

# Two-dimensional speckle tracking echocardiography, a powerful method for the evaluation of anthracyclines induced left ventricular insufficiency

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## Abstract

Anthracyclines have been one of the most important therapeutic methods in breast cancer therapy for decades. However, serious long-term toxicities, especially cardiotoxicity limits the continuous usage of anthracyclines, hence affects long term prognosis. Early detection of myocardial dysfunction during treatment is critical but challenging. Two-dimensional speckle tracking echocardiography (2D-STE) is a non-Doppler technique that can assess deformation and strain by tracking displacement of acoustic markers in the myocardium. This study aims to compare the sensitivity and precision between 2D-STE and traditional echocardiography on monitoring the left ventricular function in patients with breast cancer after anthracyclines therapy, which is the key indicator for evaluating myocardial changes.

Thirty-three patients with breast cancer were recruited from February 2019 to December 2019. All patients were treated with 4 cycles anthracycline. 2D-STE and conventional echocardiography were performed on each patient. Two-dimensional echocardiographic examination was used to collect data interventricular septum diameter (IVSD), end-diastolic left ventricular posterior wall diameter (LVPWD), left ventricular end-diastolic diameter (LVEDD) and left ventricular systole on the parasternal left ventricular long axis view. The final diameter (left ventricular end-systolic diameter [LVESD]) and the left ventricular short axis shortening rate (LVFS) was measured by M-type. The two-plane Simpson's method was used to measure left ventricular end-diastolic volume (LVEDV) and end-systolic volume (left ventricular end-systolic volume [LVESV]) to obtain left ventricular ejection fraction (LVEF). Two-dimensional speckle tracking imaging technical indicator includes left ventricular global longitudinal strain (LVGLS), subendocardial myocardial longitudinal strain (LVGLS-Endo) and epicardial myocardial longitudinal strain (LVGLS-Epi). The correlation between 2-dimensional speckle tracking imaging and conventional ultrasound parameters were analyzed.

Compared with baseline (T0), the systolic function parameter LVEF was significantly changed after four cycle chemotherapy (T4) ( $P < .05$ ). However, the conventional echocardiographic parameters including IVSD, LVPWD, LVEDD, LVESD, LVEDV, and LVESV were not statistically significant ( $P > .05$ ). Meanwhile, the two-dimensional strain parameters LVGLS, LVGLS-Endo, and LVGLS-Epi were statistically significant after T2 and T4 cycle chemotherapy ( $P < .01$ ).

The two-dimensional strain parameter GLS has higher accuracy and sensitivity for monitoring left ventricular insufficiency caused by anthracycline therapy when compared with traditional echocardiography.

**Abbreviations:** 2D-STE = two-dimensional speckle tracking echocardiography, IVSD = interventricular septum diameter, LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, LVESD = left ventricular end-systolic diameter, LVFS = left ventricular short axis shortening rate, LVGLS = left ventricular global longitudinal strain, LVPWD = left ventricular posterior wall diameter.

**Keywords:** anthracyclines, two-dimensional speckle tracing echocardiography, ventricular insufficiency

## 1. Introduction

Breast cancer has the highest prevalence among malignancies that threaten the health of women worldwide.<sup>[1]</sup> The treatment options include combination of surgery, cytotoxic chemotherapy, radiation

therapy, and molecularly targeted endocrine therapy. Early detection and advances in screening have led to a 5-year survival rate of breast cancer patients approaching 80.9% in China by far.<sup>[2]</sup>

The anthracyclines, includes doxorubicin, epirubicin, pirarubicin, daunorubicin, arubicin, idarubicin, amrubicin, are

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broad-spectrum anticancer drugs. Currently, anthracyclines are one of the main classes of first-line chemotherapy regimens for breast cancer. The side effects of anthracycline chemotherapeutics include arrhythmia, heart failure, and myocardial injury, as well as hair loss, thrombocytopenia, anemia, etc. Cardiac insufficiency has become the main cause of chemotherapy related death in postmenopausal breast cancer patients. However, cardiac insufficiency are mostly diagnosed late in the disease course, at the point when the effect is not reversible. Therefore, early detection of cardiac insufficiency is critical for improving the survival of breast cancer patients.

Two-dimensional speckle tracking echocardiography (2D-STE) is a non-Doppler technique that can assess deformation and straining by tracking displacement of acoustic markers in the myocardium. It does not have angle dependence and can track the scattered speckle information generated by small structures, which make it more objective and comprehensive than conventional echocardiography. Furthermore, 2D-STE can also provide accurate assessment for left ventricular myocardial mechanical information, which reflecting left ventricular function.

In this study, we compared the accuracy and sensitivity of conventional two-dimensional traditional echocardiography and 2D-STE, assessing left ventricular function, and exploring the value 2D-STE in the early diagnosis of left ventricular dysfunction caused by anthracycline chemotherapeutics in breast cancer patients.

## 2. Materials and Methods

### 2.1. Patient population

Thirty-three patients ( $51.36 \pm 9.77$  years old) with breast cancer were recruited in the Fourth Hospital of Hebei Medical University from February 2019 to December 2019. All patients were treated with at least one of anthracycline-based chemotherapy regimens for a total of 4 cycles. All patients underwent echocardiography within 48 hours after the completion of the fourth cycle (T4).

Inclusion criteria: Completed at least 4 cycles of anthracycline therapy after enrollment and voluntarily received follow-up; Histopathological diagnosis of breast cancer for the first time, no other malignant tumors in the past; Had normal liver and kidney function, normal electrocardiogram and conventional echocardiogram results upon enrollment (T0).

Exclusion criteria: pregnant or breast-feeding women; received radiotherapy and immunotherapy during chemotherapy; patients with poor echocardiographic image quality that cannot be collected and analyzed; uncontrolled hypertension and coronary heart disease, myocardial infarction, persistent atrial fibrillation, severe arrhythmia, cardiomyopathy, and other cardiovascular diseases; patients with hyperthyroidism, diabetes and other metabolic diseases.

The ethnics has been approved by the Ethics Committee of The Fourth Affiliated Hospital of Hebei Medical University, and all subjects signed informed consent forms.

### 2.2. Conventional two-dimensional echocardiography

The M-mode echocardiography was used to determine the levels of interventricular septum diameter (IVSD), left ventricular posterior wall diameter (LVPWD), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), and left ventricular short axis shortening rate (LVFS). The left ventricular ejection fraction (LVEF) was calculated using two-plane Simpson method.

### 2.3. Two-dimensional speckle tracking echocardiography

The dynamic images were analyzed using EchoPAC PC 203 software. First, select images of the apical 4-chamber heart, the

apical 2-chamber heart, and the apical 3-chamber heart section, and then we enter the 2D-Strain mode under the Q-analysis respectively and manually trace the left ventricular endocardium border. After that we adjusted the endocardial envelope winding accurately, and ensure the area of interest (area of interest [region of interest] [ROI]) contains complete ventricular wall information. Finally, click the approve key to confirm the tracking, and according to the pulse Doppler spectrum of the left ventricular outflow tract to determine the aortic valve closing time (AVC). The software calculates the left ventricular global longitudinal strain (LVGLS), the subendocardial myocardial longitudinal strain (LVGLS-Endo), and the epicardial myocardial longitudinal strain (LVGLS-Epi) automatically.

### 2.4. Statistical analysis

Results were analyzed using SPSS version 25.0. Results were exhibited as mean  $\pm$  standard deviation ( $\bar{x} \pm sd$ ). The comparison of indicators within each group were analyzed using paired-sample t test, the comparison of indicators between 2 groups uses unpaired t test. The differences between multiple groups were analyzed using One-way ANOVA. The data adopts 2-sided test, and  $P < .05$  is regarded as the difference is statistically significant. Bonferroni correction was used for each analysis.

## 3. Results

### 1. Comparison of general clinical data.

To examine the sensitivity and accuracy of 2D-STE and traditional echocardiography, 33 patients with breast cancer were recruited between February 2019 and December 2019. The patient's basic demographics are shown in Table 1.

### 2. Comparison of conventional parameters of left ventricle.

Compared with T0, the conventional echocardiographic parameters IVSD, LVPWD, LVEDD, LVESD, left ventricular end-diastolic volume (LVEDV), and left ventricular end-systolic volume (LVESV) that reflect the size and structure of the left ventricle were not statistically significant after T4 cycles of chemotherapy ( $P > .05$ ); compared with T0, the left ventricle The systolic function parameter LVEF was statistically significant after T4 cycle chemotherapy ( $P < .05$ ), and LVFS was not statistically significant after T4 cycle chemotherapy ( $P > .05$ ) (Table 2).

### 3. Comparison of the two-dimensional strain parameters of left ventricle.

Compared with T0, the 2-dimensional strain parameter LVGLS was statistically significant after T2 cycle chemotherapy ( $P < .01$ ) (Table 3).

### 4. The $\Delta$ LVGLS values are statistically significant in patients who are younger than 60 years old compared with the ones who are more than 60 years old (Table 4).

### 5. The 2-dimensional strain parameters of myocardial strain at each level of left ventricle (Table 5).

## 4. Discussion

Anthracyclines are a group of cytotoxic chemotherapeutic medications which can inhibit DNA replication and transcription to achieve anti-tumor effect.<sup>[3]</sup> They are a class of aromatic polyketone compounds, which were firstly used for cancer treatment in 1960s, and then broadly used for treatment of multiple types of malignant tumors. However, severe side effects of anthracyclines, especially cardiotoxic reactions limits its clinical application.<sup>[4]</sup> Until now, there is no definitive

**Table 1****The general clinical data (n = 33,  $\bar{x} \pm s$ ).**

Characteristic	$\bar{x} \pm s$
Age (yr)	51.36 $\pm$ 9.77
HR (bpm)	77.42 $\pm$ 9.05
SBP (mm Hg)	126.55 $\pm$ 14.53
DBP (mm Hg)	83.48 $\pm$ 11.01
Height (cm)	159.76 $\pm$ 4.53
Weight (kg)	65.25 $\pm$ 8.63
BMI (kg/m <sup>2</sup> )	24.72 $\pm$ 2.86
GLU (mmol/L)	4.99 $\pm$ 0.84
TC (mmol/L)	4.81 $\pm$ 0.90
TG (mmol/L)	1.23 $\pm$ 0.33
LDL-c (mmol/L)	3.10 $\pm$ 0.64
HDL-c (mmol/L)	1.39 $\pm$ 0.29
ECG	Basically normal

BMI = body mass index, DBP = diastolic blood pressure, GLU = glutamic acid, HDL-c = high-density lipoprotein cholesterol, LDL-c = low-density lipoprotein cholesterol, SBP = systolic blood pressure, TC = total cholesterol, TG = triacylglycerol.

**Table 2****The conventional parameters of left ventricle.**

	T0	T2	T4
IVSD (mm)	7.33 $\pm$ 0.74	7.51 $\pm$ 0.87	7.48 $\pm$ 0.91
LVPWD (mm)	8.09 $\pm$ 0.84	8.33 $\pm$ 0.85	8.15 $\pm$ 0.80
LVEDD (mm)	45.50 $\pm$ 2.40	45.36 $\pm$ 2.53	45.18 $\pm$ 2.27
LVESD (mm)	29.27 $\pm$ 2.82	29.79 $\pm$ 2.81	28.70 $\pm$ 2.56
LVEDV (mL)	69.42 $\pm$ 9.68	68.63 $\pm$ 10.51	68.27 $\pm$ 9.51
LVESV (mL)	24.24 $\pm$ 3.68	24.48 $\pm$ 4.02	24.97 $\pm$ 3.90
LVEF (%)	64.00 $\pm$ 2.52	63.90 $\pm$ 2.54	63.42 $\pm$ 3.17*
LVFS (%)	34.42 $\pm$ 2.51	34.24 $\pm$ 2.37	34.03 $\pm$ 2.56

\*Indicate  $P < .05$  compared with T0.

IVSD = interventricular septum diameter, LVEDD = left ventricular end-diastolic diameter, LVEDV = left ventricular end-diastolic volume, LVEF = left ventricular ejection fraction, LVESD = left ventricular end-systolic diameter, LVESV = left ventricular end-systolic volume, LVFS = left ventricular short axis shortening rate, LVPWD = left ventricular posterior wall diameter.

**Table 3****Comparison of the 2-dimensional strain parameter.**

	T0	T2	T4
LVGLS (%)	-21.34 $\pm$ 1.70	-19.85 $\pm$ 1.94**	-19.85 $\pm$ 1.94**

\*\*Indicate  $P < .01$  compared with T0.

LVGLS = left ventricular global longitudinal strain.

**Table 4****Comparison of different ages after chemotherapy.**

Groups (age)	Number	$\Delta$ LVGLS (%)
$\leq 60$	24	2.07 $\pm$ 1.31
$> 61$	9	3.68 $\pm$ 1.16
F value		10.415
P value		0.003

$\Delta$ LVGLS = LVGLST4-LVGLST0.

LVGLS = left ventricular global longitudinal strain.

safety threshold for myocardial damage caused by anthracyclines. It is reported that when the average cumulative dose of doxorubicin increases to 400 mg/m<sup>2</sup>, the incidence of heart failure reaches 5.0%; when it continues to increase to 700 mg/m<sup>2</sup>, the incidence of heart failure reaches 48.0%.<sup>[5]</sup> Therefore, the early assessment of heart damage caused by anthracycline

**Table 5****Myocardial strain at each level of left ventricle.**

	T0	T2	T4
LVGLS (%)	-21.34 $\pm$ 1.70	-19.85 $\pm$ 1.94**	-18.83 $\pm$ 2.21**
LVGLS-Endo (%)	-24.13 $\pm$ 1.83	-22.48 $\pm$ 2.02**	-21.29 $\pm$ 2.39**
LVGLS-Epi (%)	-18.73 $\pm$ 1.56	-17.42 $\pm$ 1.52**	-16.92 $\pm$ 1.76**

LVGLS = left ventricular myocardial systole global strain, LVGLS-Endo = the subendocardial myocardial longitudinal strain, LVGLS-Epi = the epicardial myocardial longitudinal strain.

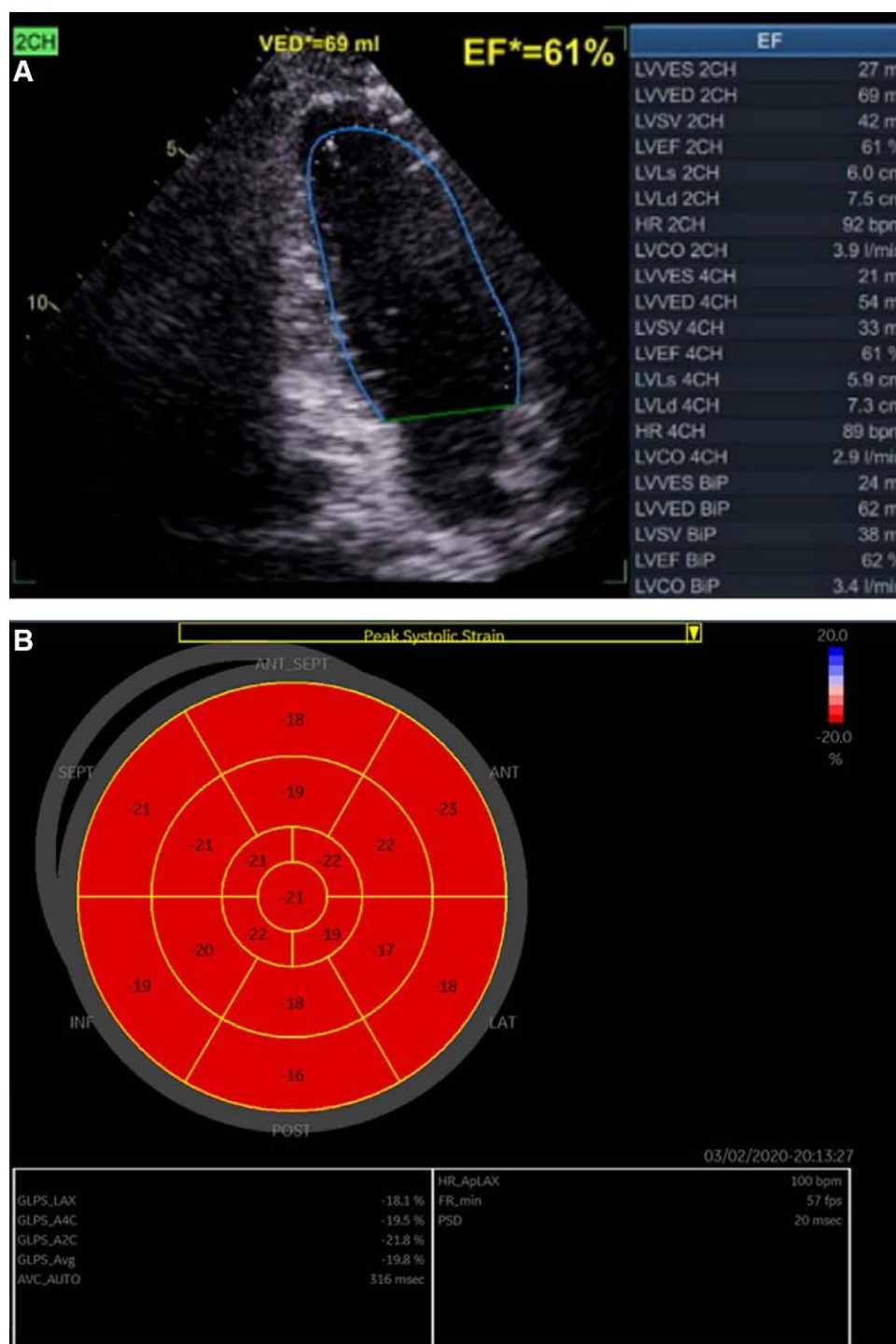
chemotherapeutics is very important to prevent cardiovascular disease event in patients with malignant tumors treated with anthracycline chemotherapy.

Traditional echocardiography assesses the left ventricular function by measuring the size and structural parameters of the ventricular cavity, and the two-dimensional Simpson biplane method to measure the related parameters of left ventricular systolic function. However, when there are some minor changes in left ventricular systolic function, conventional two-dimensional color Doppler ultrasound cannot accurately and comprehensively assess the changes in left ventricular function.<sup>[6,7]</sup> When the left ventricular function can finally be detected by traditional echo, the heart injury is too severe to be reversed. 2D-STI can track high frame rate 2-dimensional images in real time pattern, quantitative analysis of speckle echo, comprehensive observation of myocardial movement and mechanical deformation ability.<sup>[8]</sup> The levels of conventional parameters, IVSD, LVPWD, LVEDD, LVESD, LVEDV, LVESV, and LVFS was not significantly changed when compared with the same patients after the end of the T4 cycle chemotherapy, only LVEF level was significantly reduced after the T4 cycle treatment. Meanwhile, 2-dimensional strain parameters LVGLS are significantly reduced after the T4 chemotherapy cycle treatment, which is earlier than traditional echo, suggesting that the 2-dimensional speckle tracking imaging technique is more sensitive than conventional echocardiography. In this study, we observed that the degree of cardiac function damage  $\Delta$ LVGLS in patients  $\leq 60$  years old ( $P > .05$ ) was not significantly changed, but they are all less damaged than patients over 60 years old ( $P < .05$ ), this suggests that elderly patients may be more susceptible to cardiotoxicity.

In this study, LVEF and LVGLS measurements of a patient before chemotherapy showed that LVEF was 62% and LVGLS was -19.8% at baseline (shown in Fig. 1), while after chemotherapy the LVEF was 60% and the LVGLS was -14.9% at T4 (shown in Fig. 2). The LVGLS decreased significantly while LVEF was still at normal level. The anterior wall, anterior wall, inferior wall of the base and middle and the anterior wall, lateral wall of the apex of the heart were the main parts, indicating that the potential cardiac function damage had occurred at this time.

The increased specificity and accuracy of 2D-STI were also confirmed by other researchers. Kang et al monitored the patients receiving epirubicin chemotherapy by conventional echocardiography and found that GLS was significantly reduced after the third cycle of chemotherapy ( $P < .01$ ), and during and at the end of chemotherapy, but LVEF remained within the normal range. They did not find significant LVEF decrease until 4 to 6 months of follow-up ( $P < .01$ ).<sup>[9]</sup> All of the above indicate that conventional echocardiography cannot monitor early left ventricular dysfunction caused by anthracycline chemotherapy drugs.

Many factors may influence the accuracy of echocardiography for monitoring early left ventricular dysfunction. For example, the heart has a strong compensatory ability, and myocardial cell damage has occurred in the early stage. However, due to the large reserve of the heart, there is no abnormality in the indicators of the conventional 2 dimensional echocardiography; patients with cardiovascular damage caused by anthracycline

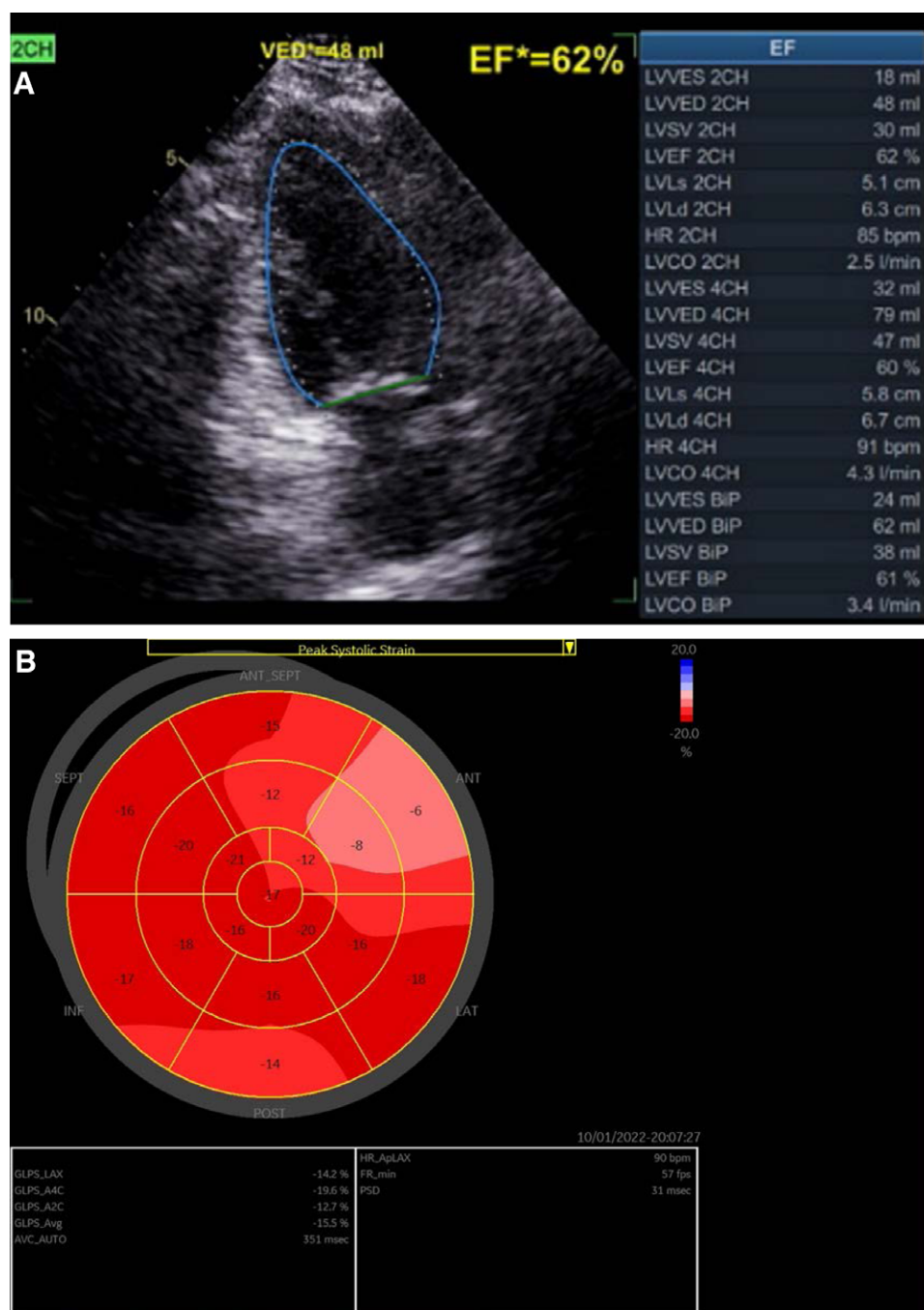


**Figure 1.** A and B are the LVEF (biplane Simpson method) and LVGLS values (bull's eye diagram) measured at the baseline level of a patient before chemotherapy, respectively. LVEF = left ventricular ejection fraction, LVGLS = left ventricular global longitudinal strain.

chemotherapy usually have a long history of smoking, high blood pressure, diabetes or hyperlipidemia, etc. These factors often lead to lung disease or cause the body surface area to increase, so that the image quality is disturbed during routine echocardiographic examinations, and the accuracy and repeatability of the measured left heart function parameters are poor; tumor patients usually suffer from dehydration due to nausea, vomiting or diarrhea, leading to the reduced load, and the 2-dimensional echocardiogram measurement parameters change temporarily, which reduces the accuracy of the measurement data.<sup>[10]</sup>

2D-STI can be used for layered strain analysis of myocardium. In this study, the strain stress relationship of myocardium layers during chemotherapy is LVGLS-Endo > LVGLS > LVGLS-Epi. This is consistent with the results of the study on the gradient characteristics of each myocardium layers in healthy adults.<sup>[11]</sup> The existence of this gradient may be related to the different curvature radius of each layer of myocardium, resulting in different tension of each layer.<sup>[12]</sup> The results show that the strain of each layer of myocardium decreases significantly after T2, which can sensitively monitor the cardiotoxicity of anthracycline drugs, but the decrease of subendocardial myocardium is





**Figure 2.** A and B respectively show the LVEF (biplane Simpson method) and LVGLS values (bull's eye diagram) measured after the fourth cycle of the same patient in Figure 2. LVEF = left ventricular ejection fraction, LVGLS = left ventricular global longitudinal strain.

the most obvious, suggesting that the subendocardial myocardium may be the most sensitive to the cardiotoxicity caused by anthracycline drugs. Some scholars believe that this is because the longitudinal fibers of subendocardial myocardium are more vulnerable to adverse factors such as toxicity, pressure, ischemia, and metabolism.<sup>[13]</sup>

Although 2D-STI has great value in the early detection of anthracyclines for the treatment of breast cancer-related cardiac insufficiency, its application also has certain limitations. Firstly, speckle tracking imaging requires high quality of 2-dimensional grayscale images, and those with poor acoustic window cannot be included in the analysis. Secondly, tracking the region of interest can be manually adjusted, although accuracy is increased, but it also increases operational error. Thirdly, the

myocardial movement is 3-dimensional, and the accuracy of the 2-dimensional plane speckle tracking is still slightly lacking.

## 5. Conclusion

2D-STI is a good method to monitor early subclinical cardiotoxicity in breast cancer patients treated with anthracyclines.

## 6. Limitations

1. The conclusion of this research depends on the results from 33 patients, which needs to be further confirmed in larger cohorts.

2. This study only analyzes the overall long-axis strain of the ventricle under the 2D-STI. Efforts can be made to include more comprehensive data including radial strain, circumferential strain and torsion function.

## Author contributions

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**Writing – review & editing:** Wenjie Li, Ruoling Han.

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