Effect of anthracycline combined with aerobic exercise on the treatment of breast cancer

Zhijun Ma*
College of Sports Science, Mudanjiang Normal University, Mudanjiang, China

Abstract: Anthracycline is a standard drug for the treatment of breast cancer. However, anthracycline has great cardiotoxicity. Some patients stop chemotherapy during severe chemotherapy and even undergo serious heart failure. At the same time, there is lack of clinical study on whether aerobic exercise can reduce the cardiotoxicity of chemotherapy drugs. The purpose of this study is to investigate the effects of aerobic exercise on the cardiac function of patients with breast cancer after anthracycline therapy. The results showed that the control group LVEF decreased significantly. In addition, the E/A value decreased and the DT interval prolonged in the control group, show that anthracycline on myocardial damage, and the observation group LVEF increased significantly ($P<0.05$), the results show that aerobic exercise can improve heart function, and to a certain extent, it could reverse the damage of chemotherapy drugs on the heart.

Keywords: Anthracycline, breast cancer, drug toxicity, VO2max, exercise tolerance.

INTRODUCTION

So far, breast cancer has taken the first place in the malignant tumor that threatens the health of women in China (Akhter *et al.*, 2009; Chandrasekhar *et al.*, 2016). At present, the main treatment of breast cancer is the use of anthracycline chemotherapy after surgical resection and anthracycline, while anthracycline has a greater side effect (Liu *et al.*, 2017). Recent studies have agreed that exercise has a favorable impact on cardiovascular disease (Kawamoto *et al.*, 2016), and even patients with severe impairment of heart function can benefit from it (Jia *et al.*, 2015; Nayir *et al.*, 2015). Anthracycline, used alone or in combination with other drugs, has been widely used in adjuvant chemotherapy for patients with breast cancer after operation. Anthracycline has been discovered as an effective antitumor drug recently, but it has a cumulative dose dependent cardiotoxicity (Kong *et al.*, 2015; De Carlo *et al.*, 2015). The main manifestations are arrhythmia, irreversible cardiomyopathy and congestive heart failure. Among them, congestive heart failure usually occurs within 1 year or later after discontinuous use, which seriously affects the curative effect of the patients (Nayir *et al.*, 2015).

Moderate exercise can improve the circulation of the coronary artery and promote the collateral circulation, and increase the blood flow and reserve of blood vessels (Paccez *et al.*, 2014; Solinas *et al.*, 2015; Ostojic *et al.*, 2015). Previous studies have confirmed that after a period of aerobic exercise, peak oxygen consumption (VO_2max) and hemodynamic indexes can be significantly improved in patients with chronic pulmonary hypertension and chronic heart failure (Fang *et al.*, 2017). It is still lacking in clinical study whether aerobic exercise can reduce the cardiac toxicity of chemotherapeutic drugs (Tural *et al.*, 2015). The purpose of this study is to investigate the effects of aerobic exercise on the cardiac function of patients with breast cancer after anthracycline therapy.

**Corresponding author:* e-mail: mzj_790125@163.com

MATERIALS AND METHODS

General information

A total of 70 women with breast cancer after operation were selected from January 2016 to June 2017. The age was (43.1±5.4) years, including 18 cases of hypertension and 7 cases of diabetes mellitus. 70 patients were randomly divided into observation group (n = 35), mean age (44.2±5.7) years old, control group (n = 35), average age (43.5±6.3) years old. There was no significant difference in age, height, weight and general status score between the two groups. All patients were approved by Ethics Committee of our hospital and signed on the informed consent.

Experimental method

The patients in the observation group and the control group received 4 cycles of anthracycline chemotherapy. On this basis, the observation group began 16 weeks of aerobic training from first cycles of chemotherapy. Before and after the beginning of the experiment, 2 exercise abilities were measured for all subjects, and the individualized scheme of aerobic exercise in the observation group was made by using the data before the experiment. In this study, the exercise test was used and the improved Bruce scheme was used to measure the exercise ability of 70 subjects. Before the experiment, each subject signed an informed consent. 12 h before the exercise to avoid vigorous physical activity, 3 h before exercise prohibition, prohibition of tobacco and alcohol. At the beginning of the experiment, all subjects for the first 10 min warm-up exercise, after treadmill exercise test to determine the VO2max, the relative maximal oxygen uptake ($VO2_{max}$/kg), peak oxygen pulse ($VO2_{max}$/HR) and maximum heart rate (HR_{max}), and the use of telemetry heart rate monitoring subjects heart rate. During the exercise, the patients were scored on the Borg fatigue scale based on the subjective physical sensation. The following conditions: termination of the trial (1) increase exercise test, but the systolic blood pressure level is decreased by more than 10mm based Hg, and other accompanying signs of myocardial ischemia; (2) and severe angina pectoris; (3) increase the neurological symptoms (such as ataxia, vertigo, syncope approximate state) (4) due to technical difficulties cannot be detected by ECG or systolic blood pressure; (5) subjects require termination; (6) sustained ventricular tachycardia.

Develop an aerobic exercise program

The patients in the observation group started from chemotherapy for 16 weeks of aerobic training until the end of chemotherapy. We set up an aerobic exercise program for the observation group based on the VO_2max and HR_{max} measured before the start of the experiment. The observation group carried out 3 treadmill exercises every week under the supervision of the medical staff. Every movement before and after were 10 min warm-up and finishing movement, including major muscles stretching during the heart rate maintained at 60%~ 70%HRmax; after 4 groups of plate movement by increasing the flat slope, speed and slope, the subjects movement period heart rate remained at 90%~ 95%HRmax. Each lasting 5 min, intermittent period of 3 min between the two groups, intermittent period subjects may be appropriate to slow down, while heart rate remained at 50% ~ 70%HRmax. The total time of each exercise is 50 min. To ensure the safety of the experiment, the speed of motion is within 5 km / h. The conditions for the termination of the experiment are as described earlier. During this period, the control group did not accept any guidance in sports and carried out normal daily activities.

Blood analysis

The NT- terminal pro brain natriuretic peptide (NT-pro BNP), blood muscle liver (SCr) and phosphokinase (CK-MB) were monitored before and after the experiment. The subjects were given blood collection after 15 min rest. Use plastic test tube to collect (EDTA anticoagulant) and examine serum in 1 h.

Echocardiography

Echocardiography was performed on all subjects before and at the end of the experiment. The examination was completed by 2 cardiologists in the absence of knowledge about the grouping. The left ventricular ejection fraction (LVEF), E peak deceleration time (DT time), the ratio of early diastolic to late diastolic velocity (E/A) and the equal volume diastolic time (IVRT interval) were measured under the quiet condition of the subjects.

STATISTICAL ANALYSIS

SPSS 19 statistical software was applied to analyze the data and the measurement data were expressed as mean ± standard deviation. The independent sample t test was used to compare the data between the two groups before chemotherapy. The paired t test was used before and after the experiment and the difference between $P<0.05$ was statistically significant.

RESULTS

Experimental result

The main endpoint of this study is VO_2max / kg change. The secondary endpoints are VO_2max, VO_2max/HR, HRmax and changes of hematology and echocardiography. There was no statistical difference between the two groups before the experiment. During the experiment, 2 patients were interrupted by chemotherapy because of severe chemotherapy reaction. 4 subjects failed to adhere to the experiment. A total of 6 subjects withdrew from the study. Finally, 64 subjects completed the experiment, including 31 cases in the observation group and 33 cases in the control group. The changes of echocardiography, electrocardiogram, BNP and CtnI in patients with breast cancer before anthracycline chemotherapy and 6 months and 12 months after the end of chemotherapy were observed in table 2. After 6 months of chemotherapy, serum BNP and CtnI levels increased significantly ($P<0.05$), while BNP and CtnI levels decreased after 6 months, which was not statistically significant compared with those before chemotherapy. Echocardiography showed that LVEF decreased significantly at 6 months after chemotherapy ($P<0.05$), but did not return to the level before chemotherapy 12 months later ($P<0.05$). During the course of chemotherapy, the heart rate and hemoglobin level of the patients were not significantly changed (table 1).

The changes of BNP, CtnI and LVEF in different age groups at different periods before and after chemotherapy were shown in table 2. The level of plasma BNP increased in the patients with cardiovascular events and increased with age (45-70 years old). The serum CtnI increased at 1 months after chemotherapy, and then decreased. There was no significant difference between patients with cardiovascular events (control group) or not (observation group). LVEF decreased significantly at 1 months after chemotherapy, especially in the control group, which decreased with age (45-70 years old).

Exercise tolerance change

There was no statistical difference between the two groups before chemotherapy ($P>0.05$). After the end of chemotherapy, the changes of aerobic exercise tolerance indicators were seen in table 1. In the observation group, VO_2max / kg increased by 7.5m L / (min kg) (54%, P<

Table 1: Test results of various indexes

Detection index	Pre-chemotherapy	6 months after chemotherapy	12 months after chemotherapy
Hb /(g·dL^{-1})	12.7±1.5	12.6±1.5	12.4±1.6
BNP/(pg·mL^{-1})	34.2±18.6	59.3±48.2	45.4±33.5
CTnI /(ng ·mL^{-1})	0.005±0.001	0.059±0.03	0.004±0.002
Heart Rate	65.3±10.5	94.2±9.8	70.3±10.2
LVEF/%	59.6±4.2	54.2±6.5	54.0±6.9

Table 2: Comparison between two groups of patients

Index		control group (n= 33)		observation group (n= 31)	
		20-45	45-70	20-45	45-70
BNP (pg·mL^{-1})	Pre-chemotherapy	35.2±5.7	55.3±40.2	25.4±12.3	24.8±10.9
	6 months after chemotherapy	56.2±10.5	98.3±41.6	35.2±14.7	43.2±20.6
	12 months after chemotherapy	51.7±9.8	84.2±48.7	35.6±18.2	40.7±15.4
CTnI (ng·mL^{-1})	Pre-chemotherapy	0.006±0.001	0.007±0.003	0.004±0.003	0.005±0.002
	6 months after chemotherapy	0.04±0.02	0.06±0.01	0.04±0.02	0.06±0.01
	12 months after chemotherapy	0.004±0.002	0.006±0.003	0.004±0.004	0.006±0.003
LVEF/%	Pre-chemotherapy	54.1±1.85	53.1±1.72	62.4±4.51	60.9±4.83
	6 months after chemotherapy	51.4±2.92	52.6±6.85	57.4±7.14	54.3±6.89
	12 months after chemotherapy	50.1±1.56	49.7±6.14	54.6±6.42	53.7±5.83

Table 3: Comparison of the experimental indexes of the two groups of patients

index	control group (n= 33)		observation group (n= 31)	
	Pre -chemotherapy	after chemotherapy	Pre -chemotherapy	after chemotherapy
Exercise tolerance				
VO2max(mL /min)	1210±258	984±157	1134±268	1594±190
VO2max/ kg	14.6±2.1	13.5±2.5	14.8±3.5	22.3±2.7
VO2max/HR	11.2±1.3	11.1±2.0	10.1±2.7	11.3±1.6
HRmax (beats /min)	127±23	124±19	125±18	116±13
Blood analysis				
NT-prp BNP (ng /L)	72.1±13.6	348.2±25.4	84.2±21.5	90.6±18.4
SCr(pmol/ m L)	55.3±2.7	85.2±5.4	60.5±1.4	61.3±1.6
CK-MB(U)	6.8±1.5	12.3±1.2	6.9±1.2	7.4±1.5
Echocardiography				
LVEF(%)	51±5.6	47±2.6	55±3.5	60±2.9
E/A value	1.5±0.6	1.5±0.9	1.3±0.2	1.3±0.3
DT interval (MS)	145±48	79±15	88±14	94±15

0.05), VO_2max increased by 460 m L / min (45%, 0.05< 0.05). There was no significant change in the indexes of the control group.

Hematological changes

The changes of NT-pro B-NP, SCr and CK-MB levels in the two groups before and after chemotherapy were observed in table 1. There was no significant change in the indexes in the observation group (P > 0.05), while the NT-pro BNP, SCr and CK-MB increased significantly in the control group (P<0.05).

Echocardiographic changes

The changes of the indexes of echocardiography in the two groups before and after chemotherapy were seen in table 1. Among them, the LVEF in the observation group was significantly increased after chemotherapy, and the IVRT interval was significantly prolonged (P<0.05), while the LVEF and E/A values in the control group were significantly decreased (P<0.05).

DISCUSSION

The incidence and mortality of breast cancer are first of the female malignant tumors, and it is one of the major malignant tumors that threaten the health of women (Claassen *et al.,* 2012; Savonitto *et al.,* 2012). Anthracycline can prolong the disease-free survival rate and overall survival rate of breast cancer as a gold standard drug for treatment of breast cancer (Sheng *et al.*, 2015). However, such drugs have great cardiotoxicity, which is mainly classified into acute cardiac toxicity and chronic congestive heart failure. Arrhythmias, conduction block, ST segment changes (Tang *et al.,* 2017), QRS wave width is to change the main ECG in patients with chronic congestive heart failure. Some studies have shown that the cardiac toxicity is closely related to oxidative stress, iron metabolism imbalance, cell apoptosis and so on, but the mechanism of specific heart failure is not clear (Udagawa *et al.,* 2012; Takahashi, 2017). Because anthracycline is more toxic to heart, some patients stop chemotherapy during severe chemotherapy, even cause serious heart failure.

VO_2max is a commonly used index of cardiopulmonary function in patients with the judgment of aerobic exercise, it reflects the whole body aerobic metabolism and energy level, and the VO_2max/kg is more suitable for comparison in different subjects between heart and lung function, VO_2max/HR and cardiac output, arteriovenous difference is closely related (Clemmensen *et al.*, 2015). Previous studies have made healthy athletes undergo endurance training for a period of time, and found that their skeletal muscle capillary production has increased significantly (Jia *et al.,* 2015; Nayir *et al.,* 2015). The body increases oxygen supply by increasing the transport, conduction and uptake of oxygen in skeletal muscle (Tural *et al.,* 2015).

This chronic vascular configuration change is likely to be an extension of the continuous changes in endothelial function caused by exercise (Vekov *et al.,* 2015). Research shows that exercise capacity after a sharp increase in the body blood flow can increase blood flow pressure in the arteries (Vagnarelli *et al.,* 2015), which in turn increases the vascular endothelial NO release, and lead to endothelial nitric oxide synthase structural (ec NOS) the expression of chronic adaptation to induce NO vasodilation of the vascular system, the configuration and function change (Akhter *et al.*, 2009; Chandrasekhar *et al.,* 2016). On the other hand, aerobic training can be approximated as a cycle of hypoxia reoxygenation process, in the training process, the oxygen and energy transport is reduced, ischemia and intermittent period through body ischemia reoxygenation restored muscle cells exposed to this cycle of hypoxia reoxygenation environment in the cause of hypoxia inducible factor 1 (HIF-1) activity increased, the activation of the transcription of IL-10 gene, thus elevated serum IL-10 level to myocardial protection (Jia *et al.,* 2015; Nayir *et al.,* 2015). The results of this study show that, compared with before chemotherapy, after chemotherapy, the observation group VO_2max and VO_2max/kg respectively increased by 42% and 54%, while the control group were lower than that, the heart and lung function in the observation group subjects body significantly improve the aerobic metabolism and energy levels rise, effective against the anthracycline cardiotoxicity.

CONCLUSION

The exercise plan for this study is higher intensity intermittent aerobic exercise. Many studies have confirmed that moderate high intensity intermittent aerobic training can significantly improve cardiac function in patients with heart failure. In this study, the control group LVEF decreased significantly, and the emergence of E/A decrease, DT interval, show that anthracycline on myocardial damage, and the observation group LVEF increased significantly ($P<0.05$), indicating that aerobic exercise can improve heart function, and to a certain extent, reverse the damage of chemotherapy drugs on the heart. In conclusion, aerobic training during postoperative anthracycline chemotherapy for breast cancer patients is beneficial to improve cardiac function and provide a new way to reduce cardiovascular events during chemotherapy.

ACKNOWLEDGMENTS

This paper is supported by (1) The reform project of higher education teaching in Heilongjiang Province in 2017, Project number: sjgy20170161; (2) Education and teaching reform project of Mudanjiang Normal College in 2016 Item number: 16-jg18078

REFERENCES

Akhter N, Milford-Beland S, Roe MT, Piana RN, Kao J, Shroff A (2009). Gender differences among patients with acute coronary syndromes undergoing percutaneous coronary intervention in the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). *Am. Heart J.*, **157**(1): 141-148.

Claassen M, Sybrandy KC, Appelman YE and Asselbergs FW (2012). Gender gap in acute coronary heart disease: Myth or reality? *World J. Cardiol.*, **4**(2): 36-47.

Clemmensen P, Roe MT and Hochman JS (2015). Long-term outcomes for women versus men with unstable angina/non-ST-segment elevation myocardial infarction managed medically without revascularization: Insights from the TaRgeted platelet Inhibition to cLarify the Optimal strate Gy to medicall Y manage Acute Coronary Syndromes trial. *Am. Heart J.*, **170**(4): 695-705.

Chandrasekhar J and Mehran R (2016). Sex-Based Differences in Acute Coronary Syndromes: Insights From Invasive and Noninvasive Coronary Technologies. *JACC. Cardiovasc. Imaging*, **9**(4): 51-64.

De Carlo M, Morici N, Savonitto S and Grassia V (2015). Sex-Related Outcomes in Elderly Patients Presenting With Non-ST-Segment Elevation Acute Coronary Syndrome: Insights from the Italian Elderly ACS Study. *JACC. Cardiovasc. Interv.*, **8**(6): 791-796.

Fang W and Ruan W (2017). Advances in uniportal video-assisted thoracoscopic surgery for non-small cell lung cancer. *Min. Invasive. Surg. Oncol.*, **1**(1): 20-30.

Jia WZ, Zhao JC, Sun XL, Yao ZG, Wu HL and Xi ZQ (2015). Additive anticancer effects of chrysin and low dose cisplatin in human malignant glioma cell (U87) proliferation and evaluation of the mechanistic pathway. *J. Boun.*, **20**(5): 1327-1336.

Kong F, Cai B, Lin S, Zhang J, Wang Y and Fu Q (2015). Assessment of radiotherapy combined with adjuvant chemotherapy in the treatment of patients with advanced nasopharyngeal carcinoma: A prospective study. *J. Boun.*, **20**(1): 206-211.

Kawamoto KR, Davis MB and Duvernoy CS (2016). Acute Coronary Syndromes: Differences in Men and Women. *Curr. Atheroscler. Rep.*, **18**(12): 73.

Liu Z, Yang R and Shao F (2017). Anastomosis using complete continuous suture in uniportal video-assisted thoracoscopic bronchial sleeve lobectomy. *Mini. Invas.e Surg. Oncol.*, **1**(1): 31-42.

Nayir E, Ata A and Arican A (2015). Do medical oncologists and cancer patients care about treatment costs of systemic anticancer therapy? *J. Boun.*, **20**(6): 1606-1611.

Ostojic SM, Knezevic DR, Perisic M, Jurisic V and Knezevic SM (2015). The importance of choice of resection procedures in T1 and T2 stage of carcinoma of the ampulla of Vater. *J. BOUN.*, **20**(5): 1206-1214.

Paccez J, Vogelsang M and Parker M (2014). The receptor tyrosinekinase Axl in cancer: Biological functions and therapeutic implica-tions. *Int. J. Cancer*, **134**(5): 1024 - 1033 .

Savonitto S and Cavallini C (2012). Early aggressive versus initially conservative treatment in elderly patients with non-ST-segment elevation acute coronary syndrome: A randomized controlled trial. *JACC. Cardiovasc. Interv.*, **5**(9): 906-916.

Solinas E, Vignali L and Ortolani P (2015). Association of bleeding, mortality and sex in acute coronary syndromes: the missing triangle. *J. Cardiovasc. Med.* (Hagerstown), **16**(5): 347-354.

Sheng W and Zhang B (2015). Laparoscopic colectomy for transverse colon cancer: comparative analysis of short- and long-term outcomes. *Int J. Clin. Exp. Med.*, **8**(9):16029-16035.

Tang N, Li X and Huo F (2017). Effect of levofloxacononone chalcone derivatives on the apoptosis and autophagy of human HCC SMMC-7721 cells. *West Chi. J. Phar. Sci.*, **32**(1): 28-32.

Tural D and Kivrak Salim (2015). Is there any relation between PET-CT SUV max value and prognostic factors in locally advanced breast cancer? *J. Boun.*, **20**(5): 1282-1286.

Takahashi Y (2017). Real-time intraoperative diagnosis of lung adenocarcinoma high risk histological features: A necessity for minimally invasive sublobar resection. *Mini. Inva. Surg. Oncol.*, **1**(1): 12-19.

Udagawa H, Ueno M, Shinohara H, Haruta S, Kaida S, Nakagawa M and Tsurumaru M (2012). The importance of grouping of lymph node stations and rationale of three-field lymphoadenectomy for thoracic esophageal cancer. *J. Surg. Oncol.*, **106**(6): 742-747.

Vekov T, Lebanova H and Grigorov E (2015). Pharmacotherapeutic recommendations for application of target oncological drug therapies for treatment of breast cancer in Bulgaria - therapeutic efficacy and cost effectiveness. *Asian Pac. J. Surg. Oncol.*, **20**(6): 1420-1425.

Vagnarelli F, Taglieri N and Ortolani P (2015). Long-term outcomes and causes of death after acute coronary syndrome in patients in the Bologna, Italy area. *Am. J. Cardiol.*, **115**(2): 171-177.