/dL)	174 ± 42	176 ± 26	0.814
LDL cholesterol (mg/dL)	106 ± 28	114 ± 21	0.153
HDL cholesterol (mg/dL)	36.1 ± 5.1	34.7 ± 9.3	0.362
Triglycerides (mg/dL)	159 ± 106	136 ± 63	0.232
hs-cTnI (ng/L)	0.34 ± 0.18	0.26 ± 0.13	0.022
hs-CRP (mg/dL)	17.2 ± 5.3	13.4 ± 4.6	0.001
NT-proBNP (pg/mL)	3315 ± 1311	2608 ± 1037	0.007
CTRP3 (ng/mL)	194 ± 10	216 ± 15	< 0.001
LVd volume (mL)	117 ± 12	107 ± 12	< 0.001
LVs volume (mL)	83.80 ± 11.86	72.97 ± 8.86	< 0.001
LVEF (%)	28.8 ± 4.81	31.6 ± 3.6	0.002
TRPG (mmHg)	36.8 ± 6.2	33.3 ± 3.9	0.002

The values were shown as mean ± standard deviation or n (%).
BMI, body mass index; BUN, blood urea nitrogen; CTRP3, complement C1q/tumor necrosis factor (TNF)-related protein-3; HDL, high density lipoprotein; HFrEF, heart failure with reduced ejection fraction; hs-CRP, high sensitive C reactive protein; hs-cTnI, high sensitive cardiac troponin I; LDL, low density lipoprotein; LVd, left ventricular diastolic; LVEF, left ventricular ejection fraction; LVs, left ventricular systolic; NYHA, New York Heart Association; TRPG, tricuspid regurgitation pressure gradient.

Table 3. Variable regression analysis for the detection of HFrEF patients with ventricular tachycardia

Variable	Odds ratio	95% confidence interval	p value
LVs volume (mL)	1.107	1.034-1.184	0.004
CTRP3 (10 ng/mL)	0.210	0.103-0.429	< 0.001

CTRP3, complement C1q/tumor necrosis factor (TNF)-related protein-3; LVs, left ventricular systolic.

tients with VT with 88.1% sensitivity and 80.2% specificity (Figure 1). In addition, ROC analysis was performed for the importance of LVd volume, LVEF, TRPG, hs-TnI, NT-proBNP and hs-CRP serum values in determining the presence of VT. The results showed an area under the ROC curve of < 0.700 for each of the six parameters.

DISCUSSION

The most important finding of our study is that serum CTRP3 value was significantly lower in the patients with HFrEF compared to the healthy controls, and that a decreased CTRP3 level was closely related to VT, which is the most important cause of mortality in patients with

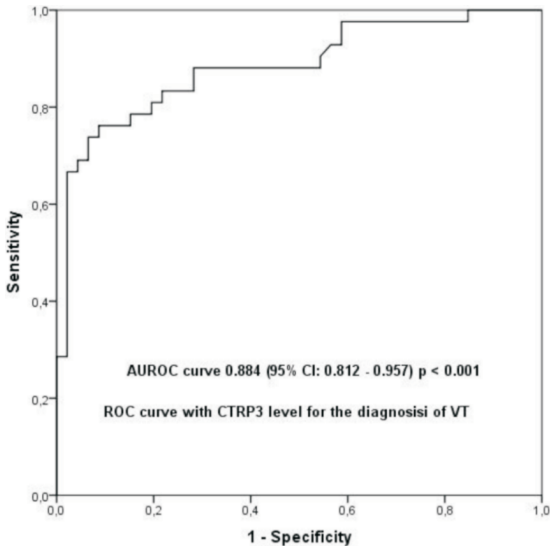

Figure 1. *ROC analysis of serum CTRP3 level in predicting the presence of ventricular tachycardia for patients with heart failure with reduced ejection fraction. AUROC, area under the receiver operating characteristic; CI, confidence interval; CTRP3, complement C1q/tumor necrosis factor (TNF)-related protein-3; ROC, receiver operating characteristic curve; VT, ventricular tachycardia.*

HFrEF. In the literature, only one study has reported lower serum CTRP3 levels in patients with HFrEF. However, our study is the first to show the importance of serum CTRP3 level in predicting VT that may develop in these patients. A serum CTRP3 cutoff level of 200 ng/mL could predict the risk of having VT with acceptable sensitivity and specificity. For this reason, our study provides important data to the literature.

Previous studies have reported that CTRP3 has the following effects on the cardiovascular system: i) reduces oxidative stress, ii) inhibits apoptosis, iii) has anti-inflammatory and anti-atherogenic effects, iv) reduces the development of fibrosis, v) inhibits gluconeogenesis, and as a result of all these effects, CTRP3 decreases CV diseases.[2-9,18,19] Accordingly, CTRP3 can physiopathologically protect and improve the clinical outcomes of patients with HF. Recent studies have reported significantly low serum CTRP3 levels in patients with HFrEF, acute coronary syndrome, stable angina pectoris and acute aortic dissection.[6,10,20]

Serum CTRP3 levels were first reported to be lower in patients with HFrEF in 2019.[10] Goa et al. investigated serum CTRP3 and CTRP9 levels in patients with HFrEF, considering that patients with HFrEF should have a new marker in addition to BNP and NT-proBNP.[10] Their results showed that both CTRP3 and CTRP9 levels were significantly lower in patients with HFrEF than in healthy controls.[10] At the same time, after 36 months of follow-up, both biomarkers were shown to be closely related to mortality and morbidity.[10] In our study, in accordance with this previous study, we found that serum CTRP3 level was significantly lower in the patients with HFrEF compared to the healthy controls.

In in vivo studies on mice, CTRP3 has been shown to improve cardiac contractile function with anti-apoptotic and pro-angiogenic effects after myocardial ischemia.[18] Similarly, in patients with acute coronary syndrome and stable angina, serum CTRP3 levels have been reported to be significantly lower than in healthy controls.[20] These positive effects may be due to anti-atherogenic and anti-inflammatory effects.[19]

The mechanism of VT pathogenesis in patients with HFrEF is unclear. The most common form of HFrEF is heart pump failure due to myocardial contraction disorder, and myocardial ischemia and infarction are mostly responsible for this condition. Cardiac adaptation mechanisms are aimed at keeping the LV ejection volume within normal limits. Chronic pressure is compensated by cardiac hypertrophy prior to loading. Then, when dilatation is added as a result of remodeling, decompensation begins. Non-cardiac adaptation mechanisms change intravascular volume and vascular resistance and are effective with many different mechanisms such as sympatho-adrenal system, renin-angiotensin-aldosterone system, natriuretic peptides, arginine vasopressin, prostaglandins, nitric oxide and cytokines. These physiopathological processes, which initially increase ventricular performance, lead to a decrease in cardiac performance and heart failure symptoms over time. As a result, this decreased angiogenesis in patients with heart failure results in increased oxidative stress, apoptosis, inflammation and fibrosis development with increased automaticity, triggered activity or re-entry mechanism leading to VT.[11-13] The fact that CTRP3 level has a positive effect on all these mechanisms that are effective in the pathophysiology of VT suggests that there may be a relationship between CTRP3 level and VT. In our study, the serum CTRP3 level was significantly lower in the patients with VT due to HFrEF compared to those without VT. Although no studies in the literature have investigated the level of CTRP3 in pa-

tients with VT, it supports other studies showing an association between a decreased CTRP3 level and negative CV events.[6,10,21]

The most important cause of sudden cardiac death and arrhythmia in patients with HFrEF is VT.[14,15] The most important parameters related to ICD indications in patients with HFrEF are the detection of arrhythmia and the LVEF value according to the patient's NYHA stage.[14,15] Serum levels of hs-TnI, hs-CRP and NT-proBNP have been reported to be useful in determining the future presence of VT/ventricular fibrillation (in patients with HFrEF.[22-25] Although HF and arrhythmia guidelines state that elevated levels of cardiac troponins, hs-CRP and NT-proBNP are sensitive markers of cardiac involvement and predictors of adverse outcomes in patients with HFrEF, there are no data to suggest that these biomarkers can be used to identify patients who might benefit from an ICD.[14,15] In our study, serum hs-TnI, NT-proBNP and hs-CRP values in HFrEF patients with VT were higher than in those without VT. However, in accordance with the literature and guidelines, none of these parameters were found to be independent or closely related to the presence of VT.

Study limitations

Our study has some important limitations. Although the results of our study were significant, it was insufficient in terms of the number of patients included in the study. The most important reason for this is the limited number of kits used for CTRP3 measurement due to economic problems. In our study, only patients with NYHA stage I-II-III were included, and there were no patients with NYHA class IV. We should also have included patients with NYHA class IV HFrEF. Although we performed biochemical measurements, CTRP3 levels were not measured from tissue samples. Findings at the level of myocytes could also be meaningful. In this study, the data of patients with HFrEF were compared with healthy controls, who were similar in age and gender. The most important reason for this is that changes in CTRP3 level can occur in patients with metabolic syndrome and various cardiometabolic risk factors.[26,27] In our study, CV risk factors were significantly higher in the HFrEF patients with VT compared to the HFrEF patients without VT. Therefore, patients with HFrEF with and without VT and similar CV risk factors could be selected in order to obtain more meaningful results. Our study was not planned as a follow-up study, however long-term follow-up would have yielded more meaningful results.

CONCLUSIONS

Serum CTRP levels were significantly decreased in the patients with HFrEF and closely related to VT, which was common in these patients. According to our study and previous studies investigating CTRP3 levels in CV diseases, serum CTRP3 levels may be a useful parameter in the diagnosis and prognosis of patients with HFrEF. Although CTRP3 was very important in detecting VT development in the HFrEF patients in this study, further studies with different patient groups and more patients are needed to verify our results.

FUNDING

No funding was received for this study.

CONFLICT OF INTEREST

All the authors declare no conflict of interest.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

REFERENCES

1. Poulos SP, Hausman DB, Hausman GJ. The development and en-

docrine functions of adipose tissue. *Mol Cell Endocrinol* 2010; 323:20-34.
2. Zhang J, He J. CTRP3 inhibits high glucose-induced oxidative stress and apoptosis in retinal pigment epithelial cells. *Artif Cells Nanomed Biotechnol* 2019;47:3758-64.
3. Schaffler A, Buechler C. CTRP family linking immunity to metabolism. *Trends Endocrinol Metab* 2012;23:194-204.
4. Li X, Jiang L, Yang M, et al. CTRP3 modulates the expression and secretion of adipokines in 3T3-L1 adipocytes. *Endocr J* 2014;61: 1153-62.
5. Wu D, Lei H, Wang JY, et al. CTRP3 attenuates post-infarct cardiac fibrosis by targeting Smad3 activation and inhibiting myofibroblast differentiation. *J Mol Med (Berl)* 2015;93:1311-25.
6. Jiang H, Wang M, Ye J, et al. Serum levels of complement-C1q/tumor necrosis factor-related protein-3 decreased in patients with acute aortic dissection. *Am J Cardiol* 2018;122:1244-8.
7. Yuan YP, Ma ZG, Zhang X, et al. CTRP3 protected against doxorubicin-induced cardiac dysfunction, inflammation and cell death via activation of Sirt1. *J Mol Cell Cardiol* 2018;114:38-47.
8. Yi W, Sun Y, Yuan Y, et al. C1q/tumor necrosis factor-related protein-3, a newly identified adipokine, is a novel antiapoptotic, proangiogenic, and cardioprotective molecule in the ischemic mouse heart. *Circulation* 2012;125:3159-69.
9. Ma ZG, Yuan YP, Xu SC, et al. CTRP3 attenuates cardiac dysfunction, inflammation, oxidative stress and cell death in diabetic cardiomyopathy in rats. *Diabetologia* 2017;60:1126-37.
10. Gao C, Zhao S, Lian K, et al. C1q/TNF-related protein 3 (CTRP3) and 9 (CTRP9) concentrations are decreased in patients with heart failure and are associated with increased morbidity and mortality. *BMC Cardiovasc Disord* 2019;19:139.
11. Streitner F, Kuschyk J, Veltmann C, et al. Prospective study of interleukin-6 and the risk of malignant ventricular tachyarrhythmia in ICD-recipients—a pilot study. *Cytokine* 2007;40:30-4.
12. Blangy H, Sadoul N, Dousset B, et al. Serum BNP, hs-CRP, procollagen to assess the risk of ventricular tachycardia in ICD recipients after myocardial infarction. *Europace* 2007;9:724-9.
13. Alvarez CK, Cronin E, Baker WL, Kluger J. Heart failure as a substrate and trigger for ventricular tachycardia. *J Interv Card Electrophysiol* 2019;56:229-47.
14. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;37:2129-200.
15. Priori SG, Blomström-Lundqvist C, Mazzanti A, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015;36:2793-867.
16. Yi W, Sun Y, Yuan Y, et al. C1q/tumor necrosis factor-related protein-3, a newly identified adipokine, is a novel antiapoptotic, proangiogenic, and cardioprotective molecule in the ischemic mouse heart. *Circulation* 2012;125:3159-69.
17. Lang RM, Bierig M, Devereux RB, et al.; Chamber Quantification Writing Group. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440-63.
18. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989;2:358-67.
19. Turer AT, Scherer PE. Adiponectin: mechanistic insights and clinical implications. *Diabetologia* 2012;55:2319-26.
20. Choi KM, Hwang SY, Hong HC, et al. Implications of C1q/TNF-related protein-3 (CTRP-3) and progranulin in patients with acute coronary syndrome and stable angina pectoris. *Cardiovasc Diabetol* 2014;13:14.
21. Yagmur E, Otto S, Koek GH, et al. Decreased CTRP3 plasma concentrations are associated with sepsis and predict mortality in critically ill patients. *Diagnostics (Basel)* 2019;9:63.
22. Streitner F, Kuschyk J, Veltmann C, et al. Role of proinflammatory markers and NT-proBNP in patients with an implantable cardioverter-defibrillator and an electrical storm. *Cytokine* 2009;47: 166-72.
23. Blangy H, Sadoul N, Dousset B, et al. hs-C-reactive protein, procollagen to assess the risk of ventricular tachycardia in ICD recipients after myocardial infarction. *Europace* 2007;9:724-9.
24. Verma A, Kilicaslan F, Martin DO, et al. Preimplantation B-type natriuretic peptide concentration is an independent predictor of future appropriate implantable defibrillator therapies. *Heart* 2006;92:190-5.
25. Deneke T, Israel CW. Diagnosis of ischemia and revascularization in patients with ventricular tachyarrhythmia. *Herzschrittmachertherther Elektrophysiol* 2017;28:157-61.
26. Choi KM, Hwang SY, Hong HC, et al. C1q/TNF-related protein-3 (CTRP-3) and pigment epithelium-derived factor (PEDF) concentrations in patients with type 2 diabetes and metabolic syndrome. *Diabetes* 2012;61:2932-6.
27. Qu H, Deng M, Wang H, et al. Plasma CTRP-3 concentrations in Chinese patients with obesity and type II diabetes negatively correlate with insulin resistance. *J Clin Lipidol* 2015;9:289-94.