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Effects of ET-1 and TNF-α levels on the cardiac function and prognosis in rats with chronic heart failure

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Abstract. – OBJECTIVE: To investigate the effects of ET-1 and TNF-α levels on cardiac function and prognosis in rats with chronic heart failure (CHF), to provide reference for clinical practice.

MATERIALS AND METHODS: 120 SD rats were randomly divided into healthy group (n=60) and heart failure group (n=60). Rats from heart failure group were made into CHF models by an intraperitoneal injection of adriamycin. According to the average serum levels of ET-1 and TNF-α, 30 rats with higher level were enrolled in high expression subgroup, while 30 rats with lower level were enrolled in low expression subgroup. The sandwich enzyme-linked immunosorbent assay (ELISA) was employed to determine the ET-1 and TNF-α in rats from healthy group and heart failure group. Doppler echocardiography was used to measure the left ventricular ejection fraction, heart rate, and aortic diameter. After the death of heart failure rats, the total heart mass and left ventricle mass were measured and compared with those of the healthy rats. The serum levels of ET-1 and TNF-α were monitored to explore the influence of ET-1 and TNF-α levels on the prognosis of rats from study group.

RESULTS: The total heart mass and left ventricle mass of the heart failure group were higher than those of healthy group ($p<0.05$). The total heart mass and left ventricle mass of the low expression subgroup were lower than those of high expression subgroup ($p<0.05$).

CONCLUSIONS: The serum levels of ET-1 and TNF-α are higher than those in healthy rats. CHF rats with higher serum levels of ET-1 and TNF-α have a worse heart function and survival. Serum levels of ET-1 and TNF-α can be used as predictors of cardiac function and prognosis in CHF rats, providing references for clinical practice.

Key Words:
ET-1, TNF-α, Chronic heart failure, Survival, Cardiac function.

Introduction

Heart failure (HF) is a clinical disease secondary to left ventricular systolic and diastolic dysfunction. Chronic heart failure (CHF) refers to the persistent state of heart failure, and CHF patients are with poor prognosis after the first admission to the hospital. Worldwide, 2% to 17% of CHF patients die on the first time of hospital admission, 17% to 45% die within 1 year after the admission, and 50% die within 5 years[1,2].

CHF brings burden to the society and serious damage to the health and quality of life of people. In addition to the search for treatment therapies, the search for methods of cardiac function assessment in CHF patients and related factors of prognosis is also urgent. Endothelin 1 (ET-1) is an important factor regulating cardiovascular function. It is involved in vascular tone regulation and inflammation promotion, playing an important role in maintaining basic vascular tone and cardiovascular system stability[3]. Plasma ET-1 level is reported to be associated with the mortality of patients with HF, and the increase of ET-1 level is linked to higher pulmonary systolic pressure on echocardiography[4]. Savoj et al[5] believed that ET-1 may be an important prognosis for HF and that higher ET-1 level is related to aggravated heart failure, decreased right ventricular function, higher pulmonary arterial pressure, and higher left atrial volume index. The above-mentioned study also

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pointed out that further research should be done to achieve a better understanding of the role of ET-1 in CHF assessment and management. Tumor Necrosis Factor (TNF-α) is a cytokine that directly kills tumor cells without causing significant toxicity to normal cells. It has an immunodetection function to be used as an indicator factor to reflect the physical condition[6]. Bozkurt et al[7] have shown that higher TNF-α level is related to the severity of CHF. Little is known about the expression mechanism of ET-1 and TNF-α in CHF. Therefore, this study tries to explore the combination of the two factors, to provide reference for clinical practice.

By conducting trials on the animal, this investigation aims to research the effects of ET-1 and TNF-α levels on cardiac function and prognosis in rats with chronic heart failure (CHF), to provide reference for clinical practice.

Materials and Methods

Research Subjects

A total of 120 Sprague Dawley (SD) rats provided by an experimental animal company of Charles River (Beijing, license no.: SCXK Jing 2009-0011) were selected, 60 females and 60 males. The rats were raised at (23±2)°C with free diet and water. They were 2 months old, weighing 200-220 g. The rats were randomly divided into healthy group (observation group, n=60) and heart failure group (study group, n=60). Rats from heart failure group were made into CHF models. According to the average serum levels of ET-1 and TNF-α, 30 rats with higher level were enrolled in high expression subgroup, while 30 rats with lower level were enrolled in low expression subgroup.

Intervention Method

Rats from heart failure group were given an intraperitoneal injection of azithromycin (HISUN-Pfizer Pharmaceutical Co., Ltd., China Food and Drug Administration Approval No. H33021980) at 4 mg/kg once a week for 6 weeks. When the azithromycin reached the total level of 24 mg/kg, rats were made into CHF models. Rats from healthy group were injected with the same amount of water. After successful modeling, according to the average serum levels of ET-1 and TNF-α, 30 rats with higher level in heart failure group were enrolled in high expression subgroup, 30 rats with lower level were enrolled in low expression subgroup. Rats from heart failure group were intragastrically administrated with lovastatin (Yabao Pharmaceutical Group Co., Ltd., China Food and Drug Administration Approval No. H20094129) at 1 mg / (100 g · d) for 7 days, while rats from healthy group were given intragastric administration of the same amount of normal saline for 7 days. All experimental procedures were approved by the local Animal Ethics Committee.

Outcome Measures

The sandwich enzyme-linked immunosorbent assay (ELISA) was employed to measure the serum concentrations of ET-1 and TNF-α and changes of sTNF-R55 level in rats from healthy group and heart failure group 1, 2, 3, and 4 weeks after the treatment. Doppler echocardiography was used to measure the left ventricular ejection fraction, heart rate, and aortic diameter 2 weeks after the treatment. High performance liquid chromatography (Shimadzu LC10ATvp, Kyoto, Japan) was used to measure the levels of serum and myocardial norepinephrine (NE). After the death of heart failure rats, the total heart mass and left ventricle mass were measured and compared with those of the healthy rats.

Statistical Analysis

Statistical analysis was performed by SPSS 19.0 (Asia Analytics Formerly SPSS China). The measurement data were expressed as [n(%)] and compared between the two groups using the χ^2-test. The count data were expressed as mean ± standard deviation (mean ± SD) and compared between the two groups using the independent sample *t*-test. The 12-week survival rates of high expression subgroup and low expression subgroup were analyzed by the Kaplan-Meier survival curve. A statistical difference was recognized when $p<0.05$.

Results

Modeling Result

Sixty rates were made into CHF models successfully.

Analysis of ET-1 and TNF-α Levels

Before the treatment, the serum levels of ET-1 and TNF-α in heart failure group were higher than those in healthy group ($p<0.05$). 1, 2, 3, and 4 weeks after treatment, the serum levels of ET-1 and TNF-α in high expression subgroup and low expression subgroup showed a decreasing trend, and they were lower than those before the treatment ($p<0.05$). The serum levels of ET-1 and TNF-α in low expression subgroup were lower than those in high expression subgroup ($p<0.05$; Tables I and II).

Table I. Analysis of ET-1 level (μg/L).

	Healthy group (n=60)	High expression group (n=30)	Low expression group (n=30)
Before the treatment	81.56±11.24	220.26±20.66[a]	184.81±20.54[ab]
1 week after treatment	81.44±11.32	197.56±18.69[ac]	171.52±19.69[abc]
2 weeks after treatment	81.50±11.30	185.66±17.67[acd]	162.97±18.35[abcd]
3 weeks after treatment	81.47±11.25	172.73±17.21[acde]	149.36±17.56[abcde]
4 weeks after treatment	81.66±11.33	165.45±16.74[acdef]	142.05±16.47[abcdef]

[a]indicates $p<0.05$ when compared with the healthy group at the same time.
[b]indicates $p<0.05$ when compared with the high expression subgroup at the same time.
[c]indicates $p<0.05$ when compared with the data of the same group before the treatment.
[d]indicates that $p<0.05$ when compared with the data of the same group 1 week after the treatment.
[e]ndicates that $p<0.05$ when compared with the data of the same group 2 weeks after the treatment.
[f]indicates that $p<0.05$ when compared with the data of the same group 3 weeks after the treatment.

Table II. Analysis of TNF-α level (pg/mL).

	Healthy group (n=60)	High expression group (n=30)	Low expression group (n=30)
Before the treatment	50.12±6.45	320.44±21.42[a]	302.64±20.87[ab]
1 week after treatment	50.13±6.47	300.58±20.59[ac]	282.13±20.74[abc]
2 weeks after treatment	50.11±6.44	279.16±20.73[acd]	262.57±18.69[abcd]
3 weeks after treatment	50.15±6.47	262.54±18.65[acde]	248.56±18.74[abcde]
4 weeks after treatment	50.20±6.41	251.64±18.09[acdef]	234.68±17.61[abcdef]

[a]indicates $p<0.05$ when compared with the healthy group at the same time.
[b]indicates $p<0.05$ when compared with the high expression subgroup at the same time.
[c]indicates $p<0.05$ when compared with the data of the same group before the treatment.
[d]indicates that $p<0.05$ when compared with the data of the same group 1 week after the treatment.
[e]ndicates that $p<0.05$ when compared with the data of the same group 2 weeks after the treatment.
[f]indicates that $p<0.05$ when compared with the data of the same group 3 weeks after the treatment.

Analysis of Left Ventricular Function

After 2 weeks of treatment, the left ventricular ejection fraction, heart rate, aortic diameter, and mean arterial pressure in healthy group were in better condition than in heart failure group (low expression subgroup had better left ventricular ejection fraction, heart rate, aortic diameter, and mean arterial pressure than high expression subgroup) ($p<0.05$; Table III).

Analysis of Heart Mass

The total heart mass and left ventricle mass of heart failure group were higher than those of healthy group ($p<0.05$). The total heart mass and left ventricle mass of low expression subgroup were lower than those of high expression subgroup ($p<0.05$; Table IV).

Analysis of the Survival of Rats

After the treatment, the survival time of high expression subgroup was significantly lower than that of low expression subgroup ($p<0.05$; Table V).

Analysis of the 12-Week Survival of Rats

Over time, the survival of high expression subgroup was significantly lower than that of low expression subgroup. More details are shown in Figure 1.

Table III. Analysis of cardiac function.

	Healthy group (n=60)	High expression group (n=30)	Low expression group (n=30)
Left ventricular ejection fraction (%)	71.41±4.72	45.65±4.21[a]	52.52±4.77[ab]
Heart rate (b/min)	410.42±30.28	332.56±28.49[a]	345.68±32.17[ab]
Aortic diameter (mm)	3.15±0.52	4.82±1.05[a]	4.18±0.98[ab]
Mean arterial pressure (kPa)	15.87±1.84	12.53±1.76[a]	13.74±1.62[ab]

[a]indicates p<0.05 when compared with the healthy group.
[b]indicates p<0.05 when compared with the high expression subgroup.

Table VI. Analysis of heart mass (g).

	Healthy group (n=60)	High expression group (n=30)	Low expression group (n=30)
Total heart mass	1.07±0.05	1.31±0.12[a]	1.23±0.13[ab]
Left ventricle mass	0.66±0.05	0.81±0.09[a]	0.71±0.06[ab]

[a]indicates $p<0.05$ when compared with the healthy group at the same time.
[b]indicates $p<0.05$ when compared with the high expression subgroup at the same time.

Table V. Analysis of the survival of rats.

	Healthy group (n=60)	High expression group (n=30)	Low expression group (n=30)
Survival time (week)	Normal survival	10.54±2.65	15.78±2.39[a]

[a]indicates $p<0.05$ when compared with the healthy group at the same time.

Change of sTNF-R55 Level

The levels of soluble TNF receptors were analyzed. The results showed that the expression level of sTNF-R55 in heart failure group was higher than that in healthy group ($p<0.05$). After treatment, the expression levels of sTNF-R55 in high expression subgroup and low expression subgroup showed a downward trend. The expression levels of serum sTNF-R55 in high expression subgroup and low expression subgroup at 1, 2, 3, and 4 weeks after treatment were lower than those before treatment ($p<0.05$). The expression level of serum sTNF-R55 in low expression subgroup was lower than that in high expression subgroup at 1, 2, 3, and 4 weeks after treatment ($p<0.05$; Table VI).

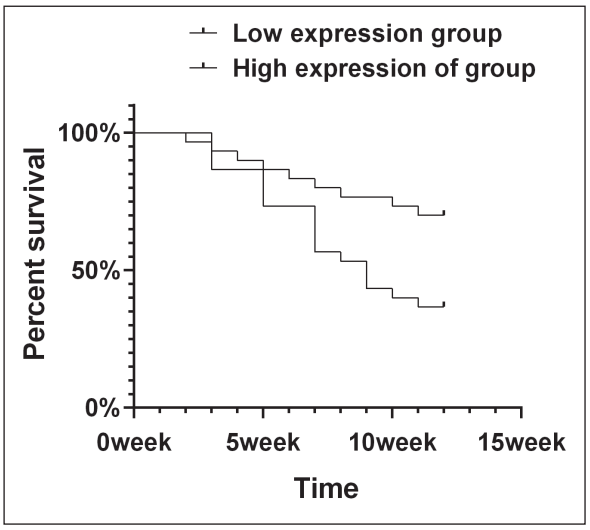

Figure 1. Analysis of the survival of rats. Over time, the survival of the high expression subgroup was significantly lower than that of the low expression subgroup.

The Comparison of NE Level

The results showed that the serum norepinephrine (NE) in low expression subgroup was significantly higher than that in high expression subgroup ($p<0.05$), while the myocardial NE in low expression subgroup was significantly lower than that in high expression subgroup ($p<0.05$; Table VII).

Discussion

As a global epidemic, HF is estimated to attack 26 million people worldwide. More than 1 million people are hospitalized for HF treatment every year in the United States and Europe. CHF patients suffer from symptoms as severe as those of cancer patients, but they have worse prognosis[8,9]. The high incidence and poor prognosis of CHF harm the health and quality of life of patients. The search for new treatment methods is urgent, so is the exploration of cardiac function assessment and related factors of the survival and prognosis of CHF patients. Widiapradja et al[10] stated that TNF can work as a judge of the patient's condition and a predictor of the prognosis of patients with rheumatoid heart disease. Upadhya and Kitzman[11] pointed out that higher ET-1 level is associated with adverse cardiovascular effects. Our research explored the effects of ET-1 and TNF-α levels on the cardiac function and prognosis of CHF patients, trying to figure out whether the combination of the two factors has a better predictive value. By conducting trials on the animal, this study aims to investigate the effects of ET-1 and TNF-α levels on cardiac function and prognosis in rats with chronic heart failure (CHF), hoping to provide a theoretical basis for clinical

Table VI. Change of sTNF-R55 level (ng/ml).

	Healthy group (n=60)	High expression group (n=30)	Low expression group (n=30)
Before treatment	0.96±0.15	3.25±0.86[a]	3.04±0.77[ab]
One week after treat-ment	0.98±0.14	3.04±0.81[ac]	2.81±0.72[abc]
Two weeks after treat-ment	0.97±0.15	2.85±0.78[acd]	2.65±0.68[abcd]
Three weeks after treatment	0.98±0.14	2.67±0.74[acde]	2.47±0.65[abcde]
Four weeks after treat-ment	0.96±0.16	2.53±0.70[acdef]	2.31±0.64[abcdef]

Compare with the healthy group at the same time, [a]$p<0.05$; compare with the high expression subgroup at the same time, [b]$p<0.05$; compare with the same group before treatment, [c]$p<0.05$; compare with the same group one week after treatment, [d]$p<0.05$; compare with the same group two weeks after treatment, [e]$p<0.05$; compare with the same group three weeks after treatment, [f]$p<0.05$.

Table VII. Change of sTNF-R55 level (ng/ml)

	Healthy group (n=60)	High expression group (n=30)	Low expression group (n=30)
Plasma NE	1.12±0.25	4.38±1.25[a]	5.46±1.41[ab]
Myocardial NE	5.24±1.46	3.64±1.06[a]	2.12±0.97[ab]

Compare with the same NE in the healthy group [a]$p<0.05$; compare with the same NE in the high expression subgroup [b]$p<0.05$.

practice. A total of 120 SD rats were collected in the animal experiment. Half of them were made into CHF models through an injection of azithromycin and enrolled in heart failure group. According to the serum levels of ET-1 and TNF-α, 30 rats with higher level in heart failure group were divided into high expression subgroup, while the last 30 were divided into low expression subgroup. After the lovastatin treatment, with a downturn trend, the serum levels of ET-1 and TNF-α in high expression subgroup and low expression subgroup were lower than those before the treatment, and the serum levels of ET-1 and TNF-α in low expression subgroup 1, 2, 3, and 4 weeks after the treatment were lower than those in high expression subgroup. After 2 weeks of treatment, the left ventricular ejection fraction, heart rate, aortic diameter, and mean arterial pressure in healthy group were in better condition than those in heart failure group (low expression subgroup had better left ventricular ejection fraction, heart rate, aortic diameter, and mean arterial pressure than high expression subgroup) ($p<0.05$). After 2 weeks of treatment, the total heart mass and left ventricle mass of heart failure group were higher than those of healthy group ($p<0.05$). The total heart mass and left ventricle mass of low expression subgroup were lower than those of high expression subgroup ($p<0.05$). According to the survival curve analysis, higher ET-1 and TNF-α levels lead to lower cardiac function and shorter survival time.

To explore the importance of two forms of ET1 in the prognosis of HF in comparison with other common biomarkers such inflammation, hemodynamic status, and cardiac physiology, Gottlieb et al[12] employed the Singulex assay to determine the active form of ET1 (Sgx-ET1) and the Brahms assay to determine the C-terminal ET-1 (CT-ET1), which is an inactive metabolite. Such a study found that the two forms of ET-1 are prognostic markers of CHF and more efficient in predicting the mortality and hospitalizations in CHF patients than common biomarkers, suggesting either complementary information or extreme prognostic importance. Although our research is an animal experiment, while the above study was based on human sample data, the results of the two studies are consistent. This investigation also showed that ET1 levels can be used as indicators of cardiac function and prognosis. In the present study, it was indicated that the levels of ET-1 and TNF-α may play a predictive role in CH. According to the result of changes in sTNF-R55 levels, the predictive role of TNF-α has been detected. The combination of the two factors is the feature of our research, and we believe it is better than ET-1 alone.

Kaplinsky et al[13] discovered an independent association between elevated ET-1 level in acute HF patients and short-term treatment outcomes and 180-day mortality[13]. Other studies indicate that ET-1 may be a risk marker for coronary heart disease. With a higher level in patients with coronary heart disease than in healthy people, ET-1 level is closely related to disease severity and car-

diac function[14,15]. According to Bossard et al[16], the expression level of ET-1 was involved not only with CHF, but also with cardiovascular diseases such as acute HF and coronary heart disease. Paradis et al[17] have shown that hypoxia stress and ET-1 synthesis increases DNA methylation and promotes terminal differentiation of cardiac myocytes in developing heart. Such premature termination of cell proliferation may result in a reduced supply of cardiomyocytes in the heart and negative effects on cardiac function. Horckmans et al[18] that performed trials on rat models believed that lower ET-1 level is associated with decreased microvascular permeability, neutrophil infiltration, and decreased expression of endothelial cell adhesion molecules. Previously, Matsa et al[19] found that an increase in ET-1 level may lead to coronary artery constriction and reduce coronary blood flow which increases left ventricular load and weaken the cardiac contractility, causing dilated cardiomyopathy phenotype and heart failure. The before-mentioned findings may be mechanisms by which ET-1 levels are independently associated with CHF. Endothelin receptor antagonist (ERA) was reported[20] to effectively improve cardiac output, lung, and systemic hemodynamics by blocking the effects of ET-1 on HF, but it has a small influence on the clinical efficacy in patients with HF. Fischer et al[21], the main adverse reactions of ERA in the treatment of cardiovascular disease were hepatic meningitis (7.91%), peripheral edema (14.36%), and anemia (6.23%). Given its poor efficacy and severe adverse reactions, ERA is not recommended to treat CHF. The role of ERA in other cardiovascular diseases remains to be studied. Diehl et al[22] pointed out that the direct effect of nebivolol on ET-1 system activity in the treatment of hypertension may be a key factor in improving endovascular health and reducing associated cardiovascular morbidity and mortality. However, nebivolol has a greater impact on ET-1, so its application in the treatment of CHF needs to be further studied. Cardiovascular disease is reported to be related to sex chromosomes. The offspring from sheep taking steroid betamethasone during pregnancy have higher mean arterial pressure. Administration of ET-1 causes a more marked effect on vascular resistance in female offspring than in male offspring[23]. Such findings make us aware of the difference in drugs for cardiovascular disease between different genders. Brouwers et al[24] suggested that routine biomarker testing should be limited to the use of natriuretic peptides and troponin-T in patients with increased cardiovascular risk. According to this study and related literature, we recommend ET-1 and TNF-α should work as independent biomarkers for CHF. They may also be suitable for detecting other cardiovascular diseases. However, the value of ET-1 and TNF-α has not been studied in rats with other cardiovascular diseases, or in humans, making this study defective. Soluble neprilysin was reported to be predictive of cardiovascular death and heart failure in HF patients[25]. We consider that the predictive sensibilities of soluble neprilysin, ET-1, and TNF-α can be compared in future studies.

Conclusions

The serum levels of ET-1 and TNF-α in CHF rats are higher than those in normal rats. CHF rats with higher serum levels of ET-1 and TNF-α have worse heart function and survival. Serum levels of ET-1 and TNF-α can be used as predictors of cardiac function and prognosis in CHF rats, providing experimental references for clinical practice.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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