Association of NT-proBNP and interleukin-17 levels with heart failure in elderly patients

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ABSTRACT. Pro-B-type natriuretic peptide (NT-proBNP) and interleukin-17 (IL-17) are involved in the pathophysiological processes of heart failure; however, the exact role of IL-17 is not clear. We explored the relationship between IL-17 and NT-proBNP, as a clinical parameter, in heart failure. The whole blood IL-17 and NT-proBNP levels and the readmission rates in 70 patients with chronic heart failure class III or IV according to the New York Heart Association and 35 patients with normal heart function (control group) were measured and compared. The left ventricle ejection fractions (LVEFs) and NT-proBNP and IL-17 levels in cardiac functional class III (40.38 ± 4.76%, 7780 ± 6393 pg/mL, 8.65 ± 3.05 pg/mL, respectively) and class IV (31.59 ± 4.31%, 13,704 ± 10,945, 21.10 ± 10.60 pg/mL, respectively) were higher than those in the control group (61.27 ± 5.66%, 420 ± 256 pg/mL, 3.53 ± 2.05

pg/mL, respectively). Compared to the cardiac functional class IV, class III showed significantly higher values for LVEF and NT-proBNP and IL-17 levels ($P < 0.05$). The readmission rates of the patients in cardiac functional class III at 3 and 6 months (15.7 and 34.4%, respectively) and cardiac functional class IV at 3 and 6 months (39.5 and 76.3%, respectively) were significantly higher than those in the control group (0 and 5.7%, respectively) ($P < 0.05$). The NT-proBNP and IL-17 levels increased as the heart function worsened. NT-proBNP and IL-17 may play essential roles in the process of heart failure.

Key words: Congestive heart failure; Interleukin-17; N-terminal pro-brain natriuretic peptide

INTRODUCTION

Heart failure is a global term for the physiological state in which cardiac output is insufficient in meeting the needs of the body and lungs. Heart failure is a common, costly, disabling, and potentially deadly condition (Flavell and Stevenson, 2001). Management of heart failure has been challenging in clinical medicine. It is clear to us that N-terminal pro-brain natriuretic peptide (NT-proBNP) plays a role in the occurrence and progression of heart failure (Lainchbury et al., 2009). NT-proBNP has been widely used as a reliable indicator when evaluating the severity and prognosis of the heart failure patients (Galinier et al., 2013; Luers et al., 2013). Recently, much attention has been paid to the role of the cytokines in the pathogenesis of heart failure. Interlukin-17 (IL-17) is an important cytokine to evaluate the severity and prognosis of heart failure (Milovanovic et al., 2012). Both NT-proBNP and IL-17 are involved in the pathophysiological processes of heart failure; however, the exact functional role of IL-17 in the development of heart failure is not clear. We studied and measured the changes in serum levels of NT-proBNP and IL-17 in senior heart failure patients for further understanding of their roles in the pathogenesis of heart failure.

MATERIAL AND METHODS

Patients

All patients were hospitalized in the People's Hospital of Liaocheng City from January 2011 to August 2012. All patients were diagnosed with heart failure based on medical history, physical exam, electrocardiogram (EKG), chest X-ray, and echocardiogram. In our study, heart failure is defined as systolic dysfunction if the ejection fraction from echocardiogram was less than 45%. We selected 70 patients with heart failure. Based on New York Heart Association (NYHA) heart failure classification, 32 of them were class III and 38 were class IV. In the 70 heart failure patients, there were 40 male and 30 female. Average age of the patients was 73.54 ± 11.5 years old. The etiology included ischemic cardiomyopathy, dilated cardiomyopathy, and hypertensive heart disease. The control group included 35 patients with normal cardiac function (19 male and 16 female, average age 70.75 ± 14.08 years old). There were no significant differences in age and sex between the study group and control group.

Exclusion criteria included: 1) chronic or acute infection; 2) autoimmune disease;

3) unstable angina and acute cardiac infarction within 3 months; 4) active rheumatoid disease within 3 months; 5) congenital heart disease; 6) diabetes mellitus, hyperthyroidism, and other endocrinology disorders; 7) recent use of immunosuppressive medications (e.g. corticosteroids); 8) abnormal hepatic or renal function; 9) cancer; or 10) pregnancy. Data collected included demographic information (age, gender, ethnic background, occupation, diet, etc.), medical history, physical exam, laboratory tests, EKG, chest X-ray, echocardiogram, and medication use.

Blood sample collection

Venous blood samples were collected at 6 am after fasting. EDTA (Beijing Solarbio Science and Technology Co., Ltd., Beijing, China) was added to samples to prevent coagulation. The samples were then processed for serum levels of NT-proBNP and IL-17.

Detection of NT-proBNP and IL-17

NT-proBNP was measured with AQT90 FLEX immunity analyzer and relative agents (Radiometer Medical APS, Denmark). IL-17 was measured with enzyme-linked immunosorbent assay (ELISA) kit (4A Biotech Co., Ltd., Beijing, China) and enzyme mark instrument (PerkinElmer Inc., USA).

Cardiac structure and left ventricle ejection fraction (LVEF)

The cardiac structure and LVEF were evaluated with a Nemio 30 color ultrasound machine (Toshiba, Shanghai, China) by a physician sonographer.

Statistical analysis

The measured data are reported as means ± standard deviation and analyzed by the SPSS13.0 software (Chicago, IL, USA). The comparison between the two groups was analyzed with the Student *t*-test, and multiple group comparisons were analyzed with ANOVA. Pairwise comparisons were performed with Bonferroni and least significant difference methods. Counted data were compared using chi-square test, and correlations were analyzed by linear correlation analysis. The difference was considered statistically significant when $P < 0.05$.

RESULTS

Comparison of LVEF

As shown in Table 1, the LVEFs of the patients in cardiac functional class III (40.38 ± 4.76%) and IV (31.59 ± 4.31%) were lower than those in the control group (61.27 ± 5.66%), while the LVEF in cardiac functional class III was significantly higher than that in class IV ($P < 0.05$).

Table 1. Comparison of LVEF among different groups of heart function.

Groups	Cases	LVEF (%)
Control	35	61.27 ± 5.66
Cardiac functional class III (NYHA)	32	40.38 ± 4.76△
Cardiac functional class IV (NYHA)	38	31.59 ± 4.31△■

△P < 0.05 compared to the control group; ■P < 0.05 compared to cardiac functional class III.

Comparison of NT-proBNP and IL-17

The levels of NT-proBNP and IL-17 elevated as cardiac function worsened and positively correlated with the degree of heart failure (Table 2). NT-proBNP levels in cardiac functional class III (7780 ± 6393 pg/mL) and IV (13,704 ± 10,945 pg/mL) were higher than those in the control group (420 ± 256 pg/mL), while the NT-proBNP levels in cardiac functional class III were significantly higher than those in cardiac functional class IV (P < 0.05). Similarly, IL-17 levels in cardiac functional class III (8.65 ± 3.05 pg/mL) and IV (21.10 ± 10.60 pg/mL) were higher than those in the control group (3.53 ± 2.05), while the IL-17 levels in cardiac functional class III were significantly higher than those in cardiac functional class IV (P < 0.05).

Table 2. Comparison of NT-proBNP and IL-17 among different groups of heart function.

Groups	Cases	NT-proBNP (pg/mL)	IL-17 (pg/mL)
Control	35	420 ± 256	3.53 ± 2.05
Cardiac functional class III (NYHA)	32	7,780 ± 6,393▲	8.65 ± 3.05▲
Cardiac functional class IV (NYHA)	38	13,704 ± 10,945▲■	21.10 ± 10.60▲■

▲P < 0.05 compared to the control group, ■P < 0.05 compared to cardiac functional class III.

Readmission rate

The readmission rates of the patients in cardiac functional class III at 3 months (15.7%; N = 5) and 6 months (34.4%; N = 11) were significantly higher than those in the control group (3 months = 0; 6 months = 5.7%; N = 2) (Table 3; P < 0.05). The readmission rates of the patients in cardiac functional class IV at 3 months (39.5%; N = 15) and 6 months (76.3%; N = 29) were significantly higher than those in the control group (3 months = 0; 6 months = 5.7%; N = 2) (P < 0.05). The readmission rates positively correlated with the NT-proBNP and IL-17 levels (P < 0.05).

Table 3. Comparison of the readmission rate among different groups of heart function.

Groups	Cases	NT-proBNP (pg/mL)	IL-17 (pg/mL)	Readmission rate at 3 months [% (N)]	Readmission rate at 6 months [% (N)]
Control	35	420 ± 256	3.53 ± 2.05	0	5.7% (2)
Cardiac functional class III (NYHA)	32	7,780 ± 6,393	8.65 ± 3.05	15.7% (5)▲	34.4% (11)▲
Cardiac functional class IV (NYHA)	38	13,704 ± 10,945	21.1 ± 10.60	39.5% (15)▲□	76.3% (29)▲□

▲P < 0.05 compared to the control group, □P < 0.05 compared to cardiac functional class III.

DISCUSSION

Heart failure is the end stage of all cardiac diseases and it is one of the leading causes of death and disability in humans. During the pathophysiological changes of chronic heart

failure, the excessive activation of nerve roots and humoral factors, such as the sympathetic nervous system, renin-angiotensin-aldosterone system (RAAS), BNP, antidiuretic hormone (ADH), and endothelin (ET), constitute an important mechanism in the occurrence and development of heart failure (Mann and Young, 1994; Sanghi et al., 2005; Palazzuoli et al., 2012; Lang and Struthers, 2013; Scollan et al., 2013; Skiendzielewski and Werner, 2014). In recent years, BNP has been seen as a natural antagonist in the RASS. Substantial evidence indicates that serum BNP levels are elevated with worsening heart failure (Niu et al., 2014). BNP plays a role as an antagonist in the RASS and the sympathetic nervous system (SNS) in both peripheral and central nervous systems to maintain fluid and electrolyte balance (Cameron and Ellmers, 2003). In addition, BNP, as an anti-fibrosis factor from the cardiac ventricle, can inhibit the proliferation of vascular smooth muscle cells, mesangial cells, and fibroblasts. Thus, BNP can regulate ventricular remodeling locally. NT-proBNP is the amino-terminal fragment of the B-type natriuretic peptide prohormone. Compared with BNP, NT-proBNP is an inactive amino-terminal fragment with a long half-life (60-120 min). It is stable, sensitive, and reproducible, and it has become an important indicator in the clinical diagnosis of heart failure.

IL-17 has been recently identified as a cellular inflammatory cytokine. IL-17 can inhibit the reconstruction of the heart by myocardial fibrosis through dissolution, breakage, and reduced synthesis of intercellular collagen by activation of the matrix metalloproteinases (MMPs). Previous studies showed that lower serum IL-17 levels helped to improve cardiac function in heart failure patients. Many scholars believe that the IL-17 plays a role through two pathways: the nuclear factor (NF)-κB-DNA pathway and mitogen-activated protein (MAP) kinase pathway. In addition, there could be a role of IL-17 through the tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6), NF-κB-inducing kinase (NIK), IκB kinase (IKK)-α, or JAK-STAT pathways (Schwandner et al., 2000; Wuyts et al., 2005)

Research using animal models showed that IL-17 caused damage to the heart through the following mechanisms: 1) IL-17 can exert direct toxic effects on myocardial cells; 2) IL-17 enhances nitric oxide synthase (iNOS) activity, which causes increased release of NO by the vascular endothelium and damage to the vascular endothelium (Krstić et al., 2013); 3) IL-17 reduces myocardial intracellular calcium levels by activating the nerve myelin sheath esterase and triggering a series of inflammatory reactions (Hu et al., 2014); and 4) IL-17 can induce the expression, increase the secretion, and enhance the activity of inflammatory factors such as IL-6 and IL-1β (Lee et al., 2009). This eventually leads to cardiac hypertrophy, vascular endothelial damage, increased cellular necrosis, accelerated myocardial apoptosis, and extracellular matrix remodeling, thus accelerating the process of heart failure (Eid et al., 2009).

It has been reported that in chronic heart failure, there was no significant increase in IL-17 levels in class I and II heart failure but there was a significant increase in IL-17 levels in class III and IV heart failure. This is consistent with the findings in our present study. Heart failure contributes to the production of TNF-α and IL-17 (and vice versa), which constitutes a vicious cycle of cardiac remodeling. Studies have shown that there is a change in the signal amplification cascade of IL-17/gp130-JAK-STAT in patients with end-stage heart failure (Podewski et al., 2003). After ischemia reperfusion, injection of IL-17/soluble IL-17R complex prevents myocardial apoptosis and reduces the size of the myocardial infarct. This indicates the protective effect of IL-17 (Matsushita et al., 2005).

Our study is consistent with the reports of Li et al. (2010), which show that the ratio of Th17/CD4 + T cells in peripheral blood was significantly higher in patients with chronic heart failure class III and IV as compared to the patients with chronic heart failure class I and II. In

our study, there was a parallel increase in the levels of NT-proBNP and IL-17 in patients with heart failure, which may indicate that both are involved in the development of heart failure. Furthermore, the levels of both factors increased as the degree of heart failure increased. BNP has become a reliable indicator to assess the prognosis and degree of heart failure and IL-17 can be used to assess the prognosis and degree of heart failure as well. Further studies with expanded sample size are needed to address the specific relationship between NT-proBNP and IL-17 and the exact mechanism underlying heart failure involving serum IL-17 levels.

Conflicts of interest

The authors declare no conflict of interest.

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