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Original Article

The protective role of valsartan in the myocardial injury of diabetic rats induced by herceptin

Yuetao Xie[1], Jinli Zhang[2] and Guang Liu[2]

[1]Cardiovascular Department, Hebei General Hospital, Shi Jiazhuang, Hebei Province, China
[2]Cardiovascular Department, The Fourth Hospital of Hebei Medical University, Shi Jiazhuang, Hebei Province, China

Correspondence
Guang Liu
Cardiovascular Department, The fourth hospital of Hebei Medical University, Shi Jiazhuang, Hebei Province, China
E-mail: 47126458@qq.com

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Correspondence
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Abstract

Objective: To evaluate the protective role of valsartan in the myocardial injury of diabetic rats induced by herceptin.

Method: 40 Sprague Dawley (SD) rats were randomly divided into control group and treatment group, 20 in each group. All the rats were faded with high sugar and high fat diet in 4 weeks, and then were given streptozotocin (STZ) by intraperitoneal injection in dose of 25mg/kg, fasting blood glucose (FBG) ≥ 16.7mmol/L as a standard of type 2 diabetes model. Two groups were given herceptin by intraperitoneal injection, 12mg/kg in the first day and then 6mg/kg in the following 6 days, but the treatment group was given valsartan by gavage before herceptin injection in dose of 10mg/kg one day, the control group was given the same dose of saline by gavage. The serum BNP were measured, echocardiogram was performed to evaluate the cardiac function before herceptin injection and after 4 weeks.

Results: After 4 weeks the BNP, LVEDD, LVESD of the control group were larger than the treatment group, and the EF were smaller, and they were statistically different.

Conclusion: Valsartan can alleviate myocardial injury diabetic rats induced by herceptin.

Introduction

With the economic development, the prevalence of breast cancer in China is a gradually rising trend [1], which has become the top place of female malignant tumors, and the onset age is younger [2].Current treatment for breast cancer includes multiple methods, surgery, radiotherapy, chemotherapy, and molecular targeted therapy, etc. In 1998 trastuzumab (Trade name, herceptin) was approved by FDA (Food and Drug Administration, USA) in treatment of breast cancer with over expression of Her-2,greatly reduced the recurrence rate and mortality of breast cancer, currently, trastuzumab has become the main target drug for the treatment of breast cancer. Morris [3] reported that patients may have asymptomatic heart failure or symptomatic heart failure after using trastuzumab. In this study, we used herceptin to replicate the heart failure model of diabetic rats and added valsartan, the objective was to investigate the effect of angiotensin II receptor antagonist on heart failure in diabetic rats induced by herceptin.

Materials and methods

Animals

Forty 8-week-old male SD rats were selected, body mass 150-230g, provided by the laboratory animal center of Hebei Medical University, production license No SCXK (Hebei) 2008-1-003.

Experimental reagents and instruments

High sugar and high fat feed (basic feed 83.25%, lard 10%, sucrose 5%, cholesterol 1.5%, 0.25% Sodium cholate) was purhased from Beijing boai port business center, Streptozotocin (STZ) was supported by SIGMA USA, trastuzumab (dose of 440 mg, batch number S20110007) was supported by Shanghai Roche Pharmaceuticals, valsartan was supported by Beijing Novartis Pharma LTD. BNP test kit was purchased from Nanjing Jiancheng Bioengineering Research Institute of China, Philips Sonos 7500 ultrasound was supported by Hebei Medical University, probe frequency 6-15MHZ.

Methods

40 rats were feeding in high sugar and high fat diet for 4 weeks, fasting for 10 hours, then given STZ by intraperitoneal injection in a dose of 25mg/kg, tail vein blood was collected, the success of diabetes model was established by fasting blood glucose (16.7mmol/L) as the standard. They were randomly divided into control group (n=20) and treatment group (n=20).The control group was given herceptin

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by intraperitoneal injection in a dose of 12mg/kg in the first day, and 6mg/kg in the following 6 days. The treatment group was given the same dose herceptin as the control group, but valsartan was administered by gavage once a day on the first day in a dose of 10mg/kg for 4 weeks, the control group was gavaged with the same dose of normal saline for 4 weeks. The content of BNP in serum was measured before and 4 weeks after administration, and echocardiography was performed at the above time to measure LVEDD, LVESD and EF.

Statistical analysis

Statistical analysis were performed using SPSS software (version 18.0).Data were expressed as the mean ± SD, Comparisons between groups were made by variance analysis, $P < 0.05$ was considered to indicated a statistically significant difference.

Results

After administration, both groups of rats showed poor mental state, less activity and decreased appetite. At 4 weeks, the spirit of the treatment group was better than that of the control group, more activity and flexible response to being grabbed. There were no deaths in both groups.

There was no significant difference in BNP between the two groups before administration, $P > 0.05$; At 4 weeks, BNP in the control group was higher than that in the treatment group ($P < 0.05$) (Table 1).

Table 1. *Serum BNP content in two groups*
**Compared with the control group, $P < 0.05$; ≥ compared with that before administration in the same group, $P < 0.05$.*

		BNP (pg/ml)
Control group	Before administration	68.32 ± 7.66
	4 weeks after administration	202.46±1.79Δ
Treatment group	Before administration	70.14±5.62
	4 weeks after administration	155.38±8.26*Δ

There was no significant difference in LVEDD, LVESD and EF between the two groups before administration, $P > 0.05$; After 4 weeks, LVEDD and LVESD in the control group increased compared with the treatment group, $P < 0.05$, and EF decreased compared with the treatment group, $P < 0.05$. (Table 2).

Disscusion

Since 1998, when FDA approved herceptin for metastatic and early breast cancer, more and more adverse reactions and related risk factors related to herceptin have been studied. The most important cardiac toxicity event is the decrease of left ventricular ejection fraction (LVEF) without symptoms, a meta-analysis [4] summarizes the major clinical trials of breast cancer patients with cardiotoxicity associated with herceptin, the probability of asymptomatic LVEF decline was 7.5%,at the same time, it is also confirmed that high age, high blood pressure and low LVEF before treatment are the high risk factors of cardiac toxicity in breast cancer patients receiving herceptin treatment. Some studies abroad found that the probability of symptomatic congestive heart failure with Herceptin was 0.4% - 3.8% [5]. However, it is generally believed that the cardiotoxic events caused by herceptin are reversible, MD Anderson's research [6] shows that the cardiac function of patients treated with long-term herceptin was recovered. In this study, the heart failure model was successfully reproduced by injecting herceptin into rats by referring to some domestic and foreign animal experiments and related doses, and there was no death in 4 weeks, indicating that it was consistent with some animal experiments abroad [7], which also shows the relative safety of single drug herceptin.

The basic pathophysiological mechanism of heart failure is myocardial remodeling, and long-term excitation and excessive secretion of neuroendocrine are the main causes of myocardial remodeling. It has been proved that the concentration of serum B-type natriuretic peptide (BNP) is positively correlated with the severity of heart failure [8], which is an important index for the diagnosis of heart failure [9].This study found that the content of BNP in the control group and the treatment group was significantly higher than that before administration, and there was significant difference, suggesting that rats occurred heart failure; The comparison between the two groups was

Table 2. *Cardiac ultrasound results of the two groups*
**Compared with the control group, $P < 0.05$; ≥ compared with that before administration in the same group, $P < 0.05$.*

		LVEDD(mm)	LVESD(mm)	EF(%)
Control group	Before administration	5.99 ± 0.46	2.60 ± 0.51	88.24 ± 2.18
	4 weeks after administration	6.71 ± 0.45Δ	3.59 ± 0.62Δ	80.12 ± 1.56Δ
Treatment group	Before administration	5.93 ± 0.32	2.58 ± 0.67	89.01 ± 1.87
	4 weeks after administration	6.22 ± 0.34*	3.32 ± 0.44*	84.22 ± 1.09*

significantly lower in the treatment group than in the control group, suggesting that valsartan has a protective effect on rats with heart failure.

Epidemiological data show that diabetes is an independent risk factor for breast cancer [10,11]. In diabetes, the sympathetic activity of the myocardium is increased, and the RAS system is overactivated, Zhang [12] and Watanabe [13] propose that, angiotensin II activates reduced nicotinamide adenine dinucleotide phosphate oxidase by binding to angiotensin I receptor, promotes the production of reactive oxygen species and causes myocardial oxidative damage. In Wu's research [14] ,valsartan can block the effect of angiotensin II and inhibit high glucose induced oxidative stress and cardiomyocyte apoptosis, so as to protect myocardium. In this study, EF in the treatment group was higher than that in the control group, suggesting that valsartan may block RAS system, reduce oxidative stress response and improve cardiac function.

Referring to the experience of Shen Xiao Qian et al. [15], this study replicated the cardiac dysfunction model of diabetic rats, and revealed the myocardial protective effect of valsartan through relevant laboratory tests and echocardiographic results, which provided a new idea for clinical application of heart failure caused by Herceptin in diabetic patients.

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