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Serum Levels of Inflammatory Cytokines and Expression of BCL2 and BAX mRNA in Peripheral Blood Mononuclear Cells and in Patients with Chronic Heart Failure

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Background: This study investigated the expression of the BCL2 and BAX mRNA, inflammatory cytokines, interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α), and cardiac function in patients with chronic heart failure (CHF). The New York Heart Association (NYHA) Functional Classification and measurement of the left ventricular ejection fraction (LVEF) evaluated cardiac function.

Material/Methods: Patients with CHF (n=60) due to coronary heart disease, hypertensive heart disease, and cardiomyopathy, and healthy controls (n=30) were studied. Enzyme-linked immunosorbent assay (ELISA) measured serum levels of IL-1β, IL-6, and TNF-α. Quantitative reverse transcription polymerase chain reaction (qRT-PCR) detected mRNA expression of BCL2 and BAX in peripheral blood mononuclear cells (PBMCs). Color Doppler ultrasound measured the LVEF, and the NYHA classification of CHF was used.

Results: In patients with CHF, levels of IL-1β, IL-6 and TNF-α, and mRNA expression of BAX were significantly increased compared with the control group ($p<0.01$); BCL2 mRNA level was significantly lower ($p<0.01$). There were no significant differences in the expression levels of inflammatory cytokines, or BCL2 or BAX mRNA in patients with CHF due to coronary heart disease, hypertensive heart disease, or cardiomyopathy. Expression levels of IL-1β, IL-6, TNF-α, and BAX mRNA were significantly associated with the degree of CHF. Cardiac function was negatively correlated with LVEF ($p<0.05$). Expression levels of BCL2 mRNA level were negatively correlated with cardiac function ($p<0.05$), and positively correlated with LVEF ($p<0.05$).

Conclusions: Levels of IL-1β, IL-6, TNF-α, and BAX mRNA were negatively correlated with cardiac function, and BCL2 mRNA expression was positively associated with CHF.

MeSH Keywords: Genes, bcl-2 • Heart Function Tests • Propafenone

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Background

Worldwide, the prevalence of chronic heart failure (CHF) has increased with an increasingly aging population, and the morbidity and mortality from CHF remain high, with a 5-year survival rate that is similar to that of the malignant tumors [1]. Current approaches to the treatment of CHF may vary in efficacy, resulting in poor quality if life, as well as high rates of re-hospitalization and increased medical costs [2].

CHF has been reported to be due to an abnormality in the neurohormonal system, resulting in damage to endothelial cells, infiltration of inflammatory cells, and vascular damage that lead to the progression of CHF [3]. Recent studies have shown that the inflammatory cytokines, interleukin-1β (IL-1β), IL-6, and tumor necrosis factor (TNF)-α, are increased in the peripheral blood of patients with CHF [4,5]. Most patients with progressive cardiac disease, including coronary heart disease, hypertensive heart disease, and cardiomyopathy will develop CHF, and may eventually die from CHF.

It has previously been reported that apoptosis of myocardial cells is associated with the development and progression of CHF and with ventricular remodeling [6]. Apoptosis reduces the number of myocardial cells, reducing myocardial contractility, which supports the role of apoptosis in the development and progression of CHF [7]. The pathogenesis of CHF is complex and also involves several inflammatory cytokines, which can cause apoptosis of cardiac myocytes, resulting in ventricular remodeling and reduced myocardial contractility [8].

Although the roles of inflammatory cytokines and myocardial cell apoptosis in the pathogenesis and progression of CHF have been studied, their relationship with cardiac function in patients with CHF remains poorly understood. Therefore, the aim of this study was to investigate the expression of the BCL2 and BAX mRNA and the inflammatory cytokines, interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α), and cardiac function in patients with chronic heart failure (CHF) due to coronary heart disease, hypertensive heart disease, and cardiomyopathy. Cardiac function was evaluated using the New York Heart Association (NYHA) Functional Classification, and measurement of the left ventricular ejection fraction (LVEF).

Material and Methods

Ethical approval

This study was approved by the Clinical Ethics Committee of the Bethune International Peace Hospital (14th March 2017), and all participants and their family signed written informed consents.

Patients

Sixty patients with chronic heart failure (CHF) patients were included in the study, who were admitted to the cardiac department of our hospital between March 2014 and December 2016. In the CHF patient group, there were 32 men and 28 women, aged between 53–72 years. Among the 60 patients with CHF, 28 patients had coronary heart disease, 15 patients had hypertensive heart disease, and 17 patients had cardiomyopathy.

The inclusion criteria for the CHF patient group included patients with chronic heart failure due to idiopathic dilated cardiomyopathy, valvular heart disease or ischemic (coronary) heart disease (IHD), who had been treated for at least three months. Patients in the CHF group had the American College of Cardiology/American Heart Association (ACC/AHA) stage C, or New York Heart Association (NYHA) functional class I–IV heart failure, and were clinically stable on the day of recruitment to the study, as determined by a cardiologist with expertise in heart failure.

The control group included 30 age-matched and gender-matched healthy subjects who attended the hospital for routine medical examinations, and who had no cardiac abnormalities. The control group included 16 men and 14 women aged between 49–70 years.

Reagents

Ficoll-Paque PLUS lymphocyte separation medium was purchased from GE Healthcare (Bethesda, MD, USA). Roswell Park Memorial Institute-1640 (RPMI-1640) culture medium and fetal bovine serum (FBS) were purchased from HyClone Laboratories (Logan, UT, USA). Enzyme-linked immunosorbent assay (ELISA) kits for interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α) were obtained from Beyotime Biotech Institute (Nantong, China). Primers for the quantitative reverse transcription polymerase chain reaction (qRT-PCR) were synthesized by Takara Bioengineering Co., Ltd. (Dalian, China). The TRIzol kit and the qRT-PCR kit were purchased from Invitrogen (Carlsbad, CA, USA).

Enzyme-linked immunosorbent assay (ELISA) for the detection of serum inflammatory cytokines

Morning fasting venous blood samples were taken (15 mL) from all study participants, placed in a water bath (37°C) for 10 min followed by centrifugation to collect the serum. An ELISA kit was used to measure the serum levels of IL-1β, IL-6, and TNF-α, according to the manufacturer's instructions.

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Table 1. The primer sequences used in the quantitative reverse transcription polymerase chain reaction (qRT-PCR).

Gene	Primer	Sequence
BAX	Forward	5'-CCCACCAGCTCTGAACAGTTC-3'
	Reverse	5'-CCAGCCACAAAGATGGTCAC-3'
BCL2	Forward	5'-CTTCGCCGAGATGTCCAG-3'
	Reverse	5'-GGCTCAGATAGGCACCCA-3'
GAPDH	Forward	5'-GCACCGTCAAGGCTGAGAAC-3'
	Reverse	5'-TGGTGAAGACGCCAGTGGA-3'

Detection of BAX and BCL2 mRNA expression by quantitative reverse transcription polymerase chain reaction (qRT-PCR)

Morning fasting venous blood samples were taken (15 mL) from all study participants followed by isolation of peripheral blood mononuclear cells (PBMCs) using Ficoll-Paque PLUS lymphocyte separation medium. PBMCs were cultured in RPMI-1640 medium supplemented with 10% FBS for 2 h (37°C and 5% CO_2). The cell suspensions were removed, and the PBMCs that were adherent to the culture plates continued to grow until they reached confluence, and the medium was replaced every 24 hours.

PBMCs were then digested and collected for extraction of total RNA with TRIzol reagent. Then, cDNA was synthesized through reverse transcription, which served as the template for qRT-PCR using the following conditions: 95°C for 3 min; 30 cycles of 95°C for 30 s; and 54°C for 30 s; and 72°C for 1 min. The primer sequences for BAX, BCL2, and GAPDH are shown in Table 1. GAPDH was used as an internal reference control. The Ct value was used to calculate the relative expression of BAX and BCL2 mRNA using the $2^{-\Delta Ct}$ method.

Evaluation of cardiac function using the NYHA and LVEF

The cardiac function of 60 patients with CHF was classified according to the criteria of the New York Heart Association (NYHA), and the left ventricular ejection fraction (LVEF) was determined by color Doppler ultrasound using the HP SONOS 5500 system (Philips, Amsterdam, the Netherlands), as previously described [9].

Statistical analysis

All experimental data were analyzed with the Statistical Product and Service Solutions (SPSS) version 13.0 software (IBM Corp, Armonk, NY, USA). Measurement data were presented as the mean ± standard deviation (SD). Student's t-test was used to compare the difference between the two study groups. The Pearson correlation coefficient (Pearson's r) was performed for correlation analysis. A P-value <0.05 was considered to be statistically significant.

Results

Comparison of the clinical characteristics of the patient groups with chronic heart failure (CHF)

Sixty patients with chronic heart failure (CHF) due to ischemic (coronary) heart disease, hypertensive heart disease, and cardiomyopathy, and 30 healthy controls were studied. As shown in Table 2, the age and the number of patients who smoked in the ischemic (coronary) heart disease group were significantly higher compared with patients with CHF in the hypertensive heart disease group and the cardiomyopathy group ($p<0.05$). The number of patients with hypertension in the hypertensive heart disease group was significantly higher compared with the ischemic (coronary) heart disease group and the cardiomyopathy group ($p<0.05$). In the cardiomyopathy group,

Table 2. Comparison of the demographic characteristics of the patients with coronary heart disease, hypertensive heart disease, and cardiomyopathy.

General clinical material	Coronary heart disease	Hypertensive heart disease	Cardiomyopathy
Case (n)	28	15	17
Age (years)	68.2±5.5	57.4±4.2*	60.7±4.4*
Sex (Male/Female)	16/12	9/6	7/10
Smoking (n,%)	15 (53.6)	5 (33.3)**	6 (35.3)**
Hypertension (n,%)	8 (28.6)	15 (100)**	2 (11.76)**##
DM (n,%)	9 (32.1)	5 (33.33)	2 (11.76)**##

* $p<0.05$ compared with the coronary heart disease group; # $p<0.05$, ** $p<0.01$ compared with the hypertensive heart disease group. DM – diabetes mellitus.

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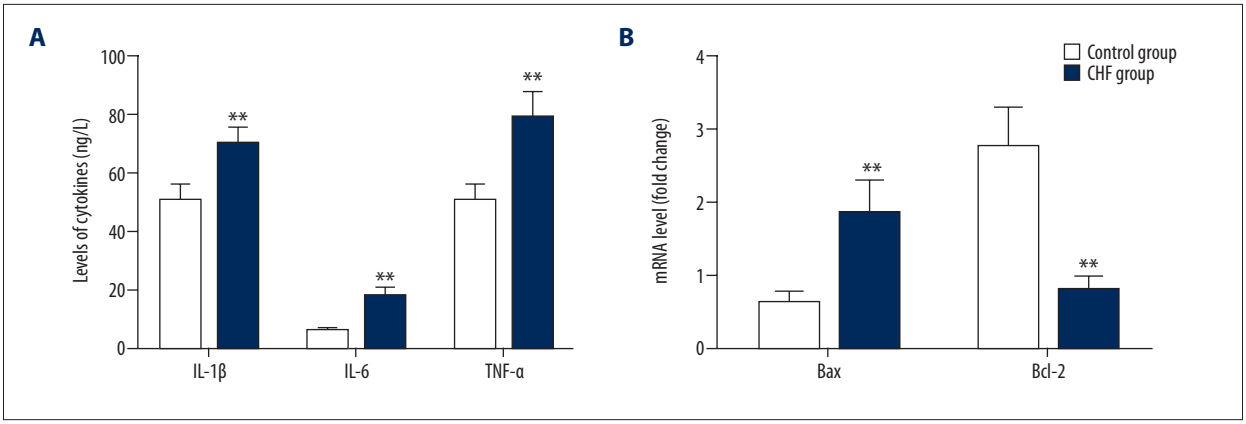

Figure 1. Bar graphs show the levels of inflammatory cytokines and mRNA fold-change in BAX and BCL2 in patients in the chronic heart failure (CHF) patient group compared with the control group. (**A**) Levels of inflammatory cytokines, interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α) (ng/L) in the chronic heart failure (CHF) patient group compared with the control group. (**B**) mRNA fold-change of BAX and BCL2 in the CHF patient group compared with the control group. Compared with the control group, ** p<0.01.

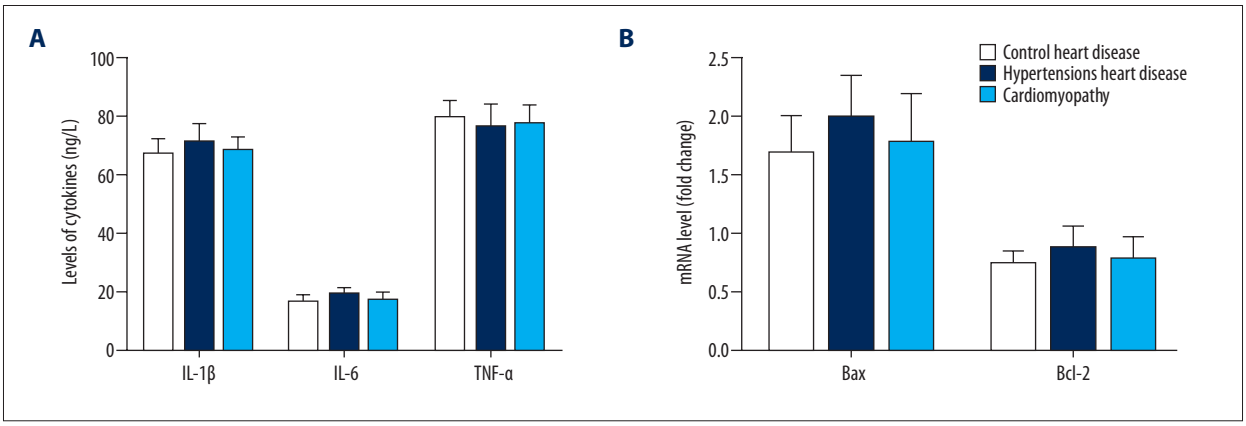

Figure 2. Bar graphs show the levels of inflammatory cytokines and BAX and BCL2 mRNA in patients with coronary heart disease, hypertensive heart disease, and cardiomyopathy compared with the control group. (**A**) Levels of the inflammatory cytokines, interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α) (ng/L) in patients with coronary heart disease, hypertensive heart disease, and cardiomyopathy compared with the control group. (**B**) mRNA fold-change of BAX and BCL2 in patients with coronary heart disease, hypertensive heart disease, and cardiomyopathy compared with the control group. Compared with the control group, ** p<0.01.

the number of patients with hypertension and with diabetes mellitus (DM) were significantly more than that those in the ischemic (coronary) heart disease group and the hypertensive heart disease group (p<0.05).

Increased levels of interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α) and BAX mRNA and decreased BCL2 mRNA in patients with CHF

As shown in Figure 1, the serum levels of the inflammatory cytokines, IL-1β, IL-6, and TNF-α, in the patients in the CHF group were significantly higher compared with those in the control group (p<0.01) (Figure 1A). In the CHF patient group, the expression levels of BAX mRNA in the peripheral blood mononuclear cells (PBMCs) was significantly higher compared with the control group (p<0.01). However, the expression level of BCL2 mRNA was significantly decreased when compared with the control group (p<0.01) (Figure 1B).

Comparison of the mRNA expression levels of BAX and BCL2 and inflammatory cytokines in patients with CHF due to coronary heart disease, hypertensive heart disease, or cardiomyopathy

There were no statistically significant differences in the levels of inflammatory cytokines, IL-1β, IL-6, and TNF-α, in patients with CHF due to coronary heart disease, hypertensive heart disease, or cardiomyopathy (p>0.05) (Figure 2A). Between the

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Table 3. Correlation between the New York Heart Association (NYHA) Functional Classification, inflammatory cytokines, and mRNA expression of BAX and BCL2.

Parameter	NYHA	
	r-Value	p-Value
IL-1β	0.482	0.031
IL-6	0.477	0.027
TNF-α	0.502	0.035
BAX	0.536	0.041
BCL2	–0.494	0.039

Table 4. Correlation between the left ventricular ejection fraction (LVEF) and inflammatory cytokines and mRNA expression of BAX and BCL2.

Parameter	LVEF	
	r-Value	p-Value
IL-1β	–0.417	0.034
IL-6	–0.478	0.029
TNF-α	–0.523	0.037
BAX mRNA	–0.446	0.043
BCL2 mRNA	0.497	0.035

different causes of CHF, there were no significant differences in the expression levels of BAX or BCL2 mRNA ($p>0.05$) (Figure 2B).

Comparison of the expression levels of BAX and BCL2 mRNA and inflammatory cytokines and cardiac function in patients with CHF

In the peripheral blood of patients with CHF, the serum levels of the inflammatory cytokines, IL-1β, IL-6, and TNF-α, were positively correlated with the New York Heart Association (NYHA) classification of cardiac function ($p<0.05$) (Table 3). A positive correlation was found between the expression levels of BAX mRNA with the NYHA class of cardiac function ($p<0.05$). However, the expression levels of BCL2 mRNA were negatively correlated with the NYHA class of cardiac function ($p<0.05$).

Comparison between the left ventricular ejection fraction (LVEF) and inflammatory cytokines and the expression levels of BAX and BCL2 mRNA

In the peripheral blood of patients with CHF, the levels of the inflammatory cytokines, IL-1β, IL-6, and TNF-α, were negatively correlated with the left ventricular ejection fraction (LVEF) ($p<0.01$) (Table 4). A positive correlation was found between the expression levels of BAX mRNA and the LVEF ($p<0.01$). The expression levels of BCL2 mRNA were positively correlated with the LVEF ($p<0.01$).

Discussion

Chronic heart failure (CHF) results from diseases that damage the heart or that affect its physiological function and is associated with significant morbidity and mortality [10]. Inflammatory cytokines, including interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α), have been shown to be involved in the development and progression of CHF [11,12]. An increase in the expression of IL-1β has been shown to increase the levels of Na^+-K^+-ATPase in myocardial cells, resulting in cardiac myocyte hypertrophy and phenotypic variation, including a negative inotropic effect [13]. IL-6 has been shown to upregulate the expression of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) in cardiac myocytes, leading to the development of CHF [14]. Also, increased levels of IL-6 are accompanied with a decline in autonomic neural function of patients with CHF [15]. TNF-α has been shown to promote the synthesis of protein and inhibit its degradation, resulting in an increased production of actin, which can contribute to cardiac myocyte hypertrophy, thinning of the left ventricular wall, dilation of the left ventricle, as well as an increase in ventricular end-diastolic diameter [16]. Increased expression of TNF-α it is also associated with the apoptosis of cardiac myocytes, resulting in myocyte loss and thinning of the wall of the ventricle, which reduces left ventricular function [17].

Recent studies have shown that apoptosis in cardiac myocytes is one of the major contributing factors to the pathogenesis of CHF, and is closely associated with dysfunction of left ventricular systole and remodeling of the left ventricle [18]. Heart failure represents a decline in the systolic function of the left ventricle caused by the reduction of cardiac myocytes due to apoptosis, which leads to ventricular remodeling [19]. Because isolation of cardiac myocytes is difficult and complicated to perform, peripheral blood mononuclear cells (PBMCs) were isolated, and apoptosis of PBMCs in patients with CHF was studied. PBMCs have previously been shown to be pluripotential progenitor cells that can differentiate into blood cells, cardiac myogenic cells, and endothelial cells when under appropriate conditions [20]. Also, a recent study showed that highly purified human cardiac myocytes could be generated from PBMC-derived pluripotential stem cells [21]. Therefore, apoptosis of PBMCs might indirectly affect the function of cardiac myocytes in patients with CHF.

The Bcl-2 family of proteins is critical to cell apoptosis and includes Bcl-2 that has anti-apoptotic effects, and Bax that has

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pro-apoptotic effects [22]. The Bcl-2 protein is mainly located on the mitochondrial membrane, nuclear membrane and smooth endoplasmic reticulum in cells, and can inhibit cell apoptosis from a variety of causes. The Bax protein is mainly distributed in the cytoplasm and migrates from the cytoplasm to the mitochondrial membrane once the cells receive apoptotic signals, leading to damage to the mitochondrial membrane, and apoptosis [23]. It has previously been reported that in the cardiac myocytes of patients with CHF, the expression of the Bcl-2 protein was decreased, while the expression of Bax protein was increased, resulting in a decreased Bcl-2: Bax ratio, indicating that cell apoptosis was increased in cardiac myocytes [24]. Increased expression of inflammatory cytokines has also previously been reported to inhibit myocardial contractility, induce left ventricular remodeling, and activate the signaling transduction required for apoptosis in cardiac myocytes [25].

The findings of the present study are supported by the findings from previously published studies on inflammatory cytokines and apoptosis in heart failure. This study showed that in patients with CHF, the levels of inflammatory cytokines, including serum levels of IL-1β, IL-6, and TNF-α, and PBMC mRNA expression of BAX were significantly higher compared with the control group. However, the mRNA expression of BCL2 was significantly lower in patients with CHF than that in the control group. Also, serum levels of IL-1β, IL-6, TNF-α, and BAX mRNA levels were positively correlated with the New York Heart Association (NYHA) classification of cardiac function and were negatively correlated with the left ventricular ejection fraction (LVEF). However, the level of BCL2 mRNA showed a negative correlation with the NYHA classification of cardiac function and the LVEF. Because this study was limited by the small number of study participants from a single center, future large-scale, multicenter, controlled clinical studies are required to confirm the findings.

Conclusions

In patients with chronic heart failure (CHF), serum levels of the inflammatory cytokines, interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α), and the expression levels of BAX mRNA in peripheral blood mononuclear cells (PBMCs) were negatively correlated with cardiac function. The expression levels of BCL2 mRNA in PBMCs were positively correlated with cardiac function. However, the mechanisms of the PBMC-associated pro-apoptotic changes in the pathogenesis of impaired cardiac function in CHF remains unclear and requires further study.

Conflict of interest

None.

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