



# Changes in clinical biochemical indexes of patients with heart failure with preserved ejection fraction or patients with hypertensive heart disease before and after treadmill exercise

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**Background:** The incidence of hypertension is continuously increasing. This study aimed to investigate the changes in clinical biochemical indexes of patients with heart failure with preserved ejection fraction (HFpEF), or patients with hypertensive heart disease (HHD) before and after treadmill exercise.

**Methods:** Seventy-eight patients with HFpEF and 78 patients with HHD who were admitted to our hospital between February 2020 and February 2021 were selected to take a treadmill exercise test. All patients continued to exercise for 1 month. Clinical biochemical indexes [hemoglobin A1c (HbA1c), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), total cholesterol (TC), N-segment pro-brain natriuretic peptide (NT-proBNP), and cardiac troponin I (cTnI)] were measured before and after the treadmill exercise test and compared between the two groups. Receiver operating characteristic (ROC) curves were drawn to analyze the optimal cutoff values of the clinical biochemical indexes in the diagnosis of HFpEF. The positive diagnostic rates of the biochemical indicators for HFpEF before and after treadmill exercise were compared using the optimal cut-off value of ROC as the positive standard.

**Results:** Before exercise, there was no significant difference in HbA1c, LDL-C, HDL-C, or TC between the two groups ( $P > 0.05$ ), but NT-proBNP and cTnI were significantly higher in the HFpEF group than in the HHD group ( $P < 0.05$ ). ROC curve analysis showed that before exercise, the best cutoff values for plasma NT-proBNP and cTnI in the diagnosis of HFpEF were 2,248.24 pg/mL and 1.14 ng/mL, respectively. After exercise, no significant difference was found in HbA1c, LDL-C, HDL-C, or TC between the two groups ( $P > 0.05$ ). However, the levels of NT-proBNP and cTnI in both groups were higher after exercise, with more significant increases seen in the HFPEF group ( $P < 0.05$ ). The positive rates of plasma NT-proBNP and cTnI in HFPEF group were statistically higher after exercise than before exercise ( $P < 0.05$ ).

**Conclusions:** The changes in plasma NT-proBNP and cTnI in patient after treadmill exercise can be used as sensitive indicators for the diagnosis and differentiation of HFpEF and HHD.

**Keywords:** Heart failure with preserved ejection fraction (HFpEF); hypertensive heart disease (HHD); treadmill exercise test; biochemical indexes

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## Introduction

As the incidence of hypertension continues to rise in China, the prevalence of hypertensive heart disease (HHD) is increasing year by year (1). Early HHD is often accompanied by left ventricular hypertrophy and decreased diastolic function, which gradually causes decreased myocardial systolic function and increased pulmonary circulatory resistance, resulting in chest tightness and shortness of breath, and eventually leading to heart failure (HF) (2). However, some patients with HHD experience normal or slightly reduced cardiac output for a long time, which is referred to as HF with preserved ejection fraction (HFpEF) (3).

Clinical data from the Chinese Heart Failure Center show that HFpEF accounted for 41% of HF cases in 2019, and is gradually becoming a major type of HF, which poses a serious threat to life, carrying a 5-year case fatality rate of 50% (4,5). At present, HFpEF is mainly diagnosed based on the patient's medical history, clinical symptoms, and comprehensive evaluation of cardiac ultrasound. However, due to some patients with HFpEF displaying a normal ejection fraction, the syndrome can be easily misdiagnosed, resulting in a delay to treatment (6). Consequently, active exploration of sensitive diagnostic indicators for HFpEF has become a hot topic in the cardiovascular research field.

Since its inception, the treadmill exercise test has been widely used to evaluate various heart diseases (7). Its mechanism is to stimulate the heart to doing extra work, through which potential cases can be identified. In the past, changes in heart rate or cardiogram indexes were commonly used as judgment indexes of treadmill exercise tests; however, few studies have focused on clinical serum biochemical index changes. Therefore, this study aimed to explore and compare the changes and significance of clinical biochemical indexes in patients with HFpEF and patients with HHD before and after treadmill exercise. We present the following article in accordance with the STARD reporting checklist (available at <https://dx.doi.org/10.21037/apm-21-1361>).

## Methods

### *General information*

This study enrolled patients with HFpEF (78 cases) and patients with HHD (78 cases) who were treated in Beijing Chaoyang Hospital from February 2020 to February 2021. The HFpEF group comprised 32 males and 46 females,

aged between 40 and 76 years old, with an average age of  $61.84 \pm 8.52$  years. The hypertension duration ranged from 5 to 12 years, with an average of  $9.37 \pm 2.30$  years. The HHD group included 36 males and 42 females, aged from 41 to 75 years old, with an average age of  $62.32 \pm 8.35$  years. The hypertension duration ranged between 5 and 11 years, with an average of  $9.21 \pm 2.26$  years. There was no significant difference between the two groups of patients in terms of general information such as age, sex, and history of hypertension ( $P > 0.05$ ). The study was approved by Beijing Chaoyang Hospital Affiliated to Capital Medical University (2020-527), and an informed consent form was signed by each patient or a family member on their behalf. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

### *Inclusion and exclusion criteria*

The inclusion criteria were as follows: (I) patients in the HHD group were with a clear history of hypertension whose transcatheter ultrasound examination results met the standards for HHD; (II) patients in the HFpEF group were with electrocardiography and echocardiography examination results meeting the diagnostic criteria for HFpEF set out in the “Chinese Guidelines for the Diagnosis and Treatment of Heart Failure (2014 Edition)” (8), [i.e., typical symptoms and signs of HF, and normal or slightly reduced ( $\geq 50\%$ ) left ventricular ejection fraction (LVEF)], and meet at least one of the following criteria: (I) abnormal diastolic function; (II) left ventricular hypertrophy or (and) left atrium enlargement; (III) no heart valve disease; and (IV) complete clinical information. The exclusion criteria were: (I) patients with secondary hypertension; (II) patients with severe liver and kidney failure; (III) patients with autoimmune disease, or acute or chronic infection; (IV) patients with congenital heart disease or cardiomyopathy; (V) patients with malignant tumors or severe bleeding tendency.

### *Treadmill exercise test*

The treadmill exercise test was performed on a T2100 treadmill (GE, USA). According to the Bruce exercise program, the exercise endpoint was the physical exhaustion that the patient could no longer adhere to the exercise or reach the extreme heart rate at their age. Before and after the exercise test, the clinical biochemical indexes of the patients were tested, and receiver operating characteristic

**Table 1** Comparison of biochemical indicators before treadmill exercise ( $\bar{x}\pm s$ )

Index	HFpEF group (n=78)	HHD group (n=78)	t	P
HbA1c (%)	6.93±1.16	6.84±1.20	0.476	0.635
LDL-C (mmol/L)	3.16±0.37	3.22±0.36	1.027	0.306
HDL-C (mmol/L)	2.42±0.50	2.38±0.51	0.495	0.622
TC (mmol/L)	4.77±0.49	4.65±0.54	1.453	0.148
cTnI (ng/mL)	1.11±0.49	0.48±0.27	9.945	0.000
NT-proBNP (pg/mL)	2,183.52±543.79	874.47±468.25	16.111	0.000

HFpEF, heart failure with preserved ejection fraction; HHD, hypertensive heart disease; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein; HDL-C, high-density lipoprotein; TC, total cholesterol; cTnI, cardiac troponin I; NT-proBNP, N-segment pro-brain natriuretic peptide.

(ROC) curves were drawn to analyze the best cutoff values for the clinical biochemical indexes. In this study, the positive standard was defined as the levels of N-segment pro-brain natriuretic peptide (NT-proBNP) and cardiac troponin I (cTnI) were  $\geq$  the best cutoff values, and the positive rate of HFpEF before and after exercise was calculated.

#### Detection of clinical biochemical indicators

Venous blood (5 mL) was collected from each participant before and after treadmill exercise in a sodium citrate anticoagulation tube and left to stand for 1 hour. The blood samples were then centrifuged at 3,000 r/min for 10 minutes, and the supernatant was collected for further testing. Glycosylated hemoglobin A1C (HbA1c), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), and total cholesterol (TC) were detected before and after treadmill exercise using the Dx C 800 automatic biochemical analyzer (Beckman, USA). The plasma levels of cTnI were detected by enzyme-linked immunosorbent assay (ELISA), and those of N-segment pro-brain natriuretic peptide (NT-proBNP) were detected by electrochemiluminescence.

#### Observation indicators

Clinical biochemical indexes including HbA1c, LDL-C, HDL-C, TC, NT-proBNP, and cTnI were determined and compared between the two groups before and after exercise. ROC curve analysis was performed to determine the best cutoff values for the clinical biochemical indexes for the diagnosis of HFpEF before treadmill exercise. The

best ROC cutoff values were used as the positive judgment standard to compare the positive rates of the biochemical indexes in the diagnosis of HFpEF before and after exercise.

#### Statistical analysis

Data were analyzed using SPSS 21.0 statistical software (IBM, New York, USA). The measurement data were expressed as mean  $\pm$  standard deviation ( $\bar{x}\pm s$ ), and comparisons between the two groups were conducted by *t*-test. Paired sample *t* tests were used to analyze differences before and after exercise in the same group. Count data were expressed as rate (%), and analyzed using the chi-squared ( $\chi^2$ ) test. ROC curves were drawn to analyze the best cutoff values of the clinical biochemical indexes in the diagnosis of HFpEF before treadmill exercise. Results with  $P < 0.05$  were considered to be statistically significant.

## Results

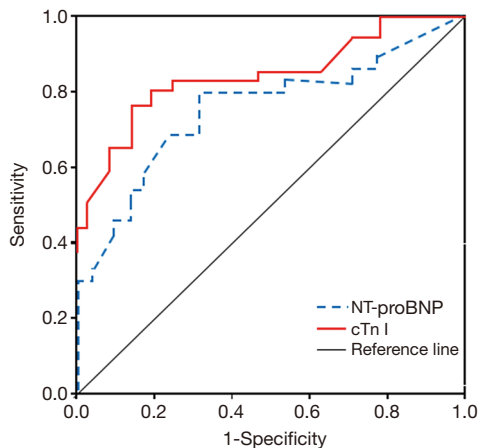
#### Comparison of biochemical indexes before treadmill exercise

Before treadmill exercise, the levels of HbA1c, LDL-C, HDL-C, and TC displayed no statistically significant differences between the two groups ( $P > 0.05$ ); however, the NT-proBNP and cTnI levels were significantly higher in the HFpEF group than the HHD group ( $P < 0.05$ , Table 1).

#### ROC curve analysis

The ROC curve analysis revealed that the areas under the

curves (AUCs) of plasma NT-proBNP and cTnI for the diagnosis of HFpEF before treadmill exercise were 0.810 and 0.843, respectively, with the best cutoff values of plasma NT-proBNP and cTnI being 2,248.24 pg/mL and 1.14 ng/mL,



**Figure 1** ROC curves of plasma NT-proBNP and cTnI in the diagnosis of HFpEF before treadmill exercise. ROC, receiver operating characteristic; NT-proBNP, N-segment pro-brain natriuretic peptide; cTnI, cardiac troponin I; HFpEF, heart failure with preserved ejection fraction.

respectively (Figure 1).

#### Comparison of biochemical indexes after treadmill exercise

After treadmill exercise, the levels of HbA1c, LDL-C, HDL-C, and TC in the two groups were compared with those before treadmill exercise, and no statistically significant differences were found ( $P>0.05$ ). However, the levels of NT-proBNP and cTnI in both groups after treadmill exercise were significantly higher than those before exercise, and the increase was more significant in the HFpEF group than the HHD group ( $P<0.05$ , Table 2).

#### Comparison of positive rates before and after treadmill exercise

The positive rates of plasma NT-proBNP and cTnI levels in the diagnosis of HFpEF after treadmill exercise were significantly higher than those before exercise ( $P<0.05$ , Table 3).

## Discussion

With the aging of society, hypertension is increasing in

**Table 2** Comparison of biochemical indexes after treadmill exercise ( $\bar{x}\pm s$ )

Index	HFpEF group (n=78)	HHD group (n=78)	t	P
HbA1c (%)	6.58±1.21	6.47±1.22	0.565	0.573
LDL-C (mmol/L)	3.06±0.32	3.13±0.30	1.409	0.161
HDL-C (mmol/L)	2.28±0.43	2.24±0.44	0.574	0.567
TC (mmol/L)	4.63±0.45	4.52±0.41	1.596	0.113
cTnI (ng/mL)	1.53±0.54*	0.72±0.36*	11.023	0.000
NT-proBNP (pg/mL)	3,894.37±415.62*	1,674.55±423.10*	33.056	0.000

\* $P<0.05$ , compared with that before the treadmill exercise. HFpEF, heart failure with preserved ejection fraction; HHD, hypertensive heart disease; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein; HDL-C, high-density lipoprotein; TC, total cholesterol; cTnI, cardiac troponin I; NT-proBNP, N-segment pro-brain natriuretic peptide.

**Table 3** Comparison of positive rate before and after exercise

Index	Positive rate (%)		$\chi^2$	P
	Before exercise	After exercise		
cTnI	53.85 (84/156)	67.95 (106/156)	6.515	0.011
NT-proBNP	53.21 (83/156)	66.03 (103/156)	5.325	0.021

cTnI, cardiac troponin I; NT-proBNP, N-segment pro-brain natriuretic peptide.

incidence. If hypertension cannot be effectively controlled for a long time, it will induce changes in the structure and function of the heart, leading to HHD (9). As the final stage of progression to heart disease, HF occurs frequently in patients with HHD. The onset of HF is dangerous and can even cause death without effective treatment (10). Despite being one of the high-incidence types of HF, HFpEF currently lacks a specific treatment plan (11). Therefore, in clinical practice, a correct diagnosis should be made early and symptomatic treatment should be given in time to control or slow the deterioration of HF symptoms as much as possible. Therefore, the search for a fast and accurate differential diagnostic method is an important direction for current HFpEF research.

Treadmill exercise tests are a non-invasive, simple, and cheap examination method, and are widely used in the diagnosis of coronary heart disease (12). By increasing the body's exercise load, the treadmill exercise test induces myocardial ischemia, which is directly reflected on the electrocardiogram. However, because some HFpEF patients with normal ejection fraction show similar symptoms to those with HHD, and the specificity and sensitivity of treadmill exercise tests are not high enough to distinguish HFpEF and HHD, it is necessary to identify other effective indicators to diagnose and differentiate HFpEF accurately.

This study showed that before treadmill exercise, the differences in HbA1c, LDL-C, HDL-C, and TC were not statistically significant between patients with HFpEF and HHD; however, the NT-proBNP and cTnI levels of the HFpEF group were significantly higher than those of the HHD group. Results of ROC curve analysis showed that the best cutoff values of plasma NT-proBNP and cTnI for diagnosing HFpEF before treadmill exercise were 2248.24 pg/mL and 1.14 ng/mL, respectively, suggesting that patients with abnormally high plasma NT-proBNP and cTnI levels at rest state may have HFpEF.

Under normal conditions, cTnI is mainly distributed in the cytoplasm of myocardial cells; however, it could be released into the blood by the stimulation of the imbalance of myocardial oxygen supply and oxygen consumption, or direct myocardial injury (13). NT-proBNP, an inactive peptide fragment secreted by stretching and stimulation of the body's ventricular myocytes, can reflect heart function, and has been widely used in the diagnosis and prognostic evaluation of HF (14). Clinical studies have confirmed that once heart morphology and function show pathological changes, cTnI and NT-proBNP, as markers of cardiac

injury, change significantly, and are negatively correlated with LVEF (15-17), which was fully verified by the results of the ROC curve analysis of this study.

The results of this study further showed that after treadmill exercise, the levels of HbA1c, LDL-C, HDL-C, and TC in the two groups were not statistically significantly different to those measured before treadmill exercise. However, the levels of NT-proBNP and cTnI in the two groups were higher after exercise than before exercise, with these increases being more significant in the HFpEF group. These results suggest that treadmill exercise can increase the expression of plasma NT-proBNP and cTnI levels.

Some scholars have reported that the plasma levels of NT-proBNP and cTnI increase significantly immediately after exercise (18,19), and the possible mechanisms are as follows. First, exercise increases the pressure of myocardial cells, thereby prompting myocardial cells to release large quantities of cardiomyocyte markers such as NT-proBNP and cTnI, which constitutes a physiological adaptation process of hemodynamic stimulation. Second, the increases in serum NT-proBNP and cTnI levels after exercise may have various contributing factors that result in "reversible damage" to the myocardium. Currently, many controversies still surround the abnormal increases observed in NT-proBNP and cTnI levels after exercise, but it is generally believed that in healthy people, increases in indexes following exercise are mostly the result of adaptation to accommodate the demands of heart function (20).

In this study, the plasma NT-proBNP and cTnI levels of patients with HFpEF increased more significantly than those of patients with HHD after treadmill exercise, which may be due to patients with HFpEF having a higher degree of myocardial damage than hypertensive patients. Therefore, it is necessary to reduce ischemia after exhaustive exercise. In patients with acute myocardial injury caused by perfusion, the levels of NT-proBNP and cTnI increase significantly to protect the myocardium. Further, we found that the positive rates of plasma NT-proBNP and cTnI in the diagnosis of HFpEF were higher after exercise than before exercise, which suggests that changes in plasma NT-proBNP and cTnI levels after treadmill exercise can be used for the diagnosis and differentiation of HFpEF and HHD. Exercise on a treadmill increases the body's heart load and oxygen consumption, which further promotes the heart's systolic or diastolic function on the basis of the original heart disease. At the same time, exhaustive exercise exacerbates acute myocardial damage, resulting in the abnormal increase of NT-proBNP and cTnI levels.

In conclusion, treadmill exercise is beneficial to the recovery of patients with HFpEF and hypertensive heart disease. More importantly, changes in plasma NT-proBNP and cTnI levels after the treadmill exercise test can be used as sensitive indexes for the assistant diagnosis and differentiation of HFpEF and HHD, with high clinical application value. However, due to the small sample size of this study, its conclusions require verification through large-sample and multicenter analysis in further prospective studies.

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### Footnote

*Reporting Checklist:* The authors have completed the STARD reporting checklist. Available at <https://dx.doi.org/10.21037/apm-21-1361>

*Data Sharing Statement:* Available at <https://dx.doi.org/10.21037/apm-21-1361>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/apm-21-1361>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by Beijing Chaoyang Hospital Affiliated to Capital Medical University (2020-527) and an informed consent form was signed by each patient or a family member on their behalf. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

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