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ORIGINAL ARTICLE
Heart failure

Serial changes of layer-specific myocardial function according to chemotherapy regimen in patients with breast cancer

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Aims Chemotherapy-induced cardiotoxicity (CIC) is a significant complication, meanwhile myocardial damage might differ depending on chemotherapy agents and their timing. The aim of this study was to evaluate serial changes of layer-specific myocardial function in patients with breast cancer and their differences by the development time of CIC and chemotherapy agent.

Methods and results A total of 105 consecutive patients with breast cancer (age: 52.3 ± 9.3 years) were enrolled. Chemotherapy-induced cardiotoxicity occurred in 20 (19%) patients during 6 months. Endocardial and midmyocardial functions decreased in patients with or without CIC, with patients with CIC showing greater decreases during follow-up. Global longitudinal strain (GLS) change at 3 months was the most sensitive parameter to detect CIC. When new development of CIC was analysed at 6 months, GLS was reduced earlier than the decrease of left ventricular ejection fraction. In patients with CIC who were treated with anthracycline-based regimen for 3 months, endocardial GLS markedly decreased at 3 months and continued to decrease until 6 months. Patients with CIC who received trastuzumab therapy after anthracycline therapy showed further reduction in endocardial GLS at the 6-month follow-up, which was not shown in patients with CIC who received taxane therapy subsequently.

Conclusion Myocardial function assessed by strain decreased in all patients with breast cancer receiving chemotherapy. The endocardial layer was the most vulnerable to chemotherapy-induced myocardial damage. Functional impairment was more profound in patients with CIC who received sequential anthracycline-trastuzumab chemotherapy. Thus, early evaluation of left ventricular function might be necessary for all patients with breast cancer to detect CIC.

Keywords Chemotherapy • Cardiotoxicity • Strain • Breast cancer • Endocardium

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Introduction

Breast cancer is the most commonly diagnosed cancer in women.[1] Although advances in early diagnosis and therapeutic agents have improved the survival and prognosis of patients with breast cancer, cardiotoxicity remains a well-known complication of chemotherapy for breast cancer and a leading cause of morbidity and mortality in breast cancer patients.[2,3]

Left ventricular ejection fraction (LVEF) measured by echocardiography plays a pivotal role in diagnosing chemotherapy-induced cardiotoxicity (CIC).[4] Although LVEF is a marker for left ventricular (LV) systolic function, a decrease in LVEF is a late phenomenon of advanced myocardial damage.[5] Left ventricular ejection fraction may underestimate the actual cardiac damage because healthy myocardium compensates to maintain cardiac output despite damaged myocardium.[6] The myocardium is composed of three layers: endocardial, midmyocardial, and epicardial. Recent advances in speckle tracking echocardiography have enabled the assessment of layer-specific strain, which is a more sensitive marker than the conventional strain for a specific disease group such as coronary artery disease[7] and hypertension.[8] However, a comprehensive assessment of serial changes in layer-specific myocardial function in patients undergoing chemotherapy has been scarcely reported. These changes could be different by the development time of CIC and recovery. Therefore, the aim of this study was to evaluate serial changes of layer-specific myocardial function in patients with breast cancer, its difference by onset of occurring CIC, and recovery.

Methods

Study population

This study included 105 patients (mean age: 52.3 ± 9.3 years) with breast cancer who underwent chemotherapy from July 2017 to May 2019. Patients who had previously undergone chemotherapy or radiotherapy were excluded from this study. Patients with significant valvular heart disease, congenital heart disease, previous cardiac surgery, or significant medical diseases were also excluded. In addition, patients who had poor image quality for strain analysis were excluded. Detailed inclusion and exclusion of this study are presented in *Figure 1*. The study protocol was approved by the Korea University Medicine Anam Hospital Institutional Review Board (approval number: 2017AN0170). Written informed consent was obtained from each patient.

Image acquisition and speckle tracking analysis

Echocardiography was performed before chemotherapy (baseline) and at 3 and 6 months after chemotherapy in all patients. All echocardiograms were recorded using a Vivid cardiovascular ultrasound system (E90 and E95, GE Healthcare, Horten, Norway) with a 2.5 MHz transducer. Strain analysis was performed using a dedicated software (EchoPAC, version 203, GE Healthcare, Horten, Norway). Cardiac chamber size and function were evaluated according to the guideline.[9]

The strain was analysed by speckle tracking echocardiography to determine myocardial function. Three apical images (four-chamber, two-chamber, and three-chamber) for calculating longitudinal strain (LS) and three parasternal images (short-axis clips at the level of the mitral valve, the papillary muscle level, and the apex) of the left ventricle for calculating circumferential strain (CS) were acquired over three cycles. The frame rate of images was set at 70–90 Hz. Strain analysis was performed by tracing the LV endocardial border in end-systole frames of images. The region of interest (ROI) was placed on the LV myocardium to cover the entire myocardium.[10] Layer-specific global longitudinal strains (GLSs) were evaluated assuming a linear distribution. Global longitudinal strains of epicardial myocardium and endocardial myocardium were assessed within the ROIs of epicardial order and endocardial order, respectively. Circumferential strain was measured within endocardial, midmyocardial, and epicardial myocardia of each LV segment. Layer-specific global circumferential strains (GCSs) were calculated as the average of basal, middle, and apical CSs within each layer. The strain difference between epicardial L(C)S and endocardial L(C)S was calculated. The change in GL(C)S during the 3-month follow-up S (ΔGL[C]S3month) was defined as the difference between GL(C)S at three months and GL(C)S at baseline (GLS at the 3-month follow-up - GLS at baseline). The reproducibility of layer-specific LS and CS was tested in 25 randomly assigned patients. Inter-and intra-observer agreements for layer-specific LS and CS were excellent except for epicardial CS (Supplementary material online, *Table S1*).

Assessment of chemotherapy-induced cardiotoxicity

Chemotherapy-induced cardiotoxicity was assessed by *de novo* decrement in LVEF during chemotherapy follow-up. According to the 2016 Committee for Practice Guidelines of the European Society of Cardiology (ESC), CIC was defined as an absolute decrease of ≥10% in LVEF from baseline.[4]

Statistical analysis

Quantitative data are presented as mean ± standard deviation. Categorical data are expressed as numbers and percentages. Continuous variables and categorical variables were compared between patients with CIC (CIC group) and patients without CIC (without CIC group) using paired *t*-test and χ^2 test, respectively. The repeated measured analysis of variance using Bonferroni adjustment was performed to evaluate and compare trends of echocardiographic parameter, including LVEF and layer-specific strains during the follow-up. These data were presented as an estimated marginal means with a 95% confidence interval. Cox regression analysis was performed to assess predictors of CIC. The receiver operating characteristics (ROC) analysis was used to estimate the predictability of GLS for developing CIC. The area under curve (AUC) was measured for accuracy of prediction by method by Delong et al (11). The cut-off of each parameter was selected by the Youden index method. The intraclass correlation coefficient was calculated to assess intra-and inter-observer variabilities. A P-value < 0.05 was regarded as statistically significant. All analyses were conducted using SPSS 25.0 for Windows (IBM, Armonk, NY, USA).

Results

Baseline characteristics

Of 105 patients, 20 (19%) developed CIC during the 6-month follow-up. Baseline characteristics of patients are described in *Table 1*. There was no significant difference in the mean age or body mass index between those with CIC and those without CIC. There was no significantly different difference in the prevalence of smoking, diabetes, hypertension, or dyslipidaemia between those with CIC and those without CIC. No patient had a history of coronary artery disease or heart failure. The proportion of patients taking angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium

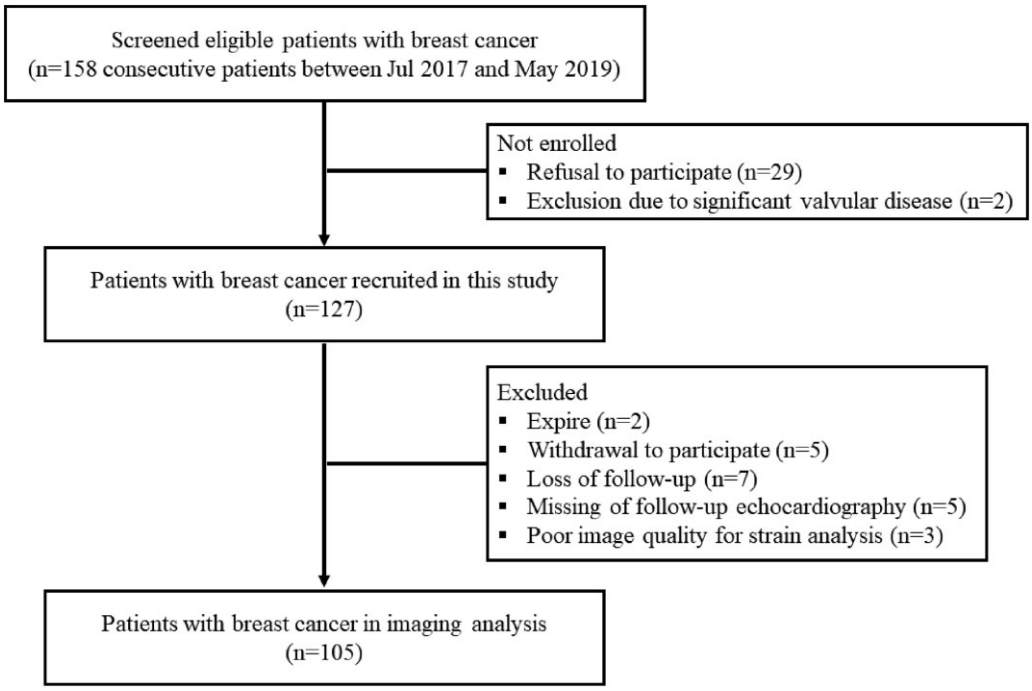

Figure 1 Flow chart showing the selection of patients.

channel blockers, beta-blockers, or statins was higher in those without CIC than in those with CIC, although the difference was not statistically significant.

The site and stage of cancer were not significantly different between the two groups (*Table 2*). Moreover, the purpose of chemotherapy was not different between the two groups. The proportion of patients who received anthracycline and the cumulative dose of anthracycline received by patients were similar in the two groups. The proportion of patients who had received taxane was also similar (96.0% vs. 93.8%, $P = 0.545$). However, the proportion of patients who had received trastuzumab was higher in the CIC group than in the group without CIC. In addition, the cumulative dose of trastuzumab was smaller in the CIC group than in the group without CIC. The proportion of patients who underwent radiation therapy did not differ between the two groups (*Table 2*).

Serial changes in global myocardial function

Baseline values of LV and left atrial size and diastolic mitral inflow parameters were not statistically different between the groups (*Table 3*). Left ventricular ejection fraction was not significantly different between the two groups at baseline. However, it decreased substantially in the CIC group during the follow-up. There was a significant ($P = 0.001$) difference in serial change of LVEF between the two groups (*Figure 2*). Changing patterns of chamber size and mitral inflow were not significantly different between the two groups (*Table 3*). In the CIC group, the GLS was significantly decreased at the 3-month follow-up. Such decrease persisted at the 6-month follow-up. The GCS progressively decreased during the follow-up. GLS and GCS were slightly reduced for the 3-month follow-up and were reduced in 6-month follow-up, even though LVEF did not decrease. The degree of GLS and GCS reduction was smaller than in patients with CIC.

Serial changes in layer-specific myocardial function

Baseline values of layer-specific GLSs, CCSs, and strain gradient were not signficiant different between patients with CIC and those without CIC. In the CIC group, endocardial and midmyocardial GLSs were significantly decreased at the 3-month follow-up. They continued to decrease until the 6-month follow-up. Endocardial and midmyocardial GCSs gradually reduced during the 6-month follow-up (*Figure 3*). Even in the group without CIC, GLSs and GCSs of endocardial and midmyocardial layers were decreased, with diminished values of GLSs and CCSs being greater in the endocardial layer than in the midmyocardial layer. However, epicardial GLS and GCS changes were not significantly different between the two groups (*Figure 2*). The CIC group showed significant reductions in epicardial–endocardial strain difference of GLS and GCS, unlike the group without CIC (*Figure 4*).

Echocardiographic predictor of chemotherapy-induced toxicity

The ΔGLS_{3month} was independently associated with CIC development during the 6-month follow-up (Table 4). The ΔGLS_{3month} was closely related to CIC development within a 3-month follow-up. The Δ GLS_{3month} showed a statistical trend about the newly occurred CIC between 3 and 6-month follow-up. The GLSs of each myocardial layer at baseline were not statistically significant in the ROC analysis.

Table 1 Baseline characteristics of the study population ($n = 105$)

	Patients without CIC ($n = 85$)	Patients with CIC ($n = 20$)	*P*-value
Age, years	52.2 ± 10.0	52.9 ± 5.2	0.738
Body mass index, kg/m^2	21.4 ± 4.9	21.0 ± 2.7	0.712
Smoking, *n* (%)	1 (1.2%)	1 (5.0%)	0.346
Diabetes, *n* (%)	8 (9.4%)	0 (0%)	0.348
Hypertension, *n* (%)	15 (17.6%)	2 (10.0%)	0.404
Dyslipidaemia, *n* (%)	17 (20.0%)	2 (10.0%)	0.296
Stroke, *n* (%)	1 (1.2%)	0 (0%)	1
CAD or HF, *n* (%)	0 (0%)	0 (0%)	
Medication			
ACEi or ARB, *n* (%)	14 (16.5%)	0 (0%)	0.128
CCB, *n* (%)	11 (12.9%)	1 (5.0%)	0.455
Beta-blocker, *n* (%)	3 (3.5%)	0 (0%)	1.0
Statins, *n* (%)	17 (20.0%)	2 (5.0%)	0.518
Anti-platelet agent, *n* (%)	6 (7.1%)	0 (0%)	0.592
Laboratory finding			
Hb, g/dL	12.7 ± 1.2	13.2 ± 1.0	0.104
Hs-CRP, mg/L	1.65 ± 2.4	1.26 ± 1.3	0.587
CK-MB, ng/mL	1.24 ± 0.7	1.07 ± 0.5	0.387
Troponin I, ng/mL	0.097 ± 0.03	0.090 ± 0.01	0.349
NT-pro BNP, pg/mL	89.3 ± 63.9	115.7 ± 96.2	0.173

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CCB, calcium channel blocker; CIC, chemotherapy-induced cardiotoxicity; CK-MB, creatinine kinase-MB fraction; Hb, haemoglobin; HF, heart failure; Hs-CRP, highly sensitive C-reactive protein; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Table 2 Breast cancer characteristics of the study population

Site, *n* (%)	Patients without CIC ($n = 85$)	Patients with CIC ($n = 20$)	*P*-value
Left	45 (53.0%)	8 (40.0%)	0.539
Right	40 (47.0%)	12 (60.0%)	
Stage, *n* (%)			
I	7 (8.3%)	3 (15%)	0.152
II	51 (60.0%)	11 (55%)	
III	24 (28.2%)	4 (20.0%)	
IV	3 (3.5%)	2 (10.0%)	
Adjuvant, *n* (%)	42 (49.4%)	9 (45.0%)	0.322
Chemotherapeutic agent			
Anthracycline, *n* (%)	46 (54.8%)	11 (55.0%)	0.985
Cumulative dose, mg/m^2	248.1 ± 37.6	252.1 ± 23.8	0.727
Trastuzumab, *n* (%)	24 (28.2%)	7 (35.0%)	0.591
Cumulative dose, mg/m^2	2086.2 ± 179.6	2665.1 ± 203.6	0.460
Use of dexrazoxane, *n* (%)	25 (34.7%)	5 (33.3%)	0.918
Radiation therapy, *n* (%)	13 (15.3%)	4 (20%)	0.736

CIC, chemotherapy-induced cardiotoxicity.

Table 3 Changes of echocardiographic parameters during 6-month of follow-up

	Baseline	3 months	6 months	*P*-value
Patients without CIC ($n = 85$)				
LVMI, g/m^2	76.0 ± 18.1	75.5 ± 16.3	75.6 ± 12.7	0.843
LVEF, %	62.6 ± 4.87	62.7 ± 5.30	61.6 ± 4.52	0.041
LA, mm	33.3 ± 4.77	33.8 ± 4.84	34.8 ± 4.69	0.425
E, cm/s	68.2 ± 16.6	64.3 ± 19.2	64.0 ± 16.7	0.219
DT, ms	184.9 ± 35.6	182.9 ± 33.9	181.0 ± 34.0	0.367
e′	8.12 ± 2.09	7.86 ± 2.08	7.75 ± 1.94	0.201
E/*e′*	8.76 ± 2.19	8.56 ± 2.47	8.61 ± 2.38	0.502
GLS	-19.6 ± 2.60	-18.4 ± 2.18	-18.3 ± 1.83	<0.001
GCS	-23.0 ± 4.16	-22.1 ± 3.74	-21.9 ± 3.70	0.019
Patients with CIC ($n = 20$)				
LVMI, g/m^2	76.5 ± 15.4	82.3 ± 10.4	81.9 ± 16.3	0.094
LVEF, %	64.1 ± 4.73 †	56.3 ± 5.96 †	55.0 ± 8.06 †	<0.001*
LA, mm	32.7 ± 3.82	34.9 ± 3.99	33.9 ± 4.28	0.072
E, cm/s	61.5 ± 13.5	57.0 ± 13.3	55.3 ± 18.0†	0.126
DT, ms	181.0 ± 34.0	170.8 ± 22.0	178.1 ± 31.7	0.794
e′	7.74 ± 1.95	7.05 ± 1.84	7.08 ± 2.05	0.141
E/*e′*	8.31 ± 2.05	8.34 ± 1.98	8.08 ± 1.94	0.573
GLS	-20.3 ± 2.32	-17.2 ± 2.15†	-16.8 ± 2.17†	<0.001*
GCS	-21.7 ± 4.13	-20.3 ± 2.23†	-19.3 ± 3.07†	0.017*

P-values were evaluating using repeated measured ANOVA.
CIC, chemotherapy-induced cardiotoxicity; DT, deceleration time; *E*, early diastolic velocity of mitral inflow; *e′*, early mitral annular velocity; *E*/*e′*, the ratio of early diastolic velocity and early mitral annular velocity; GCS, global circumferential strain; GLS, global longitudinal strain; LA, left atrium; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index.
*$P < 0.05$ for the difference in serial change of echocardiographic parameter between groups.
†$P < 0.05$ for comparison between patients with and without CIC.

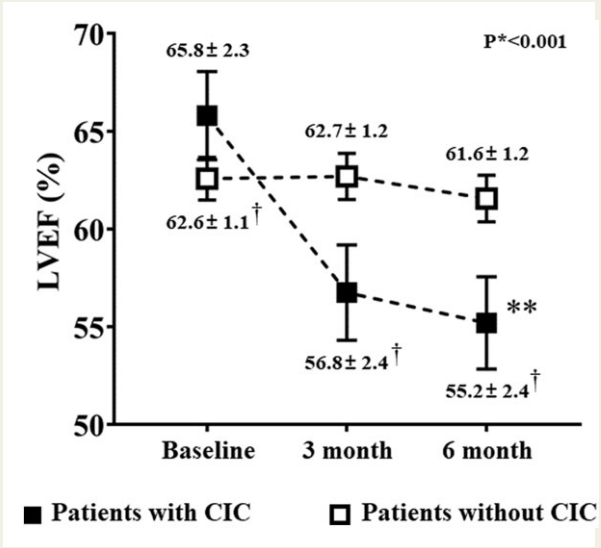

Figure 2 Comparison of changes in LVEF between patients with CIC and those without CIC. The data were presented as estimated marginal with 95% confidence interval. *$P < 0.001$ for the difference in serial change of LVEF between patients with and without CIC. **$P < 0.001$ for the trend of LVEF in patients with CIC. †$P < 0.05$ for comparison between patients with and without CIC. CIC, chemotherapy-induced cardiotoxicity; LVEF, left ventricular ejection fraction.

And AUC of these was less accurate (supplement table 2). Whereas, the predictability of Δ GLS_{3month} for detecting CIC during 6-month follow-up was acceptable (AUC=0.718, 95% CI 0.62-0.80, P <0.001) and the cut-off value was 2.7 (sensitivity=77.6% and specificity=60.0%). And the predictabilities of Δ GLS_{3month} were sufficient for developing CIC within 3month and between 3-and 6-month follow-up (AUC=0.777, 95% CI 0.69-0.85, P=0.001 and AUC=0.657, 95% CI 0.56-0.75, P =0.017).

Effects of chemotherapeutic agents on myocardial damages

A decrease of endocardial GLS at varying degrees occurred in all patients who had received chemotherapy. However, the reduction of endocardial GLS was larger in patients who developed CIC in both taxane and anthracycline groups. It continued to decrease in patients who had received anthracycline-based chemotherapy and developed CIC (Supplementary material online, *Figure S1*). Further analysis adding the use of anti-HER2 inhibitor, additional LV dysfunction by anti-HER2 inhibitor was not found in patients with taxane-based regimen. On the other hand, LV functional impairment by anti-HER2 inhibitor was more profound in patients with preceding anthracycline-based chemotherapy (Supplementary material online, *Figure S2*).

Discussion

The main findings of this study were as follows: (i) LV strain was reduced in all patients regardless of (regardless of) the development of CIC; (ii) GLS could change prior to LVEF decrease; (iii) among three myocardial layers, endocardial function showed the greatest reduction; (iv) the change of GLS during 3-month follow-up was significantly related to the development of CIC; and (v) anthracycline induced greater myocardial damage than other agents. Anti-HER2 inhibitors did not cause myocardial dysfunction in patients who received taxane-based chemotherapy. However, myocardial function was more deteriorated in patients previously treated with anthracyclines.

Recently, Chang *et al.*[11] have reported that endocardial GLS is significantly diminished after three cycles of anthracycline therapy in breast cancer patients who have developed CIC. Longitudinal and circumferential functions of the subendocardium decreased significantly in patients with CIC at an earlier stage in this study. We demonstrated that endocardial dysfunction persisted and worsened at the 6-month follow-up in patients with CIC. Li *et al.*[12] have reported early changes in cardiac function induced by anthracycline therapy. Endocardial and midmyocardial GLSs decreased in patients who did not develop CIC after four cycles of anthracycline chemotherapy. Endocardial and midmyocardial CSs of the mid- to apical LV also reduced after four cycles. The period after four cycles of chemotherapy was ∼3 months after the initiation of chemotherapy. These results are compatible with results of the present study.

Patients in this study were younger with fewer cardiovascular risk factors than those in previous studies. Baseline echocardiographic parameters and GLS, including layer-specific GLS, were not

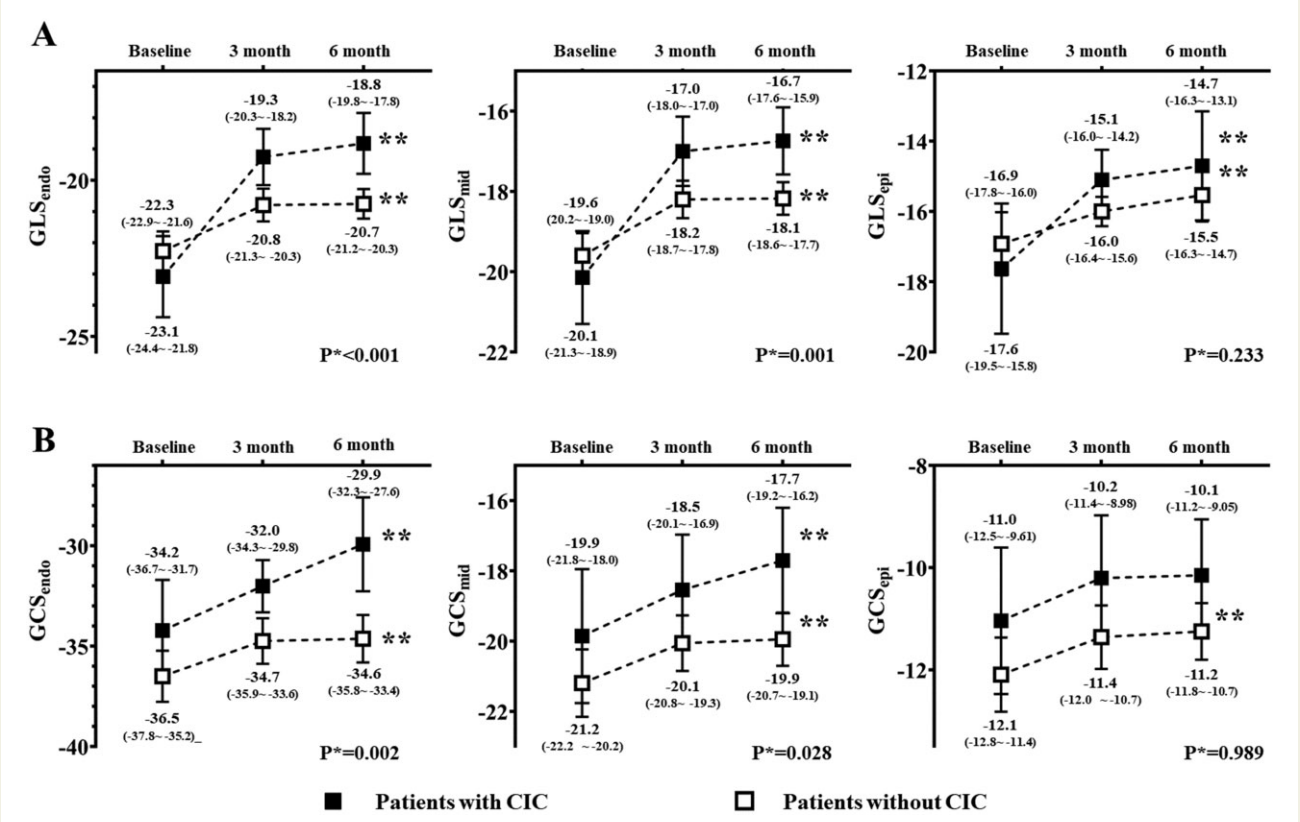

Figure 3 Longitudinal and circumferential strain trends in patients with CIC and those without CIC during a 6-month follow-up. (*A*) Global longitudinal strain (GLS) of the endocardium, midmyocardium, and picardium (GLS_{endo}, GLS_{mid}, and GLS_{epi}). (*B*) Global circumferential strain (GCS) of the endocardium, midmyocardium, and epicardium (GCS_{endo}, GCS_{mid}, and GCS_{epi}). The data were presented as estimated marginal with 95% confidence interval. *$P < 0.05$ for differences in changes of layer-specific GLS and GCS between patients with CIC and those without CIC. **$P < 0.05$ for the trend of L(C)S in each group of patients. CIC, chemotherapy-induced cardiotoxicity; GCS, global circumferential strain; GLS, global longitudinal strain.

significantly different between patients with CIC and those without CIC. However, the change of GLS at 3-month follow-up was an independent predictor of CIC development. This result could reflect the drop in LVEF at 3 months. However, in the analysis of CIC occurring after 3 months, changes of GLS during 3 months tended to predict CIC occurring between 3 and 6 months. It can be considered as a significant predictor for CIC.

Subclinical strain reduction occurred even in patients who did not develop CIC at 3 months. Of them, eight patients developed CIC at 6 months. It did not recovered or further decreased at 6 months, even in patients who did not show change of LVEF. Therefore, it may be helpful to check the strain and the LVEF during an imaging test for 3 months in clinical practice. This confirms that strain is a more sensitive marker for myocardial toxicity than LVEF. According to a recent position paper from Heart Failure Association, European Association of Cardiovascular Imaging, and the Cardio-Oncology Council of the ESC,[13] echocardiographic evaluation is recommended after four cycles of chemotherapy to patients receiving anthracyclines with a medium or high risk of cardiotoxicity. As mentioned above, the end of four cycles of chemotherapy was mostly 3 months after starting chemotherapy. The findings of this study could support the recommendation of the recent position paper. However, most patients who received anthracycline in this study ($n = 58/60$, 96.6% of anthracycline) had a low risk of cardiotoxicity. In the present study, clinical or subclinical LV function was decreased at 3 months in patients with CIC regardless of their risk status. Even in patients receiving taxane-based chemotherapy who did not have a specific recommendation in the recent position paper, LV function was reduced at 3-month follow-up. Therefore, imaging evaluation might be necessary at 3 months follow-up regardless of the chemotherapy regimen or the risk of cardiotoxicity.

Experimental data indicated a layer-specific difference in myocardial thickening. The heterogenicity of layer-specific myocardial contraction resulted from inhomogeneous blood flow in each myocardial layer, a difference in metabolism, and a relaxation mechanism.[14–16] In normal myocardium, the endocardial contraction and thickening are greater and the myocardial pressure is higher than those of epicardial myocardium.[14,17] Therefore, the endocardial myocardium with a higher energy requirement than the epicardial myocardium is vulnerable to stress.[18]

Difference in the orientation of each myocardial layer might have affected results of this study. Myocardial fibres orient differently, such

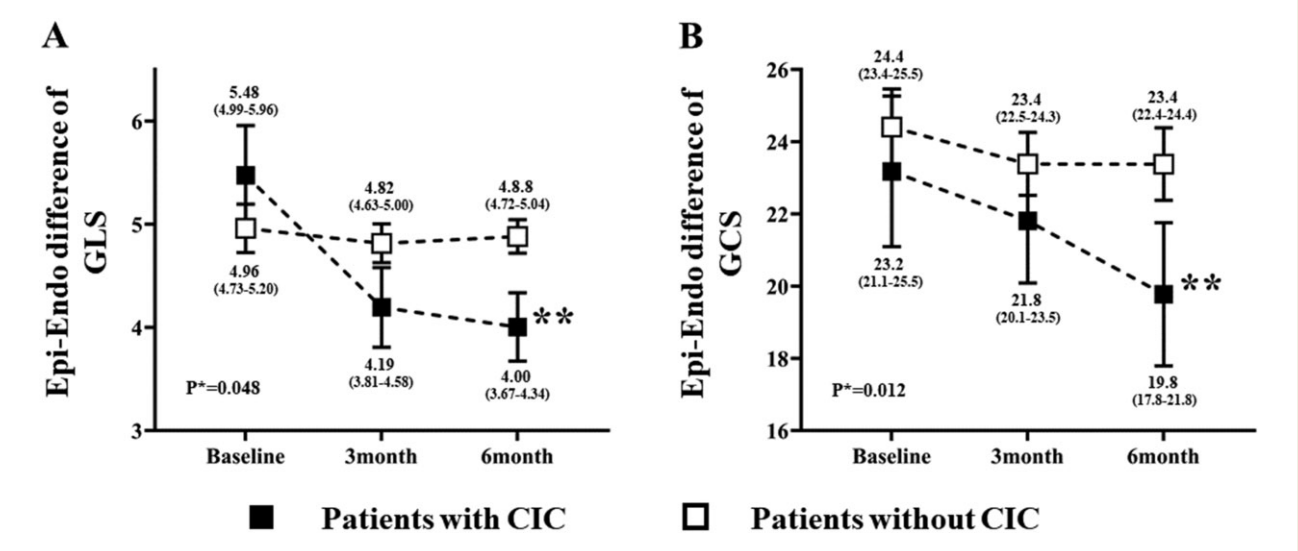

Figure 4 A comparison of epicardial to endocardial strain difference between patients with CIC and those without CIC during the 6-month follow-up. The epicardial to endocardial difference of global longitudinal strain (*A*) and global circumferential strain (*B*) at baseline and at the 3-month and 6-month follow-up. CIC, chemotherapy-induced cardiotoxicity.

Table 4 **Echocardiographic predictors of chemotherapy-induced cardiotoxicity (CIC)**

For prediction of CIC Baseline	Whole time (during 6 months)			At 3-month follow-up			At 6-month follow-up		
	RR	95% CI	*P*-value	RR	95% CI	*P*-value	RR	95% CI	*P*-value
LA	0.942	0.82–1.08	0.391	0.919	0.70–1.20	0.541	0.795	0.58–1.09	0.157
LVMI	0.988	0.96–1.02	0.366	0.990	0.95–1.03	0.601	1.035	0.96–1.11	0.352
LVEF	1.263	1.08–1.48	0.004	1.485	1.02–2.17	0.040	1.209	0.90–1.63	0.214
DT	1.003	0.98–1.02	0.757	1.004	0.97–1.04	0.775	1.011	0.96–1.06	0.641
E/*e*′	0.847	0.67–1.08	0.174	1.061	0.73–1.54	0.754	0.395	0.16–0.95	0.39
GLS_{endo}	1.352	0.50–3.63	0.550	2.448	0.61–9.83	0.207	0.336	0.01–24.7	0.619
GLS_{mid}	1.168	0.39–3.48	0.780	1.011	0.06–15.7	0.994	6.775	0.04–15.3	0.473
GLS_{epi}	0.968	0.77–1.22	0.783	0.709	0.05–10.0	0.799	1.104	0.75–1.62	0.616
GCS_{endo}	1.03	0.78–1.37	0.836	0.894	0.58–1.38	0.613	1.159	0.63–2.14	0.636
GCS_{mid}	0.928	0.48–1.79	0.824	1.140	0.43–3.01	0.792	0.581	0.13–2.61	0.478
GCS_{epi}	1.134	0.72–1.79	0.586	1.082	0.52–2.25	0.834	1.642	0.61–4.44	0.329
Δ GLS_{3month}	1.821	1.24–2.67	0.002	2.027	1.04–3.95	0.038	2.008	0.95–4.56	0.065
Δ GCS_{3month}	0.952	0.83–1.09	0.472	0.941	0.73–1.22	0.644	0.915	0.71–1.18	0.497

Cox regression analysis included different variables, such as age, smoking, hypertension, diabetes, dyslipidaemia, body mass index, and the administration of anthracycline or trastuzumab. GLS was not applied to Cox-regression analysis because values of GLS and GLS_{mid} were very similar.

Δ GLS_{3month} = GLS at the 3-month follow-up - GLS at baseline, Δ GCS_{3month} = GCS at the 3 month follow-up-GCS at baseline; 95% CI, 95% confidence interval; DT, deceleration time; *E*/*e*′, the ratio of early diastolic velocity and early mitral annular velocity; GCS, global circumferential strain; GCS_{endo}, GCS of the subendocardium; GCS_{epi}, GCS of the subepicardium; GCS_{mid}, GCS of the midmyocardium; GLS, global longitudinal strain; GLS_{endo}, GLS of the subendocardium; GLS_{epi}, GLS of the subepicardium; GLS_{mid}, GLS of the midmyocardium; LA, left atrium; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; RR, relative risk.

as longitudinally in the subendocardium, circumferentially in the mid-myocardium, and obliquely in the subepicardium.[19] Therefore, endocardial GLS is more sensitive to damage than GLS of other layers due to longitudinal orientation of the endocardial myocardium. Circumferential myocardial fibres account for most LV myofibres with a higher in base and a lower in apex.[19] Since LVEF reflects the circumferential fibre shorting, it is closely related to CS rather than LS, as shown in previous studies.[20,21] Therefore, longitudinal and circumferential functions of the subendocardium deteriorated more significantly in patients with CIC than in patients without CIC. The endocardial function might act as a sensitive and early marker for CIC. Therefore, LV function, especially endomyocardial function, needs to be followed up in all patients undergoing chemotherapy.

Subendocardium is more susceptible to damage by principal chemotherapy agents for breast cancer than other layers. The primary mechanism of anthracycline-induced cardiotoxicity is irreversible cardiomyocyte damage caused by oxidative stress by generating reactive oxygen species (ROS). Additionally, mitochondrial iron deposition is an essential mechanism of myocardial injury caused by anthracycline and topoisomerase IIβ inhibition-mediated DNA damage.[22] In the normal myocardium, the subendocardium exhibits lower mitochondrial oxidative capacity, higher nitric oxide concentration for inhibiting the mitochondrial respiratory chain, and more increased ROS than other layers.[16,23] Therefore, the subendocardium would be more vulnerable to anthracycline than other layers. Trastuzumab is a monoclonal antibody against HER2. An anti-HER2 inhibitor can impair mitochondrial function and intracellular energy metabolism.[24] Moreover, an anti-HER2 inhibitor can increase ROS production and affect apoptosis.[25] Hence, trastuzumab could cause significant damage in the subendocardium. In addition to anthracycline, taxane is a major class of chemotherapeutic agents for breast cancer. Although the enhancement of anthracycline-induced cardiotoxicity is a well-known mechanism of taxane-induced cardiotoxicity, increased oxidative stress and arterial stiffness are also associated with taxane-induced cardiotoxicity.[23] Therefore, taxane might cause more significant cardiac injury in the subendocardium than in other layers.

This study has several limitations. First, the number of patients was small. Therefore, we could not identify clinical characteristics or risk factors of the onset of CIC and recovery. This study is ongoing. More patients will be analysed later. Second, this study did not analyse cardiac markers, including NT-pro B-type natriuretic peptides (BNP) or troponin-I. According to the protocol, the measurement of cardiac markers was scheduled before chemotherapy and at 3 months and 12 months after chemotherapy. A total of 56 patients without CIC (75% of patients without CIC) and 14 patients with CIC (88% of patients with CIC) underwent blood sampling at baseline and the 3-month follow-up. Baseline values of NT-pro BNP and troponin-I were not different between the two groups. At the 3-month follow-up, troponin-I tended to be higher in patients with CIC than in patients without CIC (0.11 ± 0.05 vs. 0.09 ± 0.03, $P = 0.072$). Because troponin-I is a marker for damage to cardiac myocytes, this finding was relevant to differences in LS and CS between the two groups. Third, the analysis of the implication of dexrazoxane was not performed. Since the frequency of dexrazoxane was not different between the patients with and without CIC, the effect of dexrazoxane on the result might be negligible. Lastly, we did not demonstrate the clinical importance of subclinical myocardial dysfunction in patients without CIC. Furthermore, impaired myocardial function during the early period might be restored or deteriorate during a long-term follow-up. Long-term follow-up results of this study might provide further information on characteristics of myocardial damage and clinical consequence in patients with various courses of breast cancer.

Conclusion

The myocardial function assessed by strain decreased in all patients with breast cancer receiving chemotherapy. Among the three layers of the myocardium, the endocardium was the most vulnerable one to chemotherapy. Its might function as a sensitive and early marker for CIC. Thus, early evaluation of myocardial function should be performed for each patient with breast cancer irrespective of chemotherapeutic regimen. Anthracycline caused more remarkable myocardial damage than other chemotherapeutic agents. Trastuzumab induced more profound LV functional change in patients previously treated with anthracycline-based chemotherapy than in those treated with other chemotherapeutic agents. This may indicate that anthracycline-induced damage can make the myocardium vulnerable to trastuzumab even after discontinuation of anthracycline.

Lead author biography

Prof. Seong-Mi Park earned his MD from Korea University College of Medicine in Seoul, South Korea. She had a research fellowship of echocardiography at the Mayo Clinic, Rochester, Minnesota and was a visiting researcher in Women's Heart Center of Cedars-Sinai Medical Center. She serves as a director of research committee of the Working Group of Cardio-Oncology of the Korean Society of Cardiology. Prof. Park's work focuses on myocardial function and mechanics by echocardiography, heart failure, coronary microvascular function and valvular interventional imaging. She also serves as an editor-in chief of the International Journal of Heart Failure.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

Conflict of interest: none declared.

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