—————— Research Paper ——————

Effect of Anthracycline Chemotherapy on Cardiac Toxicity and Evaluation of Two-Dimensional Speckle Tracking Imaging in Breast Cancer

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Si *et al.*: Effect of Anthracycline Chemotherapy on Cardiac Toxicity in Breast Cancer

The main objective of this study is to investigate the cardiac toxicity of anthracycline chemotherapy in patients with breast cancer and the significance of two-dimensional speckle tracking imaging technology. In this study, 83 patients with breast cancer were selected and divided into two groups. The control group was treated with paclitaxel for 4 w, and the study group was treated with epirubicin (anthracycline) for 4 w and paclitaxel for 4 w. The treatment course was 4 cycles. The changes of peak strain dispersion, global longitudinal strain and left ventricular ejection fraction of patients were examined by two-dimensional speckle tracking imaging technique. The left atrial diameter, left ventricular end diastolic diameter, left ventricular end systolic diameter, early to late mitral inflow velocity, early diastolic mitral annular velocity, the ratio velocity of early diastolic mitral inflow velocity to early diastolic annular, the changes of myocardial enzymes and N-terminal pro-B-type natriuretic peptide were observed. Before and after chemotherapy, there was no difference in the values of left atrial diameter, left ventricular end diastolic diameter, left ventricular end systolic diameter, early to late mitral inflow velocity and the ratio velocity of early diastolic mitral inflow velocity to early diastolic annular, myocardial enzymes and N-terminal pro-B-type natriuretic peptide ($p>0.05$). Before chemotherapy, there was no difference in the values of left ventricular ejection fraction, global longitudinal strain and peak strain dispersion ($p>0.05$). After chemotherapy, the values of global longitudinal strain, global longitudinal strain-A3C, A2C and peak strain dispersion in the study group were lower than those in the control group ($p<0.05$), while the values of global longitudinal strain-A4C were not significantly different ($p>0.05$). Breast cancer patients treated with anthracyclines accompanied by targeted drug chemotherapy have obvious toxicity to left ventricular function and two-dimensional speckle tracking imaging can detect these changes more sensitively than conventional cardiac ultrasound.

Key words: Breast cancer, anthracyclines, chemotherapy, cardiotoxicity, two-dimensional speckle tracking imaging

Breast cancer is a common malignant tumor in women and is currently treated with a combination of surgery, chemotherapy, radiotherapy and endocrine therapy, which can prolong the survival time of patients[1]. Even though drugs with various chemotherapy regimens for breast cancer patients are available, anthracyclines belongs to cell cycle non-specific drugs with good antitumor effects[2]. Cardiac toxicity is the most common and dangerous side effect of anthracycline drugs, which can cause tachyarrhythmia, and even lead to a sudden cardiac death in severe cases. Beta (β)-receptor blockers are generally used for symptomatic treatment in clinic, while the overall efficacy is unsatisfactory[3,4].

As a new ultrasonic technology for evaluating myocardial function, Two-Dimensional Speckle Tracking Imaging (2D-STI) can evaluate the local and overall functions of myocardial tissue sensitively and accurately[5]. In the early stages of myocardial damage produced by anthracyclines, patients often have no changes in conventional echocardiographic parameters and obvious clinical symptoms and only have slight changes in left ventricular regional myocardial mechanics[6].

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In this study, we explored the cardiotoxicity of anthracycline chemotherapy in patients with breast cancer, and applied 2D-STI technology in the early stage to evaluate the cardiac function, so as to detect subclinical cardiac injury. Anthracycline combined with targeted drug chemotherapy is a common treatment for breast cancer patients, but it can produce significant toxicity to the left ventricular function of patients. Conventional echocardiography does not sensitively reflect early myocardial injury. In the research, 2D-STI was used for evaluating myocardial injury in breast cancer patients after anthracycline combined with targeted drug chemotherapy. It was found that 2D-STI was more sensitive to detect these changes than conventional cardiac ultrasound (fig. 1).

MATERIALS AND METHODS

General information:

A retrospective study was conducted and 83 people with breast cancer admitted to our hospital from December 2019 to December 2021 were selected by randomized number table method.

Inclusion criteria:

Patients between 19 y to 59 y old; patients who are diagnosed with breast cancer in accordance with the criteria in the "guidelines and norms for the diagnosis and treatment of breast cancer of the Chinese Anti-Cancer Association" (2019 edition)[7]; the condition of patients were confirmed by breast palpation, X-ray mammography and pathological examination; patients received anthracycline chemotherapy in our oncology department for 4 cycles; the survival time of patients were expected to be >6 mo and the Karnofsky Performance Scale (KPS) score of patients before chemotherapy was not <70 points; the study meets the basic requirements of human experimentation and medical ethics and the informed consent was signed with the patients along with their family members are included in the study.

Exclusion criteria:

Patients with metastatic breast cancer; patients with malignant tumors; patients with a history of chemo radiotherapy; patients with hypertensive heart disease, severe heart, liver and kidney underlying diseases; patients received <2 courses of chemotherapy due to intolerance of chemotherapy drugs and patients who transferred hospital for treatment are excluded from the study.

Chemotherapy methods:

The control group was treated with paclitaxel chemotherapy with the dose of 175 mg/m^2, intravenous drip more than 3 times, once every 3 w. Intravenous dexamethasone 20 mg, intramuscular diphenhydramine 50 mg and intravenous ranitidine 50 mg were given 30-60 min before treatment. The study group was treated with epirubicin (anthracycline) and paclitaxel sequential chemotherapy. Intravenous drip of epirubicin 100-120 mg/m^2, once every 3 w and the usage of paclitaxel was the same as the control group. All patients underwent 4 courses of chemotherapy.

Indicator detection methods:

The Left Atrial Diameter (LAD), Left Ventricular End Diastolic Diameter (LVEDD), Left Ventricular End Systolic Diameter (LVESD), early to late mitral inflow velocity (E/A), early mitral filling velocity (E) and early diastolic mitral annular velocity (E') were observed. 2D-STI was used to examine the Left Ventricular Ejection Fraction (LVEF), Global Longitudinal Strain (GLS), GLS-Apical 4-Chamber (GLS-A4C), GLS-Apical 3-Chamber (GLS-A3C), GLS-Apical 2-Chamber (GLS-A2C), Peak Strain Dispersion (PSD). The changes of myocardial enzymes, including Creatine Kinase (CK), Lactate Dehydrogenase (LDH) and N-Terminal Pro-B-type Natriuretic Peptide (NT-proBNP) were detected and analyzed.
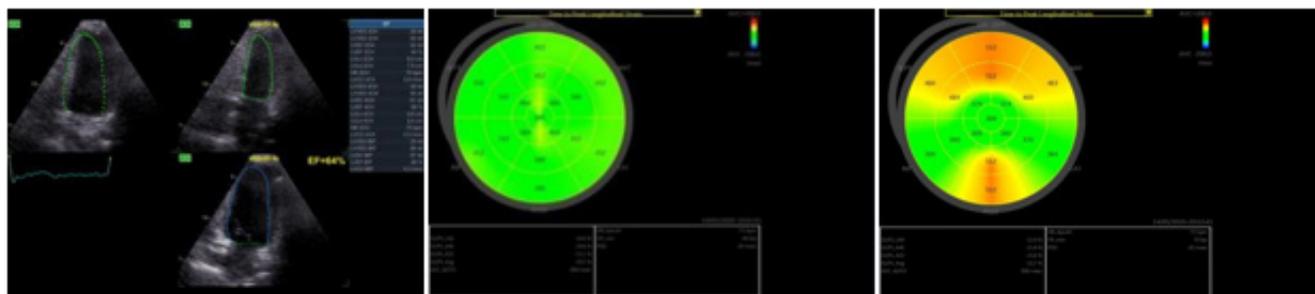
Fig. 1: Specific implementation ideas

All patients underwent conventional echocardiography and 2D-STI to evaluate cardiac function. Echocardiography was performed before and after 4 cycles of chemotherapy. Patients were asked to breathe calmly to reduce respiratory disturbance in the left lateral position. By using conventional echocardiography, the parameters were evaluated which includes LVEDD, LVESD, E/A ratio, E', and E/E'. LVEF and GLS, GLS-A4C, GLS-A3C, GLS-A2C, PSD was detected by 2D-STI technology to obtain the heart sections of A4C, A3C and A2C. All images were obtained at frame rate >50 frames/s. Three consecutive cardiac cycle images were acquired and analyzed in real time, and three sets of each were acquired to get the average value.

Instrument:

Vivid E95 Doppler ultrasound diagnostic instrument from General Electric (GE), United States of America (USA), equipped with an M5Sc probe at 1.7-3.3 MHz. The consistency of 2D-STI technology in evaluating left ventricular systolic synchronization was evaluated, and the images were collected and analyzed by two experienced doctors.

Before and after 4 cycles of chemotherapy, 3 ml fasting peripheral venous blood samples were collected and placed in vacuum. An hour later, the blood was centrifuged with the speed of 3000 r/min for 10 min. The serum was analyzed by Electrochemiluminescence for CK and LDH, and NT-proBNP was detected by enzyme-linked immunosorbent assay.

Statistical analysis:

The GLS, GLS-A4C, GLS-A3C, GLS-A2C, PSD values collected in this study were tested and expressed as (x̄±s), which were in accordance with the approximate normal distribution or normal distribution, and t test was used to made comparisons between them. Chi-square (χ^2) test was used to made comparisona between groups of non-grade counting data and professional Statistical Package for Social Sciences (SPSS) 21.0 software was used for data processing with test level Alpha (α)=0.05.

RESULTS AND DISCUSSION

WThe basic information of the two groups was compared and shown in Table 1. There was no statistically significant difference in age, Body Mass Index (BMI), blood pressure, heart rate, lesion diameter and Tumor, Node, Metastasis (TNM) stage between the two groups (p>0.05).

Before and after chemotherapy, there was no statistically significant difference in the measured values of LAD, LVEDD, LVESD, E/A and E/E' between the two groups (p>0.05) (Table 2).

Before chemotherapy, there was no statistically significant difference in the values of GLS, GLS-A4C, GLS-A3C, GLS-A2C, PSD, measurements between the two groups (p>0.05). But after chemotherapy, the measured values of GLS, GLS-A3C, GLS-A2C and PSD in the study group were lower than those in the control group, and the differences were statistically significant (p<0.05), while there was no statistically significant difference in the measured values of LVEF, GLS-A4C (p>0.05) as shown in Table 3.

Before and after chemotherapy, there was no statistically significant difference in CK, LDH and NT-proBNP between the study group and the control group (p>0.05) as shown in Table 4.

TABLE 1: COMPARISON OF BASELINE DATA BETWEEN THE TWO GROUPS OF PATIENTS

General information	Study (n=43)	Control (n=40)	t/χ^2	p
Age (years)	45.38±7.70	47.02±7.84	-0.961	0.339
BMI (kg/m^2)	22.48±1.20	22.26±1.13	0.858	0.393
Systolic pressure (mmHg)	120.6±6.4	118.5±7.0	1.428	0.157
Diastolic pressure (mmHg)	74.3±7.0	75.5±6.8	-0.791	0.431
Heart rate (time/min)	76.5±6.9	74.8±7.3	1.091	0.279
Lesion diameter (mm)	24.71±5.72	26.20±6.14	-1.145	0.256
TNM staging (%)			2.069	0.355
α	12 (27.91)	14 (37.84)		
ß	25 (58.14)	24 (60.00)		
x	6 (13.95)	2 (5.41)		

TABLE 2: COMPARISON OF CARDIAC ULTRASOUND INDICES BEFORE AND AFTER TREATMENT BETWEEN THE TWO GROUPS (x̄±s)

Group	n	LAD (cm)		LVEDD (cm)		LVESD (cm)		E/A		E/E'	
		Before	After	Before	After	Before	After	Before	After	Before	After
Study	43	31.30±3.47	32.66±3.81	45.92±4.76	47.30±5.51	29.57±4.10	31.13±4.73	1.34±0.31	1.22±0.28	8.49±2.15	9.42±2.27
Control	40	31.03±3.51	32.14±3.94	45.44±4.63	46.73±5.11	29.10±3.95	30.68±4.98	-0.434	-1.278	8.25±1.94	8.87±2.43
t		0.352	0.611	0.465	0.488	0.531	0.422	0.666	0.205	0.533	1.066
p		0.726	0.543	0.643	0.627	0.597	0.674	-0.434	-1.278	0.596	0.290

TABLE 3: COMPARISON OF 2D-STI INDICES BETWEEN THE TWO GROUPS (x̄±s)

Group	n	GLS (%)		GLS-A4C (%)		GLS- A3C (%)		GLS- A2C (%)		PSD		LVEF (%)	
		Pre	After	Pre	After	Pre	After	Pre	After	Pre	After	Pre	After
Study	43	-22.04±1.17	-17.66±1.32	-22.94±1.46	-17.43±1.20	-22.57±1.27	-17.52±1.32	-22.53±1.64	-17.48±1.43	29.64±2.77	30.82±2.80	67.83±5.20	65.14±5.74
Control	40	-21.78±1.30	-19.40±1.66	-22.67±1.60	-18.56±1.43	-22.28±1.43	-18.67±1.48	-22.80±1.55	-18.34±1.48	29.11±2.56	30.45±2.66	-0.565	-1.418
t		-0.959	5.304	-0.804	3.91	-0.978	3.741	0.769	2.692	0.903	0.616	0.574	0.160
p		0.34	0.0001	0.424	0.0001	0.331	0.0001	0.444	0.009	0.369	0.540	-0.565	-1.418

TABLE 4: COMPARISON OF CK, LDH, AND NT-PROBNP VALUES BETWEEN THE TWO PATIENT GROUPS (x̄±s)

Group	n	CK (U/l)		LDH (U/l)		NT-proBNP (pg/ml)	
		Pre	After	Pre	After	Pre	After
Study	43	46.43±8.40	48.40±11.27	176.4±38.2	183.1±36.8	243.1±54.0	251.6±49.5
Control	40	50.02±9.14	52.15±10.67	181.6±40.5	188.4±32.5	235.8±59.5	242.1±55.3
t		-1.83	-1.521	-0.59	-0.678	0.575	0.811
p		0.071	0.132	0.557	0.5	0.567	0.42

Anthracene chemotherapeutic drugs have significant effect on treating breast cancer. After treatment, the 5 y and 10 y survival rate of patients have increased to 73 % and 61 %, respectively[8]. However, anthracyclines can cause type I cardiotoxicity, which can cause irreversible myocardial damage. The mechanism is complex, including free reactive oxygen species generation, oxidative stress, Deoxyribonucleic Acid (DNA) damage, etc.,[9,10]. Type I cardiac toxicity was dose-dependent, with a high incidence (48 %) of cardiac injury, when cumulative doses of anthracyclines were up to 700 mg/m^2[11,12]. As a humanized monoclonal antibody against Human Epidermal growth factor Receptor-2 (HER2), trastuzumab has a good anti-tumor effect on HER2 positive breast cancer patients, but it can cause type II cardiotoxicity, which can lead to myocardial cell dysfunction and hinder cell repair by inhibiting the cardiac HER2 neuromodulator protein system and disrupting endogenous oxidative stress regulation[13,14]. Type II cardiotoxicity is reversible and dose-independent[15,16]. A survey found that the incidence of trastuzumab-related cardiotoxicity was 7 %-27 %[17]. Cardio toxic injury can be increased when trastuzumab and anthracycline chemotherapeutic agents are combined, while the exact mechanism remains unclear[18-20].

As commonly used clinical indicators of myocardial enzyme profile, the increased serum levels of CK and LDH can sensitively reflect the degree of myocardial injury[21,22]. NT-proBNP is an inactive fragment released equally with BNP, which has good stability and long half-life. It is often used in clinical evaluation of cardiac function, because its serum level is less affected by drugs[23,24]. It has been suggested that serum NT-proBNP levels were related to the degree of heart failure[25]. This study found that the measured values of CK, LDH and NT-proBNP in the two groups were similar at 4 w, suggesting that the changes of CK, LDH and NT-proBNP were not obvious at the early stage of cardiac injury.

Echocardiography is a widely used clinical auxiliary examination method that can noninvasively evaluate myocardial systolic and diastolic function with the advantages of being easy to perform, no trauma, no radiation exposure and repeatability[26,27]. However, conventional echocardiography cannot reflect early cardiac injury[28-30]. The study found that after chemotherapy, there was no significant difference in LAD, LVEDD, LVESD, LVEF, E/A,

E/E' and other conventional echocardiographic indices between the two groups, suggesting that conventional echocardiography could not sensitively detect early changes in cardiac toxic injury, which is generally consistent with the existing research.

2D-STI technology is a new ultrasonic technology, which uses the unique gray value mode in myocardial tissue ultrasound images, namely "spots", to track spots frame by frame in the cardiac cycle to evaluate myocardial deformation. It has been applied in the evaluation of subclinical left ventricular dysfunction[31,32]. GLS can evaluate the overall and segmental ventricular function, which has good detection value for subclinical myocardial dysfunction[33-35]. In this study, it was applied for the evaluation of cardiac toxicity induced by chemotherapy. After chemotherapy, it was found that the measured values of PSD, GLS, GLS-A3C and GLS-A2C in the patients treated with targeted drugs combined with anthracycline drugs were lower than those in the patients treated with targeted drugs only.

PSD reflects the standard deviation of the time to peak strain of the 17 segments. PSD is a reliable tool for accurate evaluation of the coordination and synchronization of myocardial mechanical movement in the early stage of disease, the smaller the PSD then the better the synchrony of myocardial motion. The result suggests that anthracycline combined with targeted drug chemotherapy in patients with breast cancer has obvious toxicity to the left ventricular function of patients, and 2D-STI is more sensitive to these changes than conventional echocardiography.

In conclusion, breast cancer patients treated with anthracycline accompanied by targeted drug chemotherapy have obvious toxicity to the left ventricular function of patients, and 2D-STI is more sensitive to these changes than conventional echocardiography.

However, this study also has certain limitations. Although patients with hypertensive heart disease and severe heart, liver and kidney basic diseases are excluded from the study, those with stable disease in the early stage of coronary heart disease are still included, it may have a certain bias on the results. In the future clinical work, patients with cardiac disease should be eliminated as much as possible to improve the accuracy of the results.

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