Superiority of left heart deformation in early anthracycline-related cardiac dysfunction detection

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ABSTRACT

Objective This study aimed to assess the incidence of early cancer therapy-related cardiac dysfunction (CTRCD) and the characteristics of left and right heart defformations during anthracycline chemotherapy.

Methods We prospectively enrolled a cohort of 351 chemotherapy-naive women with breast cancer and cardiovascular risk factors who were scheduled to receive anthracycline. The left ventricular ejection fraction (LVEF), left ventricular global longitudinal strain (LV-GLS) and right ventricular and left atrial longitudinal strains were evaluated using echocardiography at baseline, before every subsequent cycles and at 3 weeks after the final anthracycline dose. CTRCD was defined as a new LVEF reduction by ≥10 percentage points to an LVEF≤50% and/or a new relative decline in GLS by >15% from the baseline value.

Results Eighteen (5.1%) patients had evidence of asymptomatic CTRCD during anthracycline treatment, and 50% developed CTRCD before completing the chemotherapy regimen. In the CTRCD group, while LV-GLS decrease significantly after the first dose of anthracycline, the reduction of right ventricular free-wall longitudinal strain and left atrial reservoir strain were observed after the second dose. Other strain indices could not be used to identify early CTRCD.

Conclusions Cardiotoxicity appeared soon after the initiation of anthracycline chemotherapy. Among the left-heart and right-heart mechanics, LV-GLS remains the best deformation indicator for detecting early CTRCD.

INTRODUCTION

Cardiomyocyte damage can be observed within hours of administration of a single dose of anthracycline; however, data on early onset cardiac dysfunction during chemotherapy cycles are lacking. Generally, cancer therapy-related cardiac dysfunction (CTRCD) affects 9.3%–43.8% of patients receiving anthracycline-based chemotherapy, depending on the anthracycline cumulative dose, cardiovascular risk factors, follow-up time and cardiotoxicity criteria. The incidence of CTRCD has decreased with modern anthracycline-dosing regimens, in the SUCCOUR (Strain Surveillance of Chemotherapy for Improving Cardiovascular Outcomes) trial, the 3-year change in left ventricular ejection fraction (LVEF) was only −0.03%± 7.9% and most patients (85%) did not meet CTRCD criteria in the EF-guided group. Although limited data exist on early CTRCD occurrence during anthracycline treatment, the incidence of CTRCD not being high in contemporary studies challenges the necessity of frequent cardiac surveillance during chemotherapy, as recommended by recent guidelines.

LVEF and left ventricular global longitudinal strain (LV-GLS) evaluation with echocardiography have become the cornerstone imaging modality in preparation for, during, and after anthracycline-based chemotherapy. The decrease in LV-GLS related cardiac dysfunction.
permanently precedes the decrease in LVEF throughout the subsequent anthracycline doses, and the relative reduction cut-off of LV-GLS>15% without symptoms is considered the criterion for asymptomatic CTRCD. However, in most studies, this cut-off point was assessed comparing the LV-GLS value long after completing chemotherapy with the baseline strain measurement, and data on the ability of LV-GLS to predict early CTRCD during anthracycline cycles are limited. Furthermore, the involvement of the right ventricle and left atrium in CTRCD has recently become an active area of research. The prognostic roles of right ventricular global longitudinal strain (RV-GLS), right ventricular free wall longitudinal strain (RV-FWLS),9 10 and left atrial reservoir strain (LASr)11 12 have been demonstrated in separate small studies with different cut-off thresholds for CTRCD. Various questions regarding whether the right ventricle and left atrium are affected concurrently with the left ventricle and which cardiac chamber is more sensitive to anthracycline cardiotoxicity remain unexplored. To unravel such aspects, we conducted a prospective study incorporating all echocardiographic deformation indices measured at baseline and before every subsequent anthracycline cycle in a chemotherapy-naive breast cancer cohort with cardiovascular risk factors.

**METHODS**

**Design**

This was a multicentre prospective cohort study. We recruited 351 consecutive female patients who received anthracycline as adjuvant or neoadjuvant chemotherapy for newly diagnosed breast cancer (stages I–IV) at the Nhan Dan Gia Dinh Hospital and Oncology Hospital, Ho Chi Minh City, Vietnam, between 1 September 2020, and 31 December 2022. All patients received a 4-cycle anthracycline regimen (60mg/m²/cycle of doxorubicin or equivalent) with a 21-day intercycle interval. Patients were eligible for inclusion in this study if they presented at least one of the following cardiovascular risk factors: ≥60 years of age, hypertension, diabetes mellitus, dyslipidaemia, atrial fibrillation, obesity, or chronic kidney disease. Exclusion criteria included concurrent anti-HER2 chemotherapy, severe valvular heart disease and poor image quality on echocardiogram, defined as ≥2 inadequate visualised myocardial segments (in a 18-segment model). Patients were evaluated for standard demographic and clinical data, the Heart Failure Association-International Cardio-Oncology Society (HFA-ICOS) risk score for CTRCD, echocardiography findings and medical therapy at baseline. All patients underwent clinical examination and standard echocardiography before every anthracycline cycle and 3 weeks after the final dose, irrespective of the HFA-ICOS risk categories. The primary endpoint of this study was the occurrence of CTRCD during anthracycline therapy. CTRCD was defined as a new LVEF reduction by ≥10 percentage points to an LVEF<50% and/or a new relative decline in GLS by>15% from the baseline value. The persistent decline in the LV-GLS was confirmed by two subsequent cycles of strain analysis.

**Two-dimensional echocardiography**

Echocardiography was performed at a resting condition using a Philips Affiniti ultrasound system (Philips Healthcare, Andover, Massachusetts, USA) by a single examiner, according to the current guidelines of the American Society of Echocardiography and European Association of Cardiovascular Imaging. Data from four-chamber, three-chamber, and two-chamber and right ventricular-focused apical views acquired in three consecutive cardiac cycles at a frame rate of >50 fps were stored in raw DICOM format for offline analysis. Images were obtained at baseline (before the first anthracycline cycle), before every subsequent cycle, and 3 weeks after the completion of the chemotherapy. Five echocardiographic examinations were performed in each patient during the study period. All images were transferred to a core laboratory and computed by two cardiologists (HHN and DTV) who were blinded to the patients’ clinical data. Right ventricular strains (RV-FWLS and RV-GLS) and left atrial strains (LASr, LASCd and LASc) were assessed using right ventricular-focused and apical four-chamber views, respectively. Strain analyses by speckle-tracking (LV-GLS, RV-FWLS, RV-GLS, LASr, LASCd, and LASc) and semiautomatic LVEF calculations were performed using Philips aCMQ (QLAB 15.0, Philips Healthcare, Andover, Massachusetts, USA). The LA border was automatically defined for LASr, LASCd and LASc. The strain indices at each anthracycline cycle were compared with the corresponding values at baseline, and this difference was defined as the relative change (relative change at each cycle = (current strain value – baseline strain value)/baseline strain value). The baseline strain index was identical to the strain value before cycle 1.

**Statistical analysis**

Data were provided as means±SD when normally distributed, medians and IQRs for skewed distributions, and frequencies and percentages for categorical variables. A χ² or unpaired t-test was used to compare the demographic data, cardiovascular risk factors, HFA-ICOS risk levels and medical therapy between the CTRCD and normal group. Owing to the small number of high-risk patients in this study, all patients were stratified into two risk levels: moderate-high and low-risk. Paired t-test was employed to demonstrate significant changes in Δ LV-GLS, ΔRV-FWLS, ΔRV-GLS, ΔLASr, ΔLASc, and ΔLASc between the independent groups at each anthracycline cycle. Receiver operating characteristic (ROC) curves were created to define the most accurate cut-off, sensitivity, and specificity of the relative change in LV-GLS at each cycle to predict CTRCD. Statistical analyses were performed using IBM SPSS Statistics V.27 (IBM Corp) and R V.4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). Two-sided p values were used, and p<0.05 was considered statistically significant.
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RESULTS

Patient characteristics

Of the 351 patients with breast cancer and cardiovascular risk factors, 18 (5.1%) developed CTRCD during anthracycline chemotherapy and were asymptomatic at the time of detection. Among these patients, 16 (88.9%) fulfilled both the LV-GLS and LVEF criteria, and 2 (11.1%) had severe CTRCD with a new LVEF reduction to <40%. The incidence of CTRCD after the first, second, third and fourth anthracycline doses was 17%, 5%, 28% and 50%, respectively (figure 1). Patients were an average of 57.8 ± 7.5 years of age (range, 37–81 years), the median anthracycline cumulative dose after four cycles was 236 (230–241) mg/m², and, at baseline, no patient presented LVEF<50%, prior CTRCD, heart failure, or cardiomyopathy, or a history of myocardial infarction with or without coronary revascularisation. Hypertension was the predominant cardiovascular risk factor in 228 (65%) patients, followed by dyslipidaemia in 139 (39.6%), diabetes mellitus in 96 (27.4%), chronic kidney disease in 27 (7.7%), obesity in 24 (6.8%), and atrial fibrillation in four (1.1%) patients. Most of these cardiovascular risk factors at baseline were similar between CTRCD and no-CTRCD group, except for chronic kidney disease. The baseline characteristics of the patients in the CTRCD and non-CTRCD groups are summarised in table 1. According to the HFA-ICOS risk categories, 141 (40.1%) patients were classified as moderate risk and 4 (1.1%) were considered as high risk before anthracycline therapy. The moderate group comprised 77.8% of the CTRCD cases that occurred before the last dose of anthracycline.

Given that all patients possessed cardiovascular risk factors, 133 (37.9%) received cardioprotective therapy with ACE-i/ARB (23.9%) and beta-blockers (14%) before anthracycline treatment. Baseline left ventricular function (LVEF, LV-GLS), right ventricular strain (RV-GLS, RV-FWLS), and left atrial mechanics (LASr, LAScd, LASct) assessed using echocardiography did not differ between the groups.

LV-GLS evolution during anthracycline therapy

In the general cohort of 351 patients, the mean LV-GLS decreased over time during anthracyline treatment. The mean relative change of LV-GLS after chemotherapy compared with the baseline value was −0.9 ± 8.7% (p=0.044); simultaneously, the mean LVEF decreased from 64 ±5% to 62.4 ± 6% (p=0.053). Although the mean left ventricular deformation values at baseline were not different, the mean LV-GLS decreased promptly after the first dose of anthracycline (−17.0 ± 2.6% vs -18.8 ± 1.5%, p<0.010), and continued to decline after the subsequent doses of anthracyline in the CTRCD compared with no-CTRCD group. After completing chemotherapy, the mean LV-GLS in the CTRCD group was significantly lower than that in the no-CTRCD group (−14.2 ± 1.6% vs -18.7 ± 1.3%, p<0.0001). The mean relative changes of LV-GLS were gradually higher after each cycle of anthracyline in the CTRCD group, namely -7.3%, -8.3%, -13.2% and -21.7% for each of the four cycles,
respectively. These relative changes of LV-GLS were more significant than the corresponding reduction of absolute values in CTRCD group. When patients were stratified by the HFA-ICOS risk categories, the difference of the LV-GLS relative changes between the moderate–high risk and low-risk patients appeared after the first cycle of anthracycline (−0.7 ± 6.5% vs+0.6 ± 6.9%, p=0.047). In moderate–high HFA-ICOS risk patients, the mean LV-GLS after the final dose of anthracycline declined significantly, with a mean relative change of −1.9 ± 8.4% compared with −0.1 ± 8.9% in the low-risk group (p<0.01, figure 2).

Right ventricular strain evolution during anthracycline therapy
In contrast to the LV-GLS evolution, serial changes in RV-GLS were not significant in the CTRCD group. RV-FWLS started to decline after two dose of anthracycline (before cycle 3), namely, −26.5 ± 2.1% compared with −26.9 ± 1.6% at baseline (p=0.046). At the time of anthracycline therapy completion, RV-FWLS decreased
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Left atrial strain evolution during anthracycline therapy
Among the assessed left atrial mechanics, only LASr showed a persistent decline after the second dose of anthracycline compared with baseline values in the CTRCD group (40.1±8.4% vs 43.3±9.9%, p=0.032). Similar to the right ventricular longitudinal strain, the mean relative changes in LASr, however, did not differ significantly between the low-risk and moderate-to-high-risk HFA-ICOS categories (figure 4).

LV-GLS cut-off point to predict CTRCD during anthracycline chemotherapy
Although each relative change in the LV-GLS from cycles 2–4 could predict CTRCD, the incidence of CTRCD was more prevalent in cycles 2 and 4. The ROC curve of the relative change in LV-GLS at cycle four appeared to be a stronger predictor of CTRCD during anthracycline chemotherapy. Notably, the threshold of 4.8% in cycle 2 had a sensitivity of 63.6% and a specificity of 69.2%, whereas at the threshold of 4.5% before cycle 4, the sensitivity and specificity for detecting CTRCD were 80% and 58.3%, respectively (figure 5).

DISCUSSION
To the best of our knowledge, this is the first prospective study to identify the incidence of CTRCD during anthracycline therapy that monitored all left and right heart myocardial mechanics concurrently using echocardiography. The most important finding of this study was that CTRCD occurred in 5.1% of patients with breast cancer treated with anthracycline, and half of its incidence was observed before the final dose of chemotherapy. Another essential finding was that, in contrast to the no-CTRCD group, cardiac injury demonstrated by a significant decline in LV-GLS could be observed promptly after the first dose of anthracycline in the patients affected by CTRCD.

Monitoring of cardiotoxicity during anthracycline chemotherapy
Although anthracyclines are one of the bases of chemotherapy for many solid and haematological cancers,
they are the most well-known drugs responsible for cardiomyocyte toxicity.1. The development of both clinical and subclinical left ventricular dysfunction contributes to poor long-term cardiovascular and oncological prognosis.5 CTRCD events due to anthracycline were once considered prevalent, occurring in up to 40% of patients treated with such drugs2; additionally, not only the patients’ cardiovascular risk factors, but also the high cumulative doses of anthracyline employed were the main determinants of its high incidence.6 However, in the era of modern chemotherapy dosing regimens, the mean LVEF decline at 6 months after anthracycline exposure was only 5.4% (range, 3.5%–7.3%) and it may not appear as symptomatic heart failure.3 Therefore, asymptomatic left ventricular dysfunction confirmed by echocardiographic strain imaging (ie, with LV-GLS assessment) has become a cornerstone criterion for CTRCD in the current guidelines.5 However, most previous studies analysed the relative change in LV-GLS after completing anthracycline to predict symptomatic and asymptomatic CTRCD,28 and in this manner, data on CTRCD occurring during chemotherapy regimens are lacking. Therefore, the recommendations of echocardiographic surveillance during anthracycline treatment to detect asymptomatic CTRCD have had limited validation.6 Given that a reduced anthracycline dosing protocol has been applied and only a minority of high/very high-risk HFA-ICOS patients are treated with anthracyline in clinical practice,4 we targeted naïve chemotherapy patients with breast cancer and cardiovascular risk factors to better characterise the behaviour of left and right heart deformations in patients affected by CTRCD during anthracyline treatment.

According to the current European Society of Cardiology guidelines, additional echocardiography surveillance is recommended every two cycles in the high/very high-risk category and should be considered after a cumulative dose of ≥250 mg/m² of doxorubicin or equivalent in other lower risk levels.5 These recommendations were challenged by our study, as the cumulative dose of doxorubicin never exceeded 250 mg/m² and CTRCD had already developed before the final dose of anthracycline was administered in both moderate-risk and low-risk patients. If echocardiography were repeated simply after completing the anthracycline regimen in non-high-risk patients, 50% of the CTRCD cases in our study would have been diagnosed in later stages. Although the relationship between the delay from CTRCD occurrence to treatment and the likelihood of left ventricular function recovery is unknown, early CTRCD detection appears to be critical for improving cardiovascular outcomes in anthracycline-treated patients.14 Notably, when CTRCD developed in moderate-to-high-risk patients, 63.6% were identified before the final anthracycline cycle, in contrast to 28.6% in low-risk patients. Therefore, we suggest that...
the protocol of repeating echocardiography every two cycles should be applied not only to high/very high-risk patients but also to the moderate-risk ones during anthracycline treatment; moreover, an additional echocardiography must be performed routinely after a full dose of anthracycline, irrespective of HFA-ICOS risk levels.

Characteristics of left and right heart mechanics during anthracycline treatment

Pathological changes in cardiomyocytes appear to occur within hours of a single dose of anthracycline. However, evidence of this early myocardial injury has not been fully demonstrated by cardiac imaging. When all the left and right heart strain parameters at each subsequent anthracycline cycle were analysed concurrently, our results showed that the left heart mechanics (LV-GLS and LASr) were more sensitive to anthracycline toxicity than the right ones, and that the deterioration of LV-GLS preceded other strain indices in patients with CTRCD (figure 6). Relative changes in LV-GLS after anthracycline treatment were confirmed to be stronger predictors of CTRCD than absolute strain values. While sequential echocardiography was performed by only one examiner and all strain analyses were reported by two cardiologists, we showed negligible relative changes in LV-GLS and other strain parameters in the no-CTRCD group after subsequent cycles of anthracycline, and the threshold
of 4.5% of LV-GLS relative change in cycle 4 to predict CTRCD was rather small.

While data on right ventricular systolic dysfunction during chemotherapy evaluated by classical parameters including fractional area change, right ventricle ejection fraction, tricuspid annular plane systolic excursion, and right ventricle tissue Doppler S’ were inconclusive in most studies, right ventricular longitudinal strain (RV-FWLS and RV-GLS) has recently gained attention due to its consistent detection of subtle changes of right ventricular deformation. In several small studies on breast cancer treated with anthracycline, RV-FWLS and/or RV-GLS showed a significant decrease; however, right ventricular longitudinal strain was mostly reassessed more than 3 months apart, and data regarding serial changes in right ventricular longitudinal strain throughout the cycles of this regimen are lacking. Additionally, whether abnormalities in right ventricular mechanics precede LV-GLS
remains unknown. In our study, although RV-FWLS and RV-GLS at the end of chemotherapy were lower than baseline values in the CTRCD group, neither showed any significant reduction after subsequent anthracycline cycles. This finding suggests that right ventricular mechanics may deteriorate in the late stages of CTRCD.

Left atrial mechanics have emerged as important markers of early left ventricular diastolic dysfunction because of their primary function in modulating left ventricular filling. In cardio-oncology, the role of left atrial strain in CTRCD prediction has been recently proposed based on limited and inhomogeneous data. In a retrospective analysis of the SUCCOUR trial, Yu and Negishi reported that the baseline LAStr was a predictor of CTRCD at an 1-year follow-up, as well as improved the accuracy of a predictive model for CTRCD, including age, LVEF and LA volume index. Among the three LA strain parameters, Chen et al showed that only LASr declined over time in two subsequent echocardiography performed 6 months after baseline; LASct decreased only 1 year after anthracycline chemotherapy, and deterioration of LASdct was not significant after the first 6 months. In contrast, Timoteo et al concluded that LAStr, LASdct and LASct were virtually stable for 1 year after anthracycline treatment. To date, no study has described the early effects of anthracyclines on LA deformation. Our study indicated that among these three LA mechanics, LAStr was the most vulnerable to chemotherapy-induced cardiotoxicity, with a significant decline in its value after the second dose of anthracycline.

Although our study showed a persistent decrease in the LV-GLS, LASr and RV-FWLS during anthracycline treatment, the HFA-ICOS risk category played a minimal role in discriminating which group of patients presented higher relative deformation changes during subsequent chemotherapy cycles. In particular, only the relative changes in LV-GLS in moderate-to-high-risk patients were lower than those in low-risk patients after the third cycle of anthracycline. A similar difference was not observed between LASr and RV-FWLS. These findings should be validated in future studies.

Study limitations
In our study, only four patients (1.1%) were classified in the high-risk HFA-ICOS category. Therefore, our findings may not represent the behaviour of the left and right heart deformations in this group. In the echocardiography protocol, although we assessed LVEF using a well-known semiautomatic software to improve the reproducibility of this measurement, 3D LVEF is the preferred method in recent guidelines owing to its superior accuracy in detecting LV dysfunction. Furthermore, the incidence of CTRCD was low in our study, which limited the multivariate analysis. The role of cardiac biomarkers in predicting early CTRCD was also not revealed in our study.

In conclusion, the results of this prospective study suggest that frequent echocardiography surveillance, optimally every two cycles and after completing anthracycline chemotherapy, can detect early-onset CTRCD, irrespective of the HFA-ICOS risk category and anthracycline cumulative dose. Among the left and right heart deformation parameters, LV-GLS was the most reliable and sensitive tool for confirming CTRCD.

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