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Original Research

Correlation of serum BNP and ET-1 levels with cardiac pump function and ventricular remodeling in patients with heart failure

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Abstract: This study aimed to explore the correlation of serum brain natriuretic peptide (BNP) and endothelin-1 (ET-1) levels with cardiac pump function and ventricular remodeling in patients with heart failure. Eighty-one patients with chronic heart failure admitted to our hospital from March 2016 to November 2018 were enrolled as the study group, and 80 healthy individuals as the control group. Immunofluorescence was used for the detection of serum BNP, ELISA for serum ET-1, and ultrasound for related indexes of cardiac pump function and ventricular remodeling. Moreover, correlation analysis and prognostic factors analysis were carried out. Both BNP and ET-1 were highly expressed in the serum of patients with heart failure. Cardiac pump function related indexes (left atrial ejection fraction (LAEF), left atrial passive ejection fraction (LAPEF), and left atrial active ejection fraction (LAAEF)) in the study group were significantly lower than those in the control group ($P< 0.05$). While ventricular remodeling related indexes (left ventricular end-diastolic diameter (LVEDD), interventricular septum thickness (IVST), left ventricular posterior wall thickness (LVPM), and left ventricular mass index (LVMI) in the study group were significantly higher than those in the control group ($P< 0.05$). BNP and ET-1 were negatively correlated with LAEF, LAPEF and LAAEF ($P< 0.05$), and were positively correlated with LVEDD, IVST, LVPM and LVMI ($P< 0.05$). The expressions of serum BNP and ET-1 were higher in patients with cardiovascular events than those without cardiovascular events. Hypertension, hyponatremia, high BNP, high ET-1, NYHA classification, decreased LAEF and increased LVEDD were independent risk factors for cardiovascular adverse events. Serum BNP and ET-1 are closely related to cardiac pump function and ventricular remodeling in patients with heart failure and can be used as important reference indexes for prognosis evaluation.

Key words: Heart failure; BNP; ET-1; Cardiac pump function; Ventricular remodeling; Correlation.

Introduction

Chronic heart failure is a common cardiological disease characterized by changes in myocardial structure and cardiac pump function and may occur in patients with terminal cardiac diseases (1, 2). The decreased systolic and diastolic function of the left ventricle is the most important feature of chronic heart failure, which can reduce cardiac output and peripheral circulation blood perfusion, leading to the disorder of internal environment of the body, thus posing a great threat to the life and health of patients (3, 4). Ventricular remodeling, an important outcome in the process of heart failure, is mainly caused by the recurrence of interstitial inflammation, degradation of extracellular matrix and deposition disorder. In clinical practice, the evaluation of the patient's cardiac function can provide a reference for treatment selection and prognosis evaluation.

As a kind of polypeptide cardiac hormone secreted by ventricles, brain natriuretic peptide (BNP) is a sensitive indicator reflecting the cardiac function with diuretic and vasodilatory effects. Myocardial ischemia, cardiac damage and increased vascular pressure load can stimulate its secretion (6, 7). Endothelin-1 (ET-1) is a neuroendocrine factor derived from vascular endothelium with strong and lasting vascular activity and plays an important role in cardiac fibrosis and ventricular remodeling (8). At present, clinical evaluation of ventricular remodeling and cardiac function is mostly performed by color Doppler ultrasound which accurately assesses cardiac condition but fails to evaluate the overall situation of the organism. So it is not conducive to treatment selection and prognosis evaluation of patients (9, 10).

Therefore, in order to provide more options for the evaluation of cardiac pump function and ventricular remodeling, we analyzed the correlation between them and serum BNP, ET-1 in patients with heart failure.

Materials and Methods

General information

A total of 81 patients with chronic heart failure admitted to our hospital from March 2016 to November 2018 were selected as a study group, including 42 males and 39 females, with an average age of (61.46±5.92) years. Meanwhile, 80 healthy individuals undergoing physical examinations were enrolled as a control group, with an average age of (61.36±5.89) years. Inclusion criteria were as follows: Patients with previous basic

cardiac diseases and diagnosed with chronic heart failure by clinical symptoms and index tests, as well as those with NYHA II-IV. Exclusion criteria were as follows: Patients with severe liver and kidney dysfunction, immune system diseases, infectious diseases, malignant tumors, coagulation disorders, cognitive dysfunction and communication disorders, as well as those who did not cooperate with the experiment. All patients and their families agreed to participate in the experiment and signed the informed consent form. This study was approved by the Hospital Ethics Committee.

Detection of serum BNP and ET-1

The patients' venous blood (5 mL) was sampled on the next day of admission, anticoagulated with EDTA, then centrifuged at 3000r/min to obtain serum. BNP was detected by immunofluorescence (Shenzhen Micropoint Bioscience Co., Ltd., Guangdong mechanical approval No. 20172400048) on an automatic biochemical analyzer (Biosite Company, USA, Triage Meter Plus), while ET-1 was detected by ELISA (Wuhan MSK Biotechnology Co., Ltd., item number: 69-80220). The process was strictly operated in accordance with the kit instructions.

Color Doppler ultrasound

All patients were examined for cardiac function by color Doppler ultrasound (ATL Company, USA, HDI 2300 Color Doppler Echocardiography) within 24 hours after admission, with a probe frequency of 2.0-3.0 MHz. With the patient in a supine position, the cardiac pump function related ultrasonic indexes: left atrial ejection fraction (LAEF), left atrial passive ejection fraction (LAPEF), left atrial active ejection fraction (LAAEF), and ventricular remodeling related ultrasonic indexes: left ventricular end-diastolic diameter (LVEDD), interventricular septum thickness (IVST), left ventricular posterior wall thickness (LVPM) were detected respectively. Left ventricular mass index (LVMI) = ventricular weight/body surface area (BSA).

Statistical methods

In this study, the SPSS20.0 (Bizinsight (Beijing) Information Technology Co., Ltd.) was used for statistical analysis. The counting data were analyzed using the chi-squared test, and the measurement data were expressed as mean±standard deviation. t-test was used for comparison between the two groups. GraphPad Prism 6 software was used to visualize the data, and the Pearson test was used for correlation analysis. A value of $P< 0.05$ was considered statistically significant.

Results

Comparison of general data

There was no significant difference in gender, age and body mass index (BMI) between the two groups ($P> 0.05$), indicating comparability (Table 1).

Expression levels of serum BNP and ET-1

The expression levels of BNP and ET-1 in the study group were significantly higher than those in the control group ($P< 0.05$), as shown in Table 2.

Comparison of related ultrasonic indexes of cardiac pump function and ventricular remodeling

The cardiac pump function related indexes (LAEF, LAPEF, LAAEF) in the study group were significantly

Table 1. Comparison of general data**.**

Factor	Study group (n=81)	Control group (n=80)	t/χ^2	P
Gender			0.058	0.809
Male	42 (51.85)	43 (53.75)		
Female	39 (48.15)	37 (46.25)		
Age (years)			0.052	0.820
≤61	34 (41.98)	35 (43.75)		
>61	47 (58.02)	45 (56.25)		
BMI (kg/m^2)			0.006	0.941
≤ 22	43 (53.09)	42 (52.50)		
>22	38(46.91)	38 (47.50)		
Hypertension			0.004	0.950
Yes	31 (83.27)	31 (38.75)		
No	50 (61.73)	49 (61.25)		
Alanine aminotransferase (IU/L)	26.19±1.45	26.03±1.41	0.055	0.957
Aspartate aminotransferase (IU/L)	21.33±1.19	21.29±1.16	0.216	0.829
Creatinine (umol/L)	64.31±4.39	64.02±4.11	0.666	0.433
White blood cell count ($\times 10^9$/L)	6.61±1.29	6.53±1.18	0.414	0.682
Red blood cell count ($\times 10^{12}$/L)	4.71±0.45	4.67±0.39	0.602	0.548
NYHA classification			-	-
II	29 (35.80)	-		
III	30 (37.04)	-		
IV	22 (27.16)	-		

Table 2. Comparison of observation indexes.

Index	Study group (n=81)	Control group (n=80)	t	P
BNP/(ng·L-1)	519.49±41.33	96.29±21.38	81.45	< 0.001
ET-1/(ng·L-1)	89.37±21.57	42.74±10.29	17.47	< 0.001

lower than those in the control group (P< 0.05). Whereas the ventricular remodeling related indexes (LVEDD, IVST, LVPM, LVMI) in the study group were significantly higher than those in the control group (P< 0.05), as shown in Table 3.

Correlation of BNP and ET-1 with cardiac pump function and ventricular remodeling in patients with heart failure

BNP was negatively correlated with LAEF, LAPEF and LAAEF (P< 0.05), and was positively correlated with LVEDD, IVST, LVPM and LVMI (P< 0.05). ET-1 was negatively correlated with LAEF, LAPEF and LAAEF (P< 0.05), and was positively correlated with LVEDD, IVST, LVPM and LVMI (P< 0.05), as shown in Table 4 and Figure 1.

Serum BNP and ET-1 levels in patients with different prognosis

During the 12-month follow-up, 34 patients suffering from cardiovascular events were considered to have a poor prognosis. Among them, 19 died of cardiac causes and 15 patients were readmitted for heart failure. No cardiovascular events occurred in 47 patients. Comparing the serum BNP and ET-1 levels of all patients, it was found that the levels were significantly higher in patients with cardiovascular events than those without cardiovascular events, and the levels in cardiac death patients were also significantly higher than that in readmitted patients for heart failure (P< 0.05), as shown in Table 5.

Univariate analysis of poor prognosis in patients with heart failure

The patients were divided into cardiovascular event group (34 cases) and non-cardiovascular event group (47 cases). Univariate analysis showed that there was

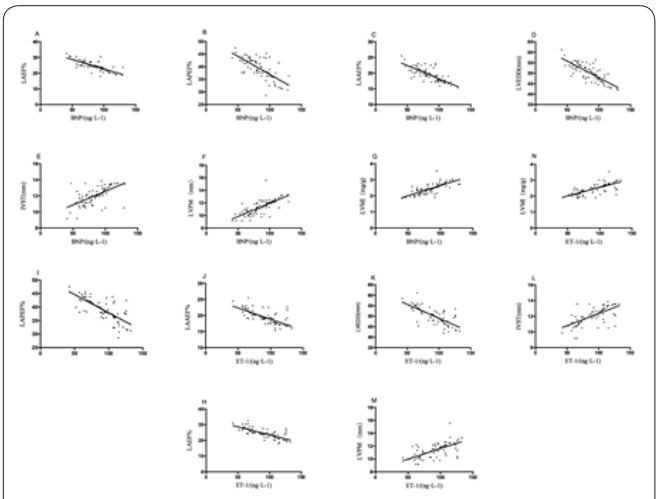

Figure 1. Correlation of BNP and ET-1 with cardiac pump function and ventricular remodeling in patients with heart failure**; A**: BNP was negatively correlated with LAEF (r=-0.779, P< 0.001); **B:** BNP was negatively correlated with LAPEF (r=-0.670, P< 0.001); **C:** BNP was negatively correlated with LAPEF (r=-0.766, P< 0.001); **D:** BNP was positively correlated with LVEDD (r=0.794, P< 0.001); **E:** BNP was positively correlated with IVST (r=0.615, P< 0.001); **F:** BNP was positively correlated with LVPM (r = 0.721, P< 0.001); **G:** BNP was positively correlated with LVMI (r=0.721, P< 0.001); **H:** ET-1 was negatively correlated with LAEF (r=-0.751, P< 0.001); **I:** ET-1 was negatively correlated with LAPEF (r=-0.743, P< 0.001); **J:** ET-1 was negatively correlated with LAAEF (r=-0.716, P< 0.001); **K:** ET-1 was positively correlated with LVEDD (r=0.749, P< 0.001); L: ET-1 was positively correlated with IVST (r=0.633, P< 0.001); **M:** ET-1 was positively correlated with LVPM (r=0.632, P< 0.001); N: ET-1 was positively correlated with LVMI (r=0.714, P< 0.001).

Table 3. Comparison of related ultrasonic indexes of cardiac pump function and ventricular remodeling.

Index	Study group (n=81)	Control group (n=80)	t	P
LAEF%	38.93±4.23	52.23±7.14	14.40	< 0.001
LAPEF%	23.85±3.24	36.87±5.95	17.21	< 0.001
LAAEF%	19.45±2.33	34.79±4.31	28.14	< 0.001
LVEDD(mm)	50.04±4.27	39.81±5.20	13.65	< 0.001
IVST (mm)	11.92±1.18	9.07±1.03	16.32	< 0.001
LVPM (mm)	11.37±1.22	9.11±1.09	12.39	< 0.001
LVMI (mg/g)	2.47±0.31	1.73±0.11	20.13	< 0.001

Table 4. Correlation of BNP and ET-1 with cardiac pump function and ventricular remodeling.

Index	BNP		ET-1	
	r	P	r	P
LAEF%	-0.779	<0.001	-0.751	< 0.001
LAPEF%	-0.670	<0.001	-0.743	< 0.001
LAAEF%	-0.766	<0.001	-0.716	< 0.001
LVEDD (mm)	0.794	<0.001	0.749	< 0.001
IVST (mm)	0.615	<0.001	0.633	< 0.001
LVPM (mm)	0.721	<0.001	0.632	< 0.001
LVMI (mg/g)	0.750	<0.001	0.714	< 0.001

Table 5. Serum BNP and ET-1 levels in patients with different prognosis.

Factor	Cardiac death group (n=19)	Heart failure group (n=15)	Non- cardiovascular event group (n=47)	F	P
BNP/(ng·L-1)	601.89±45.22	520.03±39.53*	461.82±34.12**	93.60	< 0.001
ET-1/(ng·L-1)	100.17±23.45	87.31±19.03*	72.91±16.84**	14.73	< 0.001

no significant difference in gender, age, BMI, LAAEF, IVST, LVPM between the two groups (P> 0.05). While there were significant differences in hypertension, hyponatremia, high BNP, high ET-1, NYHA classification, LAEF, LAPEF, LVEDD and LVMI (P< 0.05) based on Table 6.

Multivariate analysis of poor prognosis in patients with heart failure

Hypertension, hyponatremia, high BNP, high ET-1, NYHA classification, LAEF, LAPEF, LVEDD and LVMI were included in the analysis and were assigned as variables (Table 7). The logistic regression model was used to analyze the risk factors of cardiovascular events, and the results showed that hypertension, hyponatremia, high BNP, high ET-1, NYHA classification, decreased LAEF and increased LVEDD were independent risk factors for adverse cardiovascular events (Table 8).

Table 6. Univariate analysis of poor prognosis in patients with heart failure.

Factor	Cardiovascular event group (n=34)	Non-cardiovascular event group (n=47)	t/χ^2	P
Gender			0.015	0.901
Male	20 (58.82)	27 (57.45)		
Female	14 (41.18)	20 (42.55)		
Age (years)	61.34±5.86	61.49±5.96	0.113	0.911
BMI (kg/m^2)	22.87±2.61	22.61±2.58	0.445	0.657
Hypertension			13.69	<0.001
Yes	21 (83.27)	10 (38.75)		
No	13 (61.73)	37 (61.25)		
Hyponatremia			7.124	0.008
Yes	19 (55.88)	39 (82.98)		
No	15 (44.12)	8 (17.02)		
BNP/($ng\cdot L^{-1}$)	572.12±33.16	461.82±34.12	14.53	< 0.001
ET-1/($ng\cdot L^{-1}$)	93.12±18.34	72.91±16.84	5.135	< 0.001
NYHA classification			5.818	0.016
II ~ III	20 (58.82)	39(82.98)		
IV	14 (41.18)	8(17.02)		
LAEF%	34.28±3.51	39.91±4.01	5.565	< 0.001
LAPEF%	20.28±1.91	26.83±2.14	14.21	< 0.001
LAAEF%	19.34±2.31	19.41±2.34	0.134	0.894
LVEDD (mm)	54.61±2.54	45.28±2.12	17.98	< 0.001
IVST (mm)	11.81±1.13	11.75±1.12	0.237	0.813
LVPM (mm)	11.72±0.57	11.64±0.62	0.593	0.555
LVMI (mg/g)	2.82±0.22	2.23±0.17	60.00	< 0.001

Table 7. Assignment table**.** Hypertension, hyponatremia, high BNP, high ET-1, NYHA classification, LAEF, LAPEF, LVEDD and LVMI were included in the analysis.

Factor	Assignment
Hypertension	Yes =1, No =2
Hyponatremia	Yes =1, No =2
BNP	>519.49$ng\cdot L^{-1}$=1, ≤519.49$ng\cdot L^{-1}$=2
ET-1	>89.37$ng\cdot L^{-1}$=1, ≤89.37$ng\cdot L^{-1}$=2
LAEF	>38.93%=1, ≤38.93%=2
LAPEF	>23.85%=1, ≤23.85%=2
LVEDD	>50.04mm=1, ≤50.04mm=2
LVMI	>2.47mm=1, ≤2.47mm=2
NYHA classification	II ~ III = 1, IV =2

Table 8. Multivariate analysis of poor prognosis in patients with heart failure.

Factor	β	S.E	Wald	OR	95%CI	P
Hypertension	0.223	0.061	3.173	1.231	1.082~1.403	< 0.01
Hyponatremia	0.482	0.031	3.864	1.617	1.019~4.195	0.032
BNP	0.193	0.429	7.194	1.226	1.172~4.391	< 0.01
ET-1	0.343	0.239	2.306	1.421	1.719~6.136	< 0.01
LAEF	-0.619	0.105	6.465	0.542	0.349~0.762	0.022
LAPEF	-0.081	0.155	0.261	0.933	0.681~1.252	0.592
LVEDD	0.042	0.019	5.437	1.039	1.009~1.087	0.021
LVMI	0.161	0.142	1.223	1.169	0.891~1.582	0.251
NYHA classification	0.896	0.051	5.863	2.422	1.364~4.639	0.031

Discussion

Chronic heart failure, one of the common diseases in cardiology, is the end-stage outcome of various cardiac diseases. It mainly characterized by changes in ventricular structure and cardiac pump function, as well as neurohumoral dysfunction and other pathological features (11, 12). As the progress of chronic heart failure, the cardiac pump function gradually declines due to the increase of blood flow resistance caused by the damage of endothelial function (13).

BNP is an active polypeptide secreted by ventricular myocytes, while ET-1 is a vasoactive polypeptide with strong stimulation to vasoconstriction (14, 15). This study aimed to explore the correlation of BNP and ET-1 with cardiac pump function and ventricular remodeling in patients with heart failure. And the results showed that BNP and ET-1 were highly expressed in the serum of patients. At the same time, the related ultrasonic indexes of cardiac pump function and ventricular remodeling were detected. The results found that patients with heart failure showed significantly lower cardiac pump function related indexes (LAEF, LAPEF, LAAEF) but significantly higher ventricular remodeling related indexes (LVEDD, IVST, LVPM and LVMI) than controls. The development of chronic heart failure weakens the cardiac pump function of patients, which in turn increases the burden on ventricles and promotes the synthesis of BNP (16). Therefore, it is clinically believed that changes in BNP expression can evaluate the severity of chronic heart failure (17). A study revealed that elevated ET-1 could increase the expression of various vasoactive substances (18). In addition, another study (19) demonstrated that the expression of ET-1 in patients with heart failure was significantly higher than that in healthy individuals. The above results were consistent with ours.

Then the correlation of BNP and ET-1 with cardiac pump function and ventricular remodeling was further analyzed. The results showed that BNP and ET-1 were negatively correlated with LAEF, LAPEF and LAAEF, and were negatively correlated with LVEDD, IVST, LVPM and LVMI. These suggested that the expressions of BNP and ET-1 reflected the changes in cardiac pump function and ventricular remodeling and evaluated the condition of patients with heart failure. At present, the expression of serum BNP was reported to have a linear relationship with left ventricular end-diastolic pressure and cardiac functional classification. The pathological basis of chronic heart failure is the decrease of cardiac pump function and the deepening of ventricular remodeling. The main manifestation of cardiac pump function decrease is the significant decrease of its ultrasonic indexes (LAEF, LAPEF and LAAEF), and that of the deepening of ventricular remodeling is the increase of its ultrasonic indexes (LVEDD, IVST, LVPM and LVMI). Our results suggested that the increase of BNP and ET-1 was closely related to the decrease of cardiac pump function and the deepening of ventricular remodeling (21-33).

In order to further analyze the correlation between BNP, ET-1 and heart failure, we followed up the patients for 12 months, and divided them into cardiovascular event group and non-cardiovascular event group, and analyzed the influencing factors of cardiovascular events. The results showed that the serum BNP and ET-1 expressions of patients in the cardiovascular event group were significantly higher than those in the non-cardiovascular event group. Moreover, univariate and multivariate analysis indicated that hypertension, hyponatremia, high BNP, high ET-1, NYHA classification, decreased LAEF and increased LVEDD were independent risk factors for adverse cardiovascular events. In recent years, BNP has been recommended as an effective biological indicator for evaluating the prognosis of patients with heart failure, and its expression is considered to be of great value (34, 35). Another study (36) considered hyponatremia to be an independent risk factor for severe heart failure death because patients with heart failure complicated with hyponatremia had a higher in-hospital mortality rate, which was consistent with our conclusion. Besides, our study also suggested that the prognosis of patients with heart failure was related to the decrease of LAEF and the increase of LVEDD. The decreased LAEF represents the decrease of cardiac pump function, and the increased LVEDD represents the deepening of ventricular remodeling, which causes the further aggravation of heart failure in patients, thus leading to poor prognosis (37, 38). There was also a study (39) clearly indicating that LVEDD might be an independent risk factor for cardiac death in patients with heart failure, which was similar to our conclusion.

To sum up, serum BNP and ET-1 are closely related to cardiac pump function and ventricular remodeling in patients with heart failure and can be used as important reference indexes for prognosis evaluation. However, there are also some limitations to this study. Firstly, we did not explore the mechanism of the influence of serum BNP and ET-1 on the cardiac pump function and ventricular remodeling in patients with heart failure, and its internal mechanism was not elaborated either. Secondly, other factors affecting cardiac pump function and ventricular remodeling in patients with heart failure need to be further explored through larger samples and multicenter studies.

Authors' contributions

LQ conceived the study and drafted the manuscript. LQ designed research; XL performed research; YL contributed new reagents and analytic tools; XL analyzed data. All authors read and approved the final manuscript.

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