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EFFECTS OF ANTHRACYCLINES ON LEFT VENTRICULAR FUNCTION ON BREAST CANCER PATIENTS

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ABSTRACT

Objective: To investigate the effect of Anthracyclines on left ventricular function on breast cancer patients at Thong Nhat Hospital. **Objects and methods:** A prospective descriptive study on 43 patients with breast cancer treated with Anthracyclines with 4 to 6 cycles as determined by the clinical doctor at Thong Nhat Hospital. **Results:** Percentage of left ventricular ejection, total deformation of the vertical systolic stage decreased significantly after treatment: EF before and after treatment were 60.23 ± 3.46 and 59.44 ± 3,67 (%), respectively; GLS before and after treatment were -20.01 ± 1.62 and -19.14 ± 1.82 (%), respectively. The incidence of cardiotoxicity was 6.98%. The proportion of patients with subclinical left ventricular dysfunction was 23.26%. After treatment, the proportion of respectively. The proportion of patients with subclinical systolic dysfunction was higher in the decreased diastolic function group compared to the group with normal diastolic function. Patients with normal diastolic function after treatment decreased, the proportion of patients with diastolic dysfunction increased significantly, accounting for 41.86% and 58.14% No association was found between the type of anthracycline used, also disease stage and the effect of anthracycline on left ventricular function. **Conclusion:** Left ventricular ejection fraction, total deformation of the vertical systolic stage reduced. The prevalence of cardiac toxicity and subclinical left ventricular dysfunction were moderate. After treatment, the proportion of patients with normal diastolic function decreased, the diastolic dysfunction increased. There was no relationship between the type of Anthracycline used, also the disease stage and the effect of Anthracycline on left ventricular function.

Keywords: Breast cancer, left ventricular function, Anthracyclines.

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1. INTRODUCTION

In breast cancer treatments, the role of adjuvant chemotherapy in reducing the risk of recurrence has long been confirmed. Anthracycline-containing adjuvant regimens improve disease-free survival (DFS) and overall survival (OS) compared with other chemotherapy regimens. Therefore, this regimen is used as a standard adjuvant chemotherapy in early breast cancer [1]. However, anthracyclines have side effects on a number of organs, including effects on the heart (dilated cardiomyopathy, supraventricular tachycardia, myocarditis, ECG changes, and sudden death) [2]. So we conducted this study with the aim of accessing the effects of anthracyclines on left ventricular function on breast cancer patients.

2. RESEARCH SUBJECTS AND METHODS

2.1. Patient population

43 breast cancer patients treated with 4-6 cycles of anthracyclines at Thong Nhat hospital.

* Exclusion criteria:

- Patients receiving trastuzumab-containing regimens at the time of this study.

- Patient previously received radiation or chemotherapy with another regimen; coronary artery disease, valvular heart disease (moderate or severe).

- History of atrial or ventricular arrhythmias, LVEF <50%.

- Previous heart surgery or implanted devices.

- The patient refused to participate in the study

- Incomplete medical records

- Patients taking other medications that have been shown to affect myocardial function

2.2. Research methods

Study design: A prospective, descriptive study.

***Sample size*:** Choosing the whole sample, including all patients who met the inclusion criteria during the study period.

Research variables:

- Clinical characteristics: Heart rate, blood pressure before and after treatment.

- Features on ultrasound: Changes of left ventricular systolic function including: Left ventricular diameters, fractional shortening FS, LVEF, left ventricular volumes, left ventricular muscle mass, stroke volume, global longitudinal strain); Changes of diastolic function indices including: peak E-wave velocity; peak A-wave velocity; E/A ratio; TRV - tricuspid regurgitation velocity; peak E' velocity; peak A'-wave velocity; ratio of E/E′.

- Relationship between left ventricular function after treatment and some factors (medications, stages of BC).

2.3. Statistical analysis: Data were entered and analyzed using IBM SPSS software version 22.0.

3. RESULTS

Table 1. Clinical changes

Clinical characteristics	Before treatment	After treatment	p
Heart rate	71.51 ± 11.41	78.82 ± 12.11	< 0.05
Mean arterial pressure	94.43 ± 10.22	94.82 ± 11.34	> 0.05

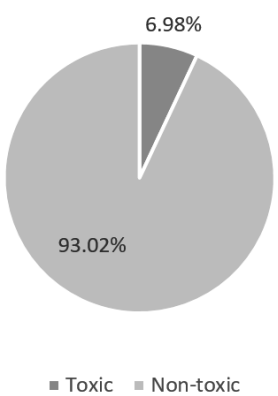
Heart rate increased significantly after treatment. Difference in mean blood pressure was not statistically significant.

Table 2. Changes of left ventricular systolic function

Parameters	Before treatment	After treatment	p
LV mass	75.54 ± 17.85	7.38 ± 16.4	> 0.05
EDV	55.31 ± 9.32	56.18 ± 11.42	> 0.05
ESV	21.26 ± 4.31	22.62± 5.23	< 0.05
FS	27.78 ± 5.23	26.80 ± 7.08	> 0.05
SV (ml)	30.20 ± 6.14	30.41 ± 6.42	> 0.05
EF (%) (Teicholz)	62.74 ± 8.97	61.61 ± 10.24	< 0.05
EF (%) (Simspson)	60.23 ± 3.46	59.44 ± 3.67	< 0.05
GLS	-20.01 ± 1.62	-19.14 ± 1.82	< 0.05

Left ventricular end-systolic volume increased significantly after treatment. Left ventricular ejection fraction and GLS both decreased significantly after treatment. Difference in left ventricular end- diastolic volume was not statistically significant.

Figure 1. Cardiotoxicity after treatment



The proportion of patients with cardiotoxicity and without cardiotoxicity was 6.98% and 93.02%, respectively.

Table 3. Subclinical left ventricular dysfunction

Subclinical LV dysfunction	Number of patients	Percentage
Yes	10	23.26
No	33	76.74
Total	43	100.00

The proportion of patients with subclinical left ventricular dysfunction was 23.26% (10/43 patients)

Table 4. Changes of diastolic function

Indices	Before treatment	After treatment	p
E	0.68 ± 0.12	0.65 ± 0.15	< 0.05
A	0.63 ± 0.11	0.64 ± 0.13	> 0.05
E/A	1.12 ± 0.30	1.03 ± 0.27	< 0.05
E’	9.21 ± 2.53	8.31 ± 2.32	< 0.05
A’	9.17 ± 2.4	9.21 ± 2.19	> 0.05
E/E’	7.42 ± 2.25	7.83 ± 2.42	> 0.05

Peak E-wave velocity and E/A ratio had significant changes after treatment ($p<0.05$). Peak E’ wave velocity decreased significantly changes after treatment ($p<0.05$).

Table 5. Diastolic dysfunction before and after treatment

Diastolic function	Before treatment		After treatment		p
Normal	23	53.49	18	41.86	< 0.05
Grade 1	19	44.19	24	55.81	< 0.05
Grade 2	1	2.33	1	2.33	-
Grade 3	0	0	0	0	-

The percentage of patients with normal diastolic function decreased significantly after treatment (p<0.05). The percentage of patients with grade 1 diastolic dysfunction increased significantly after treatment (p<0.05).

Table 6. Relationship between subclinical systolic dysfunction and degrees of diastolic dysfunction

Diastolic function	Without subclinical systolic dysfunction	With subclinical systolic dysfunction	p
Decrease	16	9	p < 0.05
Normal	17	1	
Total	33	10	

The proportion of patients with subclinical systolic dysfunction in the group with reduced diastolic function was statistically significantly higher than in the group with normal diastolic function (p<0.05).

Table 7. Relationship between systolic dysfunction after treatment and types of anthracycline

	Without systolic dysfunction	With systolic dysfunction	p
Doxorubicin	19	6	p > 0.05
Epirubicin	14	4	
Total	33	10	

There was no significant difference in the subclinical decrease in systolic function according to types of anthracycline used.

Table 8. Relationship between systolic dysfunction after treatment and stages of breast cancer

	Without systolic dysfunction	With systolic dysfunction	p
Stage I	2	1	p > 0.05
Stage II	12	3	
Stage III	17	3	
Stage IV	2	3	

There was no significant difference in subclinical systolic function reduction according to breast cancer stages.

4. DISCUSSION

In this study, we evaluated the effect of Anthracycline on left ventricular function in breast cancer patients treated at Thong Nhat hospital. Research results show that:

Clinical changes:

Heart rate after treatment with anthracyclines increased significantly. The mean blood pressure change was not statistically significant. These changes were quite consistent with the subclinical results. The proportion of patients with cardiotoxicity (10% reduction in EF and EF <53%) was 6.98% (3/343 patients). Anita Boyd et al (2017) reported similar results. After treatment, the heart rate change was statistically significant, while the blood pressure change was not significant [3].

Systolic function changes:

There are several methods of assessing cardiac function. In this study, ultrasound was used to evaluate left ventricular function including systolic function and diastolic function.

ESV increased significantly after treatment with anthracyclines ($p<0.05$). Meanwhile, increase in EDV was not statistically significant after treatment ($p>0.05$). According to Anita Boyd et al (2017), ESV increased slightly after anthracycline treatment ($p = 0.02$), while EDV did not change significantly ($p = 0.07$) [3].

Both EF and GLS decreased significantly after treatment. EF (%) (Simspson) before and after treatment was 60.23 ± 3.46 and 59.44 ± 3.67, respectively. In the study by Anita Boyd et al (2017), EF significantly decreased after anthracycline treatment ($p = 0.04$) [3]. According to Paul W. Stoodley (2013), EF at baseline and 7 days after the end of anthracycline chemotherapy were 58 ± 3% and 57 ± 3% ($p < 0.001$). EF decreased relatively 2% (mean EF within the clinically normal range). In two other foreign studies with longer follow-up time and/or higher doses of anthracyclines, left ventricular ejection fraction decreased slightly [4].

We evaluated the proportion of patients with cardiotoxicity by measuring EF (%), and evaluated the proportion of patients with subclinical left ventricular dysfunction by measuring GLS for early detection. The proportion of patients with cardiotoxicity was 6.98%. The proportion of patients with subclinical left ventricular dysfunction was 23.26%. Many patients did not have a significant decrease in EF but decrease in GLS was significant. Author Anita Boyd (2017) also reported similar results. In that study, left ventricular subclinical dysfunction (measuring GLS) were present in 22% of patients, whereas there was no evidence of cardiotoxicity by measurement of EF. The author suggested that GLS should be used in assessing cardiac function in patients treated with anthracyclines and some chemotherapy agents, in order to detect early subclinical changes without significant EF changes and then provide appropriate management [3].

Diastolic dysfunction following anthracycline chemotherapy has been reported previously. However, those studies had small sample sizes. The rate of patients with diastolic dysfunction after anthracycline chemotherapy is up to 57% of patients. This disorder was independently predicted by patient age and BMI [5]. Furthermore, there have also been reports of early diastolic stress following anthracycline therapy [4].

According to the study of Anita Boyd (2017), left ventricular diastolic function was worse in the group of patients after anthracycline chemotherapy. More importantly, diastolic dysfunction was more common in the group with >11 % reduction in GLS. This demonstrates a close relationship between systolic and diastolic function. In fact, the only predictor of >11 % reduction in GLS were early diastolic velocity and peak E velocity. Changes in premature left ventricular relaxation leads to enhanced active atrial contractility with increased atrial fraction and end diastolic velocity to compensate for the decrease in volume delivered during early diastole. However, these changes are clearly shown only by Doppler parameters, not atrial volume measurements, which are more reflective of the chronic nature of left ventricular diastolic dysfunction. Monitoring of diastolic function is of particular importance because changes in diastolic function with relatively preserved systolic function can also lead to heart failure.

In this study, we evaluated the changes in diastolic function after chemotherapy. Peak E-wave velocity and E/A ratio had significant changes after treatment ($p<0.05$). Peak E' wave velocity decreased significantly changes after treatment ($p<0.05$).

Diastolic dysfunction after chemotherapy

In this study, the percentage of patients with normal diastolic function decreased significantly after treatment ($p<0.05$). The percentage of patients with grade 1 diastolic dysfunction increased significantly after treatment ($p<0.05$).

In Anita Boyd's study (2017), echo parameters (including peak E velocity, ratio E/A, pulmonary venous diastolic velocity, E' velocity and early diastolic strain rate) were significantly reduced after anthracycline therapy. Left atrial ejection fraction and end-diastolic strain rate increased after treatment. Meanwhile, cases with diastolic dysfunction increased from 46% to 57% ($p < 0.001$). Patients with normal diastolic function decreased from 53% to 42% ($p < 0.001$) [3].

Cardiovascular toxicity remains a devastating complication of cancer treatment. Heart failure on anthracycline treatment has a 2-year mortality rate of up to 60%, 3.5-fold higher than in patients with idiopathic dilated cardiomyopathy. With many cancers being curable, cardiovascular complications have become a major threat to cancer survivors. Methods for earlier and more sensitive identification of patients at risk of future left ventricular dysfunction are paramount, as these patients may benefit from cardioprotective regimens - or in severe cases, change cancer therapy. EF, mitral annular velocity, and myocardial deformation indices have been shown to identify subclinical dysfunction in chemotherapy-induced cardiotoxicity. Evaluation of mitral annular velocity and myocardial deformation can detect preclinical changes in systolic function, prior to changes in EF. In the study of Negishi (2013), of 52 patients with a significant change in GLS, only 14 patients had a decrease in EF according to the diagnostic criteria for cardiotoxicity [6].

Relationship between subclinical systolic dysfunction and diastolic dysfunction

The proportion of patients with subclinical systolic dysfunction in the group with reduced diastolic function was statistically significantly higher than in the group with normal diastolic function ($p<0.05$). Anthracycline-induced cardiotoxicity may

primarily affect the subendocardium of left ventricular layer, composed primarily of longitudinal fibers as measured by GLS [7]. Ejection fraction is measured by assessing changes in radius of the ventricle. Therefore, changes in left ventricular ejection fraction may not be apparent until the myocardium has changed significantly. Similar results were also recorded in the study of Anita Boyd (2017). Patients with > 11% decrease in GLS significantly increased diastolic dysfunction compared with those with no change in GLS (30% vs 11%; p = 0.04). Furthermore, there was a larger change in early diastolic strain rate (p < 0.001), E velocity (p < 0.001) and E' velocity (p = 0.007) in the group with subclinical systolic dysfunction compared with those without subclinical systolic dysfunction. Multivariate regression analysis showed that changes in early diastolic strain rate (p = 0.004) and E velocity (p = 0.01) were predictors of >11% decrease in GLS [3].

Relationship between systolic dysfunction after treatment and types of anthracycline

Doxorubicin and epirubicin are the most frequently used anthracyclines in breast cancer regimens. In our study, all patients received chemotherapy with one of these 2 anthracyclines. The percentages of doxorubicin and epirubicin used were 58.14% and 41.86%, respectively.

Both agents cause dose-dependent cardiotoxicity; however, toxicity of doxorubicin may be greater than that of epirubicin. However, in this study, there was no significant difference in subclinical reduction in systolic function according to the type of anthracycline used.

This result is similar to the study of Anita Boyd (2017). There was no significant difference in left ventricular function (EF and GLS) between doxorubicin group and epirubicin group. Post-treatment EF of patients receiving doxorubicin and epirubicin were 59 ± 2% and 60 ± 2%, respectively (p = 0.23) [3].

Because anthracycline cardiotoxicity is type I cardiotoxicity, detection of myocardial damage is fundamental to identify patients who may go on to develop left ventricular dysfunction.

However, several studies have shown that early administration of beta-blockers improved GLS in patients with subclinical left ventricular dysfunction treated with anthracyclines, trastuzumab, or both. Furthermore, Seicean et al reported in a large observational study that randomized and continuous beta-blocker treatment reduced the onset of new heart failure in patients treated with anthracyclines and trastuzumab [8].

In this study, there are some limitations. This is an observational study so there are potential errors related to selection bias and relatively small sample size. Another limitation of this study is the exclusion of biomarkers. The importance of biomarkers for the preclinical detection of cardiac dysfunction is controversial in chemotherapy-induced cardiotoxicity.

5. CONCLUSION

*** Left ventricular systolic function:**

- EF and GLS decreased significantly after treatment: EF before and after treatment were 60.23 ± 3.46 and 59.44 ± 3.67 (%) respectively; GLS before and after treatment were -20.01 ± 1.62 and -19.14 ± 1.82 (%).

- The proportion of patients with cardiotoxicity

and without cardiotoxicity was 6.98% (3/43 patients)

- The proportion of patients with subclinical left ventricular dysfunction was 23.26% (10/43 patients)

*** Left ventricular diastolic function:**

- The proportion of patients with normal diastolic function after treatment decreased. The proportion of patients with diastolic dysfunction increased significantly, accounting for 41.86% and 58.14%, respectively.

- The proportion of patients with subclinical systolic dysfunction in the group with reduced diastolic function was higher than in the group with normal diastolic function.

*** Some factors related to the influence of Anthracycline on LV function:**

- No relationship was found between types of anthracycline used and stages of cancer on the effect of anthracycline on LV function.

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