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Cardiac Image

The Early Predictive Value of Right Ventricular Strain in Epirubicin-Induced Cardiotoxicity in Patients with Breast Cancer

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Background: As cancer therapies have improved, patient life spans have been extended but quality of life has been threatened by chemotherapy induced cardiotoxicity. Most cardiac complications remain unobserved until specific symptoms develop. Speckle-tracking echocardiography is a sensitive imaging modality in detecting early occult myocardial dysfunction.

Methods: A total number of 35 patients newly diagnosed with breast cancer and preparing for epirubicin therapy were prospectively recruited. Echocardiography, including speckle-tracking echocardiography, was performed sequentially at baseline (T1), after the first cycle (T2) and after the third cycle (T3) of epirubicin. At each visit, the severity of dyspnea was evaluated by the assessment scale.

Results: Compared with the baseline, right ventricular longitudinal strain (RVLS_FW) at T2 significantly declined (-22.49 ± 4.97 vs. -18.48 ± 4.46, p = 0.001), which was also positively associated with the development of dyspnea (R^2 = 0.8, p = 0.01). At T3, both the left ventricular global longitudinal strain and RVLS_FW were significantly impaired (-21.4 ± 4.12 vs. -16.94 ± 6.81%; -22.49 ± 4.97 vs. -16.86 ± 7.27%, p = 0.01; 0.001, respectively). Also, the accumulating dose of epirubicin positively correlated with the development of dyspnea (R^2 = 0.38, p = 0.04) and the decline of RVLS_FW (R^2 = 0.53, p = 0.02). Notably, compared with the other echocardiographic parameters only RVLS_FW at the early stage (T2) significantly correlated with the development of dyspnea (odds ratio: 1.84, 95% confidence interval: 1.22-2.78, p = 0.04).

Conclusions: RVLS_FW sensitively predicts dyspnea development in breast cancer patients receiving epirubicin therapy. However, larger scale studies are required to validate its role in long-term patient survival.

Key Words: Dyspnea • Epirubicin • Right ventricle • Speckle-tracking echocardiography

INTRODUCTION

Worldwide, breast cancer manifests most frequently in women.[1] However, with the advent and advancement of chemotherapeutic drugs, patient survival has increased. Nonetheless, the subsequent cardiotoxicity of such therapy not only threatens the quality of patient life but cardiovascular outcomes as well.[2] Among these chemotherapeutic regimens, Doxorubicin has been known for the notorious effect of cardiotoxicity and has been gradually replaced by epirubicin.[3] Nevertheless, epirubicin is still concerning arising from its potential for

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causing cardiac damage. Although there is a growing recognition of the need for improved cardiotoxicity prevention, like adjusting the dose of chemotherapies and sequential monitoring cardiac function, a reliable and sensitive detector of subclinical myocardial dysfunction remains lacking. Oppositely, most cardiac complications eluded recognition until specific symptoms developed.

The current definition of chemotherapy-induced cardiotoxicity is based on the measurement of left ventricular (LV) ejection fraction (EF) with serial transthoracic echocardiography.[4,5] However, LVEF assessment depends on hemodynamic conditions and allows only the late diagnosis of cardiac dysfunction, which might already be irreversible. Speckle-tracking echocardiography (STE) is a noninvasive technique allowing the early detection of LV systolic dysfunction, before a decrease in LVEF.[6] Emerging studies have validated STE's role in evaluating doxorubicin, epirubicin or trastuzumab induced cardiac dysfunction.[6] Of note, although LV functions after chemotherapy have been investigated, scant few studies have focused on the right ventricular (RV) functions, a major determinant of exercise capacity in patients with or without heart failure.[7,8] One study indicated a subclinical decrease in right ventricular fractional area change (RVFAC) and tricuspid annular plane systolic excursion (TAPSE) after onset of chemotherapy, though primarily in the normal range.[7] Therefore, the application of STE in early detection of RV dysfunction may help differentiate patients with subsequent development of functional declines. Whereas most studies regarding RV have focused on congenital heart defects, pulmonary hypertension, pulmonary embolism and right cardiomyopathy,[9-11] none have investigated the relationship between RV speckle-tracking and chemotherapy induced cardiotoxicity. Hence, by using STE, we aimed to study the early effect of epirubicin on RV and functional capacity in patients with breast cancer. We also searched for the relationship between RV echocardiographic indices and serum levels of brain natriuretic peptide (BNP) and high-sensitivity troponin I (hsTnI), which are well-known markers of cardiac damage.

MATERIALS AND METHODS

Objective

Forty three patients who were newly diagnosed with breast cancer at Chi-Mei Medical Center were initially included in our study, which was conducted between June 2014 – March 2015. In addition, 10 age and gender matched controls were also enrolled. The study was conducted according to the recommendations of the Declaration of Helsinki on Biomedical Research involving human subjects and was approved by the local ethics committee (IRB: 10307-003), where written informed consent was obtained from each participant. We excluded 8 patients who underwent or were undergoing prior chemo- or radiotherapy, valvular heart disease (more than mild), renal failure (serum creatinine > 1.6 mg/dL), and hepatic dysfunction (serum aspartate aminotransferase, alanine aminotransferase above the upper limit), impaired systolic function (LVEF < 50%) at baseline or having inadequate echocardiographic view (Figure 1). Ultimately, 35 patients were enrolled in this study. Participants received or planned to receive six to eight cycles of epirubicin therapies, 21 days apart. All participants have undergone echocardiographic and serologic evaluation before the onset of the chemotherapeutic regimen (T1), on the day after the first cycle (T2), and after the completion of three cycles of the regimen (T3). The severity of dyspnea was evaluated at each visit using a dyspnea assessment scale by which patients indicated the severity of shortness of breath they have experienced over the past 2 weeks when climbing stairs, from 0 (none) to 10 (most severe).

Serology

Study subjects provided blood samples to obtain complete blood count, biochemistry, and serum BNP and hs-TnI (Abbott Laboratories, Abbott Park, IL, USA). An electrochemiluminescence immunoassay was used to determine serum BNP and hs-TnI levels, which had a reference range below 125 pg/ml and 26 pg/ml, respectively. These cardiac-associated biomarker measurements were repeated on each visit. The other serum biochemical tests were performed using routine methods according to the clinical needs of each patient.

Echocardiography

Standard echocardiography was performed (Vivid E9; GE Vingmed Ultrasound AS, Horten, Norway) with a 3.5-MHz multiphase-array probe in accordance with the recommendations of the American Society of Echocardio-

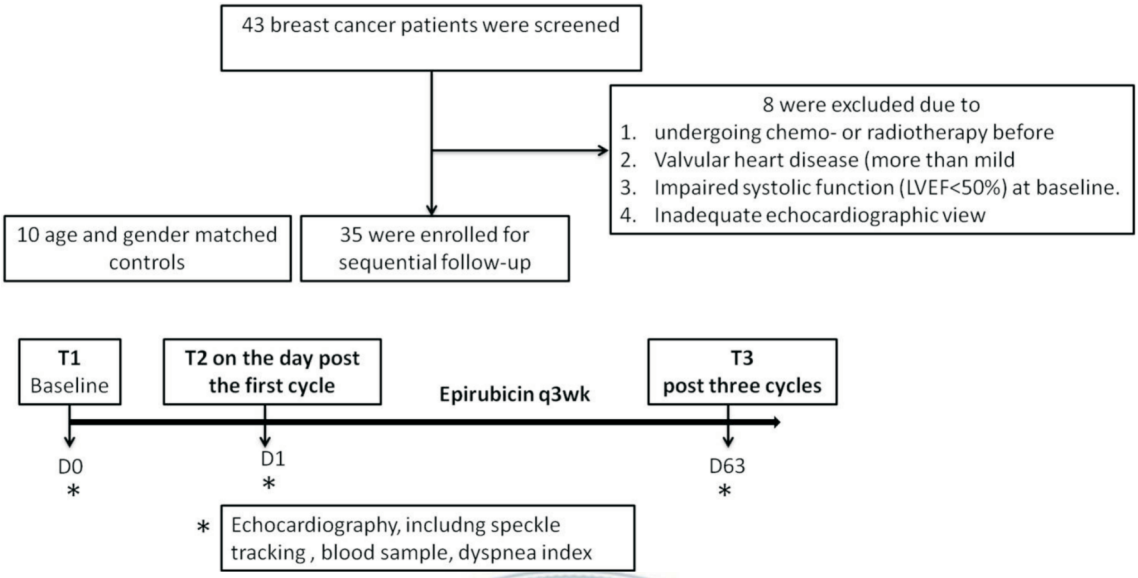

Figure 1. *The flow chart of the inclusion and exclusion of the studied population and the timeline of the sequential follow-up. T1, regimen; T2, after the first cycle; T3, after the completion of three cycles of the regimen.*

graphy.[12] LVEF was measured by use of the biplane Simpson's method. Right ventricular end-diastolic area and end-systolic area were measured from the apical four-chamber view to calculate RVFAC.[13] Right ventricular outflow tract dimensions were noted at the proximal or subvalvular level (RVD1), at the distal or pulmonic valve (RVD2). RV dimensions were defined as basal (RVD3), mid-cavity (RVD4) and longitudinal diameter (RVD5) in an apical 4-chamber view. RV wall thickness was obtained in the sub-costal view. To determine TAPSE, an M-Mode cursor was placed at the junction of the tricuspid valve plane with the right ventricular free wall, using the images of the apical four-chamber view.[13] In addition, pulmonary artery systolic pressure was obtained by the summation of the estimated trans-tricuspid valve pressure and the estimated right atrial pressure. LV and RV diastolic function associated parameters including isovolumic contraction time (IVCT), isovolumic relaxation time (IVRT), ejection time (ET), deceleration time (DT), trans-mitral and tricuspid early filling velocity (E) to atrial velocity (A) ratio. Tissue Doppler imaging (TDI) values of the right and left ventricles were obtained from the apical four-chamber view using a sample volume placed at the lateral corner of the tricuspid annulus, and in the anterior and lateral sections of the mitral annulus. Peak systolic annular velocity (S'), early (e'), and late (a') annular diastolic velocities were measured. In addition, myocardial performance index (MPI), also known as the Tei index, was calculated by the equation of (IVCT+IVRT)/ET.

Speckle-tracking echocardiography analysis for deformation

Standard apical 4-, 2- and 3-chamber views were recorded in digital loops for deformation analysis of the LV, and an apical 4-chamber view focusing on the RV was used for RV deformation. The images were acquired with frame rates of 70-90 frame/s and stored for three cycles. The images were analysed off-line using computer software (EchoPAC, GE-Vingmed Ultrasound AS, Horten, Norway). As described before,[14] we used an automated function imaging software to measure the left ventricular peak systolic global longitudinal strain (LVGLS). In brief, the LVGLS was calculated automatically by the software after defining the timing of the aortic valve closure. In addition, LV circumferential and radial strains were also obtained by the short axis view at the papillary muscle level. RV deformation was measured by two-dimensional STE in the apical 4-chamber view.[15] Right ventricular free wall longitudinal strain (RVLS_FW) and strain rate were derived from the average of three regional strains comprising the lateral wall.

Statistical analysis

Differences among patients with or without end-

points were compared using the Student's *t* tests for normally-distributed continuous variables, non-parametric test for non-normally distributed continuous variables and x^2 tests for categorical variables. Group differences were analyzed using analysis of variance (ANOVA). Factors with $p < 0.1$ based on the univariate analyses were included in the multivariate logistic regression analyses. Degrees of association between continuous variables were calculated by Spearman's correlation analysis. A p value of less than 0.05 was considered to be statistically significant. All analyses were performed with SPSS version 18 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline clinical characteristics in breast cancer patients receiving Epirubicin and in the control group

The mean breast cancer patient age was 45.33 ± 8.48 years old among the 35 enrolled patients, which was similar to the control group of 50.22 ± 10.43 years old (p = 0.25) (Table 1). In addition, the serum glucose, lipid profile, renal function, BNP and hsTnI were not significantly different between the control and the patients at baseline. During the follow-up period, none of the patients required termination of the treatment due to cardiotoxicity or major cardiovascular complications, including myocardial infarction, hospitalization due to heart failure or stroke. No significant change was observed in heart rate or blood pressure between the basal values and after the fist or the third cycle of therapy. Among these patients, two received concomitant radiotherapy. The average dose of epirubicin accumulated to 354.19 ± 336.08 mg/M^2 after three cycles. Along with the accumulation of epirubicin, the severity of dyspnea developed in an increasing trend. Consequently, 5 patients reported significant dyspnea on exertion (the scoring index above 5) at the third visit. Grossly, neither of the sequentially followed BNP or hsTnI differentiated the development of dyspnea.

Conventional and tissue Doppler echocardiographic characteristics in breast cancer patients receiving epirubicin and in the control group

Regarding the echocardiographic measurements, neither the LV nor the RV dimensions specifically changed in the sequential follow-up. The average LVEFs were similar

Table 1. Clinical characteristics of the normal control and breast cancer patients at baseline (T1), on the day post the first cycle (T2) and post three cycles of epirubicin (T3)

	Normal control (n = 10)	T1 (n = 35)	T2 (n = 35)	T3 (n = 35)	F value	p-value
Age (years)	50.22 ± 10.43	45.33 ± 8.48	-	-		0.25
Body height (cm)	160.2 ± 6.41	157.57 ± 5.74	-	-		0.47
Body weight (kg)	58.06 ± 7.81	56.88 ± 6.86	-	-		0.62
Body surface area (M^2)	1.62 ± 0.05	1.63 ± 0.21	-	-		0.66
Heart rate (bpm)	69.81 ± 7.36	73.5 ± 8.24	72.38 ± 11.74	67.46 ± 8.48	0.55	0.64
Systolic blood pressure (mmHg)	120.22 ± 16.49	129.66 ± 14.01	123.1 ± 17.24	121.33 ± 15.54	0.86	0.46
Diastolic blood pressure (mmHg)	83 ± 8.09	82.66 ± 7.37	85.52 ± 13.79	84.44 ± 9.47	0.42	0.73
Serology data						
Serum glucose (ac, mg/dl)	95.33 ± 9.68	92 ± 10.58	98.75 ± 18.96	91.66 ± 41.5	2.09	0.11
Creatinine clearance rate (ml/min)	95.88 ± 24.6	83.71 ± 34.05	108.7 ± 45.81	87.71 ± 26.94	1.25	0.29
Triglyceride (mg/dl)	122.66 ± 51.13	129 ± 6.92	-	-	0.64	0.59
Cholesterol (mg/dl)	178.77 ± 32.66	178.66 ± 38.63	-	-	0.49	0.67
hsTnI (pg/ml)	2.5 ± 1.87	2.6 ± 2.54	3.9 ± 4.28	3.8 ± 3.04	0.53	0.25
BNP (pg/ml)	12.5 ± 11.3	12.89 ± 12	12.54 ± 7.7	10.07 ± 7.98	0.26	0.27
Therapeutic regimens						
Mean single dose of Epirubicin (mg/M^2)	0	0	119.17 ± 8.91	114.32 ± 7.12	0.34	0.71
Accumulating dose of Epirubicin (mg/M^2)	0	0	119.17 ± 8.91	354.19 ± 336.08	0.43	0.24
Concomitant radiotherapy	0	0	2 (10)	2 (10)	0.43	0.13
Dyspnea index, median (IQR)	0 (0,0)	0 (0,1)	2 (0,3)	3 (0,5)	1.41	0.08

Data are expressed as mean ± SD, or median, indicates interquartile ranges (IQR).
BNP, brain natriuretic peptide; HsTnI, high-sensitivity troponin I.

between the patients and the control group (68.17 ± 4.05% vs. 65.85 ± 6.46%, p = 0.58) at baseline (Table 2). After consequent epirubicin therapy, no significant decline of LVEF was observed (62.43 ± 15.75% at T2 and 65.78 ± 8.74% at T3, p = 0.62). Similarly, the average RVFAC was 60.59 ± 12.34% at T1, 61.57 ± 9.83% at T2 and 55.48 ± 7.31% at T3 (p = 0.34). Conversely, TAPSE values presented a significant decline of 1.94 ± 0.47 cm, 1.57 ± 0.61 cm and 1.22 ± 0.62 cm, respectively (p = 0.005). There was no significant change of estimated pulmonary artery pressure, MPI and RV S' between each visit.

Regarding diastolic function, LV e' presented a significant decrease from 10.83 ± 2.74 cm/s, 8.19 ± 1.39 cm/s to 6.47 ± 2.98 cm/s (p = 0.01), which implied a progression of LV diastolic dysfunction. Likewise, IVRT also decreased (96.66 ± 13.21 ms, 80.74 ± 21.5 ms and 71.43 ± 35.32 ms, respectively, p = 0.01). Correspondingly, the estimated intra-ventricular pressure (E/e') increased (7.45 ± 1.4, 10.83 ± 2.81 and 12.15 ± 3.56, respectively, p = 0.01). In the evaluation of RV diastolic function, the tricuspid e' measured by TDI exhibited a significant attenuation along with the accumulation of epirubicin

Table 2. Conventional and tissue Doppler echocardiographic characteristics of the normal control and breast cancer patients at baseline (T1), on the day post the first cycle (T2) and post three cycles of epirubicin (T3)

	Normal control (n = 10)	T1 (n = 35)	T2 (n = 35)	T3 (n = 35)	F value	p-value
Left heart						
Left atrium dimension (cm)	3.24 ± 1.08	3.1 ± 0.55	2.83 ± 1.14	3.71 ± 1.21	1.64	0.18
LVMI (g/m^2)	83.32 ± 29.19	80.85 ± 39.88	85.71 ± 40.21	79.21 ± 23.84	0.13	0.93
LVIDd (cm)	4.26 ± 0.89	4.11 ± 0.86	4.12 ± 1.07	4.22 ± 1.08	1.11	0.35
LVIDs (cm)	2.45 ± 0.98	2.48 ± 0.42	2.59 ± 0.71	2.43 ± 0.53	3.19	0.2
LVEF (%)	60.85 ± 6.46	68.17 ± 4.05	62.43 ± 15.75	65.78 ± 8.74	1.13	0.64
E (cm/s)	70.85 ± 18.93	69.35 ± 12.73	82.71 ± 21.34	78.41 ± 22.98	1.3	0.58
E/A	0.99 ± 0.38	1.08 ± 0.28	0.97 ± 0.74	0.89 ± 0.27	2.41	0.06
e' (cm/s)	9.32 ± 2.21	10.83 ± 2.74	8.19 ± 1.39	6.47 ± 2.98	4.53	*0.01*
E/e'	7.61 ± 2.47	7.45 ± 1.4	10.83 ± 2.81	12.15 ± 3.56	3.68	*0.01*
IVRT (ms)	93.79 ± 23	96.66 ± 13.21	80.74 ± 21.5	71.43 ± 35.32	3.81	*0.01*
DT (ms)	209.35 ± 68.56	154.16 ± 42.2	198.4 ± 43.72	174.8 ± 50.28	4.52	0.93
MPI	0.42 ± 0.18	0.48 ± 0.03	0.45 ± 0.12	0.43 ± 0.16	2.38	0.35
Right heart						
RVD1 (cm)	2.49 ± 0.34	2.15 ± 0.99	2.26 ± 1.02	2.23 ± 0.87	5.07	0.43
RVD2 (cm)	2.06 ± 0.58	2.18 ± 0.98	1.7 ± 1.12	2.08 ± 0.99	1.34	0.24
RVD3 (cm)	2.39 ± 0.46	2.44 ± 1.26	2.58 ± 1.08	2.43 ± 1.3	2.57	0.74
RVD4 (cm)	2.56 ± 0.47	2.42 ± 1.27	3 ± 1.98	2.98 ± 1.34	3.81	0.3
RVD5 (cm)	5.95 ± 0.47	5.42 ± 2.43	6.2 ± 2.31	6.08 ± 2.98	9.12	0.62
RV wall thickness (cm)	0.42 ± 0.15	0.4 ± 0.08	0.37 ± 0.09	0.31 ± 0.18	4.21	0.42
RV FAC (%)	60.13 ± 9.64	60.59 ± 12.34	61.57 ± 9.83	55.48 ± 7.31	7.31	0.34
RV E/A	0.72 ± 0.31	0.90 ± 0.37	0.45 ± 0.32	0.58 ± 0.47	5.21	0.28
RV e' (cm/s)	8.79 ± 3.41	8.33 ± 1.96	7.12 ± 2.71	5.12 ± 3.47	9.43	*0.01*
RV E/e'	8.93 ± 4.12	8.03 ± 2.43	11.2 ± 4.35	10.83 ± 5.21	6.08	0.24
RV S' (cm/s)	15.38 ± 4.31	14.77 ± 3.49	11.95 ± 4.38	12.84 ± 6.72	7.32	0.73
RV MPI	0.30 ± 0.14	0.34 ± 0.12	0.29 ± 0.21	0.38 ± 0.14	4.32	0.21
TAPSE (cm)	1.7 ± 0.27	1.94 ± 0.47	1.57 ± 0.61	1.22 ± 0.62	5.31	*0.01*
Est. pulmonary systolic pressure (mmHg)	19.69 ± 7.52	15.03 ± 5.08	20.84 ± 7.08	17.85 ± 8.34	4.05	0.12

Data are expressed as mean ± SD, or median. *Italicizing* values indicate statistical significance.

DT, deceleration time; E/A, trans-mitral valve E to A velocity ratio; E/e', mitral early filling velocity to early diastolic mitral annular velocity ratio; FAC, fractional area change; IVRT, isovolumic relaxation time; LVEF, left ventricular ejection fraction; LVIDd, left ventricular interior dimension at end diastole; LVIDs, left ventricular interior dimension at end systole; LVMI, left ventricular mass index; MPI, myocardial performance index; RV, right ventricular; RVD, right ventricular dimension; RVFAC, right ventricular fraction area change; S', tricuspid annular systolic excursion in tissue Doppler imaging; TAPSE, tricuspid annular plane systolic excursion.

(8.33 ± 1.96 mg/M^2, 7.12 ± 2.71 mg/M^2 and 5.12 ± 3.47 mg/M^2, p = 0.01).

STE in breast cancer patients receiving epirubicin and in the control group

At baseline, LVGLS were similar between the breast cancer patients and the control group (-21.4 ± 4.12% vs. -21.12 ± 5.79%, p = 0.52) (Table 3). Despite no significant changes at T2, a significant decline of LVGLS was noted at T3 (-23.01 ± 8.72% vs. -16.94 ± 6.81%, p = 0.008). None of the other STE parameters, including LV radial strain, circumferential strain and strain rates, presented significant changes. Notably, RVLS_FW presented significant impairments at the subsequent visits (-22.49 ± 4.97%, -18.48 ± 4.46% and -16.86 ± 7.27%, p = 0.001).

The association between STE and the development of dyspnea

As a sensitive detector of myocardial dysfunction, RVLS_FW on the day T2 was positively associated with the development of dyspnea in the following period (R^2 = 0.79, p = 0.01) (Figure 2A). Conversely, LVGLS did not present significant impairment until T3 (Table 3). Also, the accumulating dose of epirubicin positively correlated to the development of dyspnea (R^2 = 0.38, p = 0.04) (Figure 2B), and the decline of RVLS_FW (R^2 = 0.53, p = 0.02) (Figure 2C). This was noted prior to left ventricular systolic or diastolic dysfunction measured by conventional echocardiography.

The characteristics of patients developing significant dyspnea

To investigate the early changes (T2) of echocardiographic parameters in differentiating the severity of dyspnea, we categorized the patients according to the development of significant dyspnea on exertion (the scoring index above 5) at the third visit. Among these parameters which were significantly correlated to the development of significant dyspnea, only RVLS_FW presented the predictive value (odds ratio: 1.84, 95% CI: 1.22-2.78, p = 0.04) (Table 4). Notably, this result indicated that patients with an early decline of RVLS_FW at T2 specifically predicted the subsequent development of dyspnea.

In addition, among these patients with established severe dyspnea the value of BNP increased significantly at T3 (14.14 ± 6.84 pg/ml, 20.32 ± 10.27 pg/ml and 23.96 ± 10.92 pg/ml at T1, T2 and T3, p = 0.4 between T1 and T2, p = 0.01 between T2 and T3, respectively) (Figure 3A). Correspondingly, the amplitude of LVGLS (-24.02 ± 3.42%, -21.12 ± 4.04% and -14.94 ± 4.57% at T1, T2 and T3, p = 0.2 between T1 and T2, p = 0.05 between T2 and T3, respectively) (Figure 3B), and RVLS_FW (-23.2 ± 1.61%, -17.51 ± 2.9% and -9.1 ± 5.09% at T1, T2 and T3, p = 0.01 between T1 and T2, p = 0.01 between T2 and T3, respectively) also declined at T3 (Figure 4). The result implicated the potential associations

Table 3. Speckle-tracking echocardiographic characteristics of the normal control and breast cancer patients at baseline (T1), on the day post the first cycle (T2) and post three cycles of epirubicin (T3)

	Normal control (n = 10)	T1 (n = 35)	T2 (n = 35)	T3 (n = 35)	F value	p-value
Left heart						
LVGLS (%)	-21.12 ± 5.79	-21.4 ± 4.12	-23.01 ± 8.72	-16.94 ± 6.81	4.85	0.05
LVRS (%)	25.57 ± 8.43	28.76 ± 9.72	26.51 ± 9.98	22.09 ± 9.68	3.76	0.07
LVCS (%)	-25.82 ± 7.61	-26.98 ± 5.96	-26.88 ± 6.28	-24.98 ± 7.4	5.78	0.53
LVLSR (s^{-1})	-1.29 ± 0.60	-1.35 ± 0.76	-1.28 ± 0.42	-1.34 ± 0.3	6.27	0.58
LVRSR (s^{-1})	1.68 ± 0.98	1.79 ± 1.05	1.64 ± 0.34	1.72 ± 0.76	4.12	0.4
LVCSR (s^{-1})	-1.97 ± 0.82	-1.88 ± 0.8	-1.86 ± 0.72	-2.04 ± 0.98	3.18	0.74
Right heart						
RVLS_FW (%)	-19.01 ± 3.49	-22.49 ± 4.97	-18.48 ± 4.46	-16.86 ± 7.27	3.80	*0.001*
RVLSR_FW (s^{-1})	-1.90 ± 0.53	-1.88 ± 0.58	-1.89 ± 0.57	-1.54 ± 0.26	7.08	0.37

Data are expressed as mean ± SD, or median. *Italicizing* values indicate statistical significance.
LVCS, left ventricular circumferential strain; LVCSR, left ventricular circumferential strain rate; LVGLS, left ventricular global longitudinal strain; LVLSR, left ventricular longitudinal strain rate; LVRS, left ventricular radial strain; LVRSR, left ventricular radial strain rate; RVLS_FW, right ventricular free wall longitudinal strain; RVLSR_FW, right ventricular free wall longitudinal strain rate; SD, standard deviation.

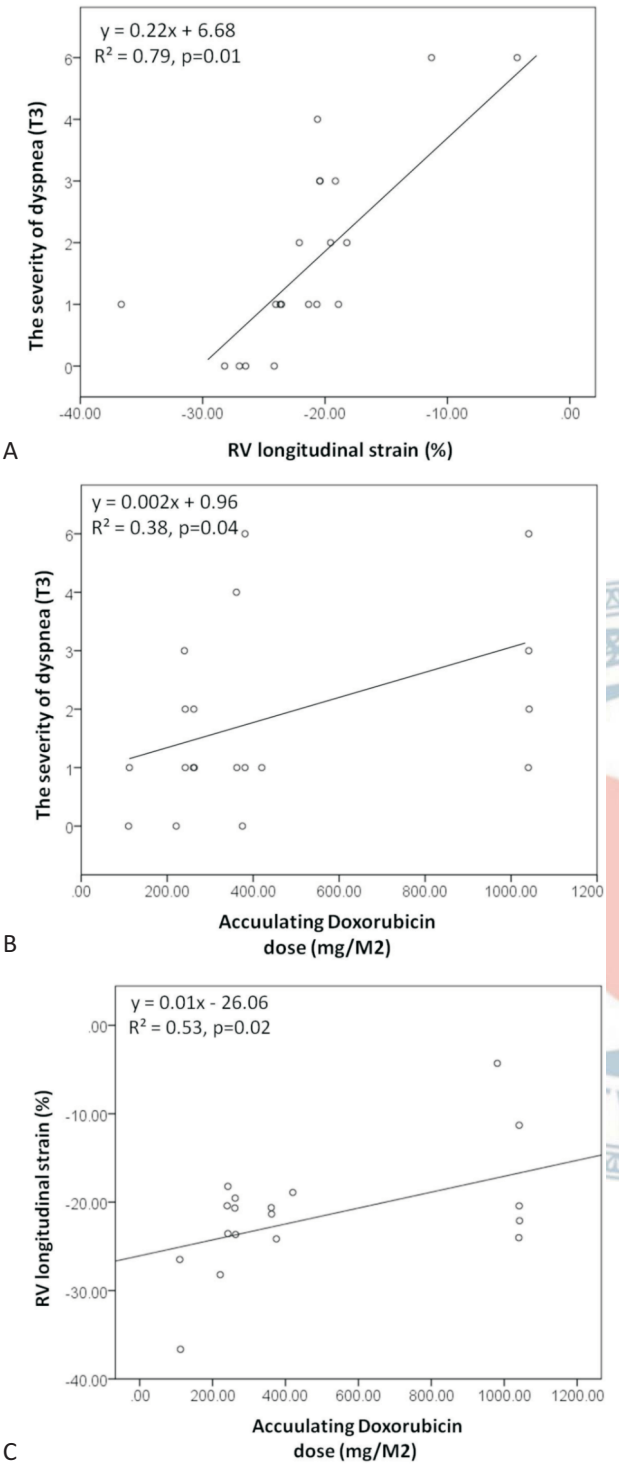

Figure 2. *(A) RVLS_FW on the day post the first cycle of chemotherapy (T2) was significantly attenuated along the development of dyspnea in the following period (R^2 = 0.8, p = 0.01). (B) The accumulating dose of epirubicin positively correlated to the development of dyspnea (R^2 = 0.38, p = 0.04). (C) The accumulating dose of epirubicin was positively correlated with the decline of RVLS_FW (R^2 = 0.53, p = 0.02). RVLS_FW, right ventricular free wall longitudinal strain.*

between the impairment of left or right heart strain and epirubicin induced heart failure, which was represented as dyspnea in exertion in these patients.

DISCUSSION

There are three main findings of the present study: (1) echocardiographic parameters, including TAPSE, LV and RV diastolic parameters, LVGLS and RVLS_FW significantly changed post epirubicin therapy at the early stage; (2) the accumulating dose of epirubicin positively correlated with the development of dyspnea, and the decline of RVLS_FW. (3) RVLS_FW significantly correlated with the development of dyspnea.

In spite of various definitions of chemotherapy-induced cardiotoxicity, the general consensus definition is a decrease in the LVEF of > 10% and to a value < 53%.[5] Although LVEF is a robust predictor of cardiac outcomes in the general population, it has low sensitivity for the detection of small changes in LV function.[5] Also, the anthracyclines, including doxorubicin and epirubicin-induced type I cardiotoxicity, is usually irreversible and leads to severe complications.[5,16] Thus, early detection of subclinical cardiac damage is crucial. In numerous studies involving anthracyclines, LV diastolic impairment was observed to precede systolic dysfunction.[3,7,17] To investigate diastolic function, TDI has been regarded as the preferred method.[17] Nevertheless, it required an extremely high frame rate and was angle dependent. With the advancement of imaging modalities, STE which directly depicts the myocardial deformation has been recently reported to detect the subclinical myocardial damage earlier than myocardial velocity measurements.[3,6]

A recent systematic review indicated that 21 studies have reported the sensitivity of STE in the detection of subclinical LV dysfunction in patients treated for cancer.[6] The decrease in myocardial systolic function induced by anthracyclines appears to be extremely rapid, as early as 2 hours after the first anthracycline dose.[18] Similar to most of the other studies, the decrease in deformation indices preceded the decrease in LVEF and persisted during the subsequent cancer treatment.[3,5] Early decreases in radial and longitudinal strain and strain rate were noted after three cycles of anthracyclines.[19] Strain rate measurements may be more sensitive than strain to

Table 4. Univariate and multivariate logistic regression of echocardiographic parameters in predicting the development of significant dyspnea in breast patients receiving epirubicin therapy

Parameter	Univariate model		Multivariate model	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
e′ (cm/s)	0.82 (0.67-0.97)	0.05	0.94 (0.85-2.47)	0.43
E/e′	1.75 (0.85-2.14)	0.43	-	-
IVRT (ms)	1.02 (0.94-2.31)	0.32	-	-
RV e′ (cm/s)	1.08 (0.82-1.74)	0.08	1.08 (0.47-2.08)	0.74
TAPSE (cm)	0.88 (0.78-0.97)	*0.02*	1.32 (0.83-3.21)	0.21
LVGLS (%)	1.89 (0.63-4.42)	0.53		
RVLS_FW (%)	2.53 (1.43-4.47)	*0.01*	1.84 (1.22-2.78)	*0.04*

Italicizing values indicate statistical significance. p-value < 0.05. Parameters with p-value < 0.1 in the univariate model were enrolled in the multivariate model.

e′, tissue Doppler early diastolic mitral annular velocity; E/e′, mitral early filling velocity to tissue Doppler early diastolic mitral annular velocity ratio; IVRT, isovolumic relaxation time; LVGLS, left ventricular global longitudinal strain; RV e′, right ventricular tissue Doppler tricuspid annular velocity; RVLS_FW, right ventricular longitudinal strain; TAPSE, tricuspid annular plane systolic excursion.

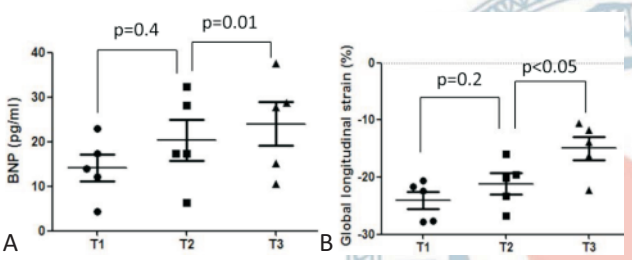

Figure 3. *Among the five patients who developed significant dyspnea on exertion, (A) the values of BNP, (B) LVGLS and at each visit. BNP, brain natriuretic peptide; LVGLS, left ventricular global longitudinal strain.*

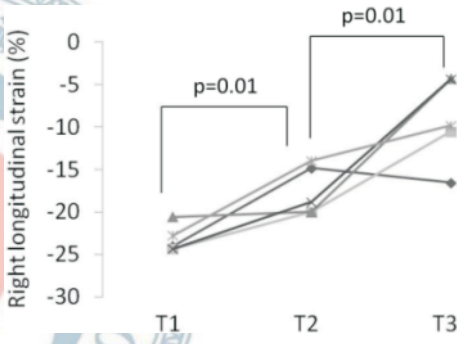

Figure 4. *The sequential changes of RVLS_FW among the five patients who developed significant dyspnea on exertion at each visit. RVLS_FW, right ventricular free wall longitudinal strain.*

subtle changes in cardiac function, but its application may be more challenging in clinical practice.[5] In one recently published study, the changes of LVGLS were believed to be the strongest predictor of chemotherapy-induced cardiotoxicity at the 6-month mark. Using 11% reduction as the optimal cutoff, the sensitivity and specificity reached 65% and 94%, respectively.[20] Also, the prognostic value of early measurement of STE has been evaluated in only a few studies. In Rhea's work, LVGLS were significantly associated with all-cause mortality in patients with cancer with normal ejection fractions receiving anthracycline.[21] However, the normal values for GLS depend on the measurement position in the myocardium, the version of the analysis software and the echo machine vendor, resulting in considerable heterogeneity.[5]

Additionally, RV function has been found to be highly associated with oxygen change, hemodynamics and functional capacity.[8] It is generally understood that RV is affected by chemotherapy, as early studies often included RV biopsies.[22] However, the frequency of RV involvement or its prognostic impact has not yet been well-studied. There was only one study reporting subclinical decrease in RV systolic and diastolic functions using TDI.[7] With the improvement of STE, RV strain has been applied in different diseases but focused on pulmonary hypertension, congenital heart defects, and right cardiomyopathy.[10,11,23] The present study is the first investigation using STE to investigate epirubicin-induced early RV dysfunction and its associated functional declines.

In previous studies, the majority of cardiovascular events occurred in TnI positive patients.[24] A persistent TnI increase was associated with an increase in the severity of chemotherapy induced cardiotoxicity.[5,24] Fur-

thermore, BNP was also regarded as a biomarker for the prediction of cardiotoxicity.[5,24] However, BNP still cannot replace advanced cardiac imaging, like gated equilibrium radionuclide ventriculography, in monitoring of anthracycline induced cardiotoxity.[25] Also, in a recently published article,[26] despite a significant rise of serum NT-proBNP following the first cycle of doxorubicin therapy in breast cancer in patients who subsequently developed a LVEF reduction, at the third cycle of therapy, there was no distinction observed between the levels of NT-proBNP of patients with or without cardiac systolic dysfunction. This may stem from the relatively low sensitivity and the high variability in the measurement of NT-proBNP, especially when detecting a small change. In our study, it was shown that neither BNP nor hsTnI was significantly changed along with the consequent therapies. We believed the discrepancy was caused by measurement at the very early stage and the difference between individuals. Interestingly, when we focused on the five patients who subsequently developed specific dyspnea, a significant increase of BNP was detected at T3, corresponding to the impairment of LVGLS and RVLS_FW. The result implied that the decline of left and right heart strain may be caused by epirubicin induced heart failure. Nevertheless, regarding the early diagnosis of subclinical myocardial dysfunction, the roles of current biomarkers have remained indeterminate.

In our findings, RVLS_FW exhibited a superior ability to detect occult RV systolic dysfunction compared with other traditional echocardiograpic parameters in patients receiving epirubicin, and therefore correlated to the development of dyspnea. This finding may imply that in an inherently thinner structure, RV may be more vulnerable to chemotherapy induced toxicity than LV. Also, the impaired RV function, even occult, may remarkably affect the cardiopulmonary function. Although clinical deterioration did not occur in a relatively short time, this investigation may give rise to attention to the right heart in cancer patients.

We recognize several limitations of this study. First, a control group of breast cancer patients who did not receive chemotherapy would help to ameliorate the effect of cancer per se on myocardial function, while cancer-induced systemic inflammation may also contribute to cardiac dysfunction.[27] However, regarding one ethical issue, patients not receiving chemotherapy were difficult to recruit. Instead, we enrolled gender- and age-matched healthy subjects as the control. Second, in a relatively short period, none of the study patients suffered major cardiovascular complications or the guideline defined cardiotoxicity as described above.[5] Even though the design of this study focused on early detection of functional decline, like dyspnea on exertion, a continuous follow-up will be conducted. In addition, dyspnea may not specifically reflect the cardiac dysfunction while cardiopulmonary function tests may provide more details, like oxygen consumption. Third, owing to the complex geometry of RV, the restrictive window may cause limitations in comprehensively observing RV. In our opinion, three-dimensional echocardiography may alternatively resolve this technical issue. Fourth, the severity of dyspnea was subjectively graded. Conversely, functional evaluations, such as cardiopulmonary exercise testing, will provide more specific information. Nevertheless, as most of the patients suffered from general weakness and gastroenterological symptoms and such functional evaluations were difficult to perform.

CONCLUSIONS

In this study, RVLS_FW was superior to other parameters in early detecting the development of dyspnea in breast cancer patients receiving epirubicin therapy. However, studies with a larger scale and longer follow-up duration are required to evaluate the effect of RVLS_FW on predicting outcomes and the reversibility of cardiotoxicity.

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CONFLICT OF INTEREST

None.

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