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# Right heart function deteriorates in breast cancer patients undergoing anthracycline-based chemotherapy

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## Abstract

**Background:** Cardiotoxicity from anthracycline-based chemotherapy is an important cause of early and late morbidity and mortality in breast cancer patients. Left ventricular (LV) function is assessed for patients receiving anthracycline-based chemotherapy to identify cardiotoxicity. However, animal studies suggest that right ventricular (RV) function may be a more sensitive measure to detect LV dysfunction. The purpose of this pilot study was to determine if breast cancer patients undergoing anthracycline-based chemotherapy experience RV dysfunction.

**Methods:** Forty-nine breast cancer patients undergoing anthracycline-based chemotherapy at the Ottawa Hospital between November 2007 and March 2013 and who had 2 echocardiograms performed at least 3 months apart were retrospectively identified. Right atrial area (RAA), right ventricular fractional area change (RV FAC) and RV longitudinal strain of the free wall (RV LSFW) were evaluated according to the American Society of Echocardiography guidelines.

**Results:** The majority (48/49) of patients were females with an average age of 53.4 (95% CI: 50.1–56.7 years). From baseline to follow-up study, average LV ejection fraction (LVEF) decreased from 62.22 (95% CI: 59.1–65.4) to 57.4% (95% CI: 54.0–60.9) ( $P=0.04$ ). During the same time period, the mean RAA increased from 12.1 cm<sup>2</sup> (95% CI: 11.1–13.0 cm<sup>2</sup>) to 13.8 cm<sup>2</sup> (95% CI: 12.7–14.9 cm<sup>2</sup>) ( $P=0.02$ ), mean RV FAC decreased ( $P=0.01$ ) from 48.3% (95% CI: 44.8–51.74) to 42.1% (95% CI: 38.5–45.6%), and mean RV LSFW worsened from –16.2% (95% CI: –18.1 to –14.4%) to –13.81% (95% CI: –15.1 to –12.5%) ( $P=0.04$ ).

**Conclusion:** This study demonstrates that breast cancer patients receiving anthracycline-based chemotherapy experience adverse effects on both right atrial size and RV function. Further studies are required to determine the impact of these adverse effects on right heart function and whether this represents an earlier marker of cardiotoxicity.

## Key Words

- ▶ right heart function
- ▶ chemotherapy
- ▶ cardiotoxicity
- ▶ echocardiography

## Introduction

Breast cancer patients undergoing chemotherapy have an increased risk of developing cardiovascular complications including heart failure (1, 2). Of the various chemotherapeutic agents used in breast cancer treatment, anthracyclines and their related compounds are some of the most frequently implicated agents (1, 2). Anthracycline-based chemotherapy is associated with a dose-dependent risk of congestive heart failure that can occur years after completion of chemotherapy. The clinical impact of this latent toxicity can be significant. A study carried out in older women (>66 years of age) who had been treated for breast cancer demonstrated a higher risk of death from cardiovascular disease than recurrence of breast cancer 7–8 years after completion of breast cancer treatment (2). Although a number of studies have reported the adverse impact of anthracycline-based agents on left ventricular (LV) systolic and diastolic function, limited data exists on their impact on right ventricular (RV) function. Preliminary human and animal studies have suggested that the detrimental/toxic effect of doxorubicin provokes global cardiac injury that extends to both the left and right ventricles (3, 4, 5). Importantly, RV function is a strong incremental predictor of prognosis in patients with LV systolic dysfunction and various LV pathologies (6, 7). The evaluation of RV function using traditional echocardiographic methods, as well as novel methods such as deformation imaging (strain, strain rate imaging), as recommended in the recent multimodality guidelines to detect subclinical LV dysfunction, may provide evidence of associated right ventricular cardiotoxicity (8).

In our study, we hypothesized that breast cancer patients undergoing anthracycline-based chemotherapy would show evidence of right ventricular dysfunction identifiable using transthoracic echocardiography and currently available echocardiographic techniques.

## Materials and methods

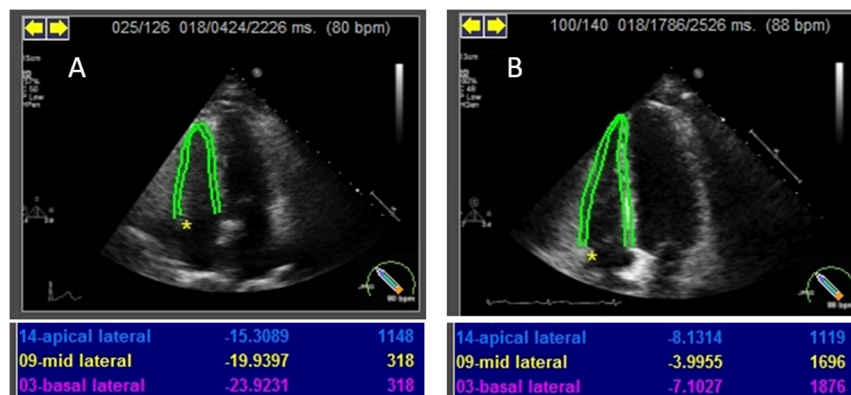
Using the University of Ottawa Local Breast Cancer Registry, we retrospectively identified 49 patients with early-stage human epidermal growth factor receptor 2 negative breast cancer (stage I–III) who underwent anthracycline-based chemotherapy at the Ottawa Hospital between November 2007 and March 2013. All of these 49 patients had undergone at least two echocardiograms performed at least 3 months apart. The majority of patients (i.e., 80%) had undergone echocardiogram before the completion of first cycle of chemotherapy (mean: 30 days; 95% CI: 3–57 days before chemotherapy). All patients had their follow-up echocardiography after the completion of chemotherapy cycle (mean: 125 days; 95% CI: 107–142 days). The Breast Cancer Registry was approved by the Human Research Ethics Board, and all patients provided written informed consent for the use of their data.

### Echocardiography and image analysis

Comprehensive echocardiographic examinations were carried out according to the standard recommendations of the American Society of Echocardiography (ASE) (9, 10). All echocardiographic images were digitally stored and conventional echocardiographic parameters were measured. The parameters of cardiac structure and function were measured as per the guidelines of ASE (9, 10).

Right atrial area (RAA) measurements were performed in the apical four-chamber view. RAA was estimated by planimetry at the end of ventricular systole (largest atrial volume), tracing the RA endocardium from the lateral aspect of the tricuspid annulus to the septal aspect, excluding the area between the leaflets and annulus, and the right atrial appendage.

Right ventricular fractional area change (RVFAC) was calculated from the apical four-chamber view using



**Figure 1**  
Panel A is a pre-chemotherapy image depicting normal right ventricle free wall longitudinal strain. Panel B is a post-chemotherapy image from the same patient showing reduced right ventricle free wall longitudinal strain.

**Table 1** Baseline characteristics of study population.

	<b>n=49</b>
Age (years)	53.4±3.3 (50.1–56.7)
Women	48 (98.0%)
Body mass index (kg/m <sup>2</sup> )	25.9±1.3 (24.6–27.2)
Cardiac risk factors	
Smoker/ex-smoker	21 (42.9%)
Hypertension	12 (24.5%)
Dyslipidemia	7 (14.3%)
Diabetes	7 (14.3%)
Family history of coronary artery disease	2 (4.1%)
Cardiac history	
Prior coronary artery disease	2 (4.1%)

the percentage change in the RV end-diastolic and end-systolic areas.

RV longitudinal strain of the free wall (RV LSF<sub>W</sub>) was measured offline using speckle-tracking method and dedicated TomTec software (TomTec Imaging Systems, Unterschleissheim, Germany). In brief, the endocardial border of the RV was manually traced (approximately 10 points) over 1 frame, and endocardial borders were automatically tracked throughout the cardiac cycles by the software. The software determines myocardial velocity as the ratio between frame-to-frame displacement of the speckles and the time interval, and derives the systolic longitudinal strain. Longitudinal strain (LS) of the RV free wall was measured as the average of three segmental strain values (base, mid and apex) (Fig. 1).

Images were reviewed and analyzed offline by two independent observers blinded to the clinical

characteristics of the study population. Reproducibility analysis for right heart parameters was performed in a subset of patients (*n*=10) and intra-class correlation coefficient value was 0.81 (95% CI: 0.58–0.91).

### Statistical analysis

MedCalc for Windows version 12.0 (MedCalc Software, Ostend, Belgium) was used for analysis of the data. For the continuous variables, parametric test conditions were first tested. The Shapiro–Wilk test was used to determine whether the continuous variables were normally distributed. Descriptive statistics were shown as mean±s.d. or median (minimum–maximum), where appropriate. To compare the echocardiography variables, paired *t*-test was used and statistical significance was defined as two-tailed probability value of *P*<0.05.

## Results

### Baseline characteristics

Baseline characteristics of study population are provided in Table 1. The mean age was 53.4 years (95% CI: 50.2–56.6 years) and the majority of patients had no pre-existing cardiovascular disease. All but one (*n*=48) patients were female and most were nonsmokers and had no history of hypertension or hyperlipidemia. A total of 15 patients received doxorubicin-based chemotherapy (doxorubicin/cyclophosphamide every 3 weeks×4 cycles±paclitaxel). The mean total dose of doxorubicin

**Table 2** Echocardiography parameters.

	<b>Baseline</b>	<b>Follow-up</b>	<b>Significance <i>P</i></b>
LVEF	62.2% (95% CI: 59.1–65.4)	57.4% (95% CI: 54.0–60.9)	0.04
LV GLS	−15.4 (95% CI: −16.3 to −14.5)	−12.8 (95% CI: −13.8 to −11.9)	<0.0001
LV diastole (cm)	4.6 (95% CI: 4.5–4.7)	4.9 (95% CI: 4.8–5.1)	<0.0001
LV systole (cm)	3.0 (95% CI: 2.9–3.2)	4.0 (95% CI: 2.9–5.1)	0.10
IV septum (cm)	0.84 (95% CI: 0.80–0.89)	0.84 (95% CI: 0.80–0.87)	0.75
Posterior wall (cm)	0.87 (95% CI: 0.83–0.91)	0.87 (95% CI: 0.83–0.90)	0.96
Fractional shortening (%)	33.9 (95% CI: 31.8–36.0)	30.3 (95% CI: 27.8–32.7)	0.003
Mitral valve E Max velocity (cm/s)	74.9 (95% CI: 70.7–79.2)	73.8 (95% CI: 69.0–78.6)	0.60
Mitral valve A Max velocity (cm/s)	71.1 (95% CI: 64.6–77.7)	73.8 (95% CI: 68.4–79.1)	0.20
Mitral valve E/A	1.14 (95% CI: 1.02–1.30)	1.08 (95% CI: 0.95–1.21)	0.15
Left atrium (cm)	3.3 (95% CI: 3.1–3.5)	3.4 (95% CI: 3.2–3.5)	0.12
Aortic root (cm)	2.8 (95% CI: 2.6–2.9)	2.9 (95% CI: 2.7–3.0)	0.14
RV FAC	48.3% (95% CI: 44.8–51.7)	42.1% (95% CI: 38.5–45.6%)	0.01
RAA	12.7 cm <sup>2</sup> (95% CI: 11.1–13.1 cm <sup>2</sup> )	13.8 cm <sup>2</sup> (95% CI: 12.7–14.9 cm <sup>2</sup> )	0.02
LS RVFW	−16.2% (95% CI: −18.1 to −14.4%)	−13.8% (95% CI: −15.1 to −12.5%)	0.04
Heart rate (beats/min)	83 (95% CI: 74–92)	79 (95% CI: 74–84)	0.32

LS RVFW, longitudinal strain of the RV free wall; LV GLS, longitudinal strain of the LV; LVEF, LV ejection fraction; RAA, right atrial area; RV FAC, right ventricular fractional area change.

was 232 mg/m<sup>2</sup> (95% CI: 214.84–249.16 mg/m<sup>2</sup>). A total of 34 patients received epirubicin-containing chemotherapy (fluorouracil/epirubicin/cyclophosphamide every 3 weeks × 3 ± docetaxel). The average total dose of epirubicin was 294.12 mg/m<sup>2</sup> (95% CI: 285.78–302.46 mg/m<sup>2</sup>).

### Echocardiographic variables

The average LV ejection fraction (LVEF) decreased from 62.2% (95% CI: 59.1–65.4) at their first echocardiogram to 57.4% (95% CI: 54.0–60.9) on follow-up echocardiogram ( $P=0.04$ ) (Table 2). Similarly, the mean LV global LS decreased from –15.4% (95% CI: –16.3 to –14.5) to –12.8 (95% CI: –13.8 to –11.9) on follow-up ( $P<0.0001$ ).

Mean RAA significantly increased from 12.1 cm<sup>2</sup> (95% CI: 11.1–13.0 cm<sup>2</sup>) to 13.8 cm<sup>2</sup> on follow-up echocardiogram (95% CI: 12.7–14.9 cm<sup>2</sup>) ( $P=0.02$ ). Mean RV FAC significantly decreased from 48.3% (95% CI: 44.8–51.7) to 42.1% on follow-up ( $P=0.01$ ). Mean RV LSFw worsened from –16.2% (95% CI: –18.1 to –14.4%) to –13.8% on follow-up (95% CI: –15.1 to –12.5%) ( $P=0.04$ ).

### Discussion

Whereas previous studies involving anthracycline-based chemotherapy in breast cancer patients have identified clinical and subclinical LV dysfunction, we have demonstrated that anthracycline-based chemotherapy can adversely affect right heart function. Moreover, in this study we have identified a previously unreported abnormality in RV function (RV LSFw) evident in breast cancer patients receiving anthracycline-based chemotherapy using myocardial deformation parameters, the latter considered an important marker of subclinical dysfunction for the left ventricle (8).

### Right heart assessment and its implications

It is increasingly recognized that RV function plays an important role in determining prognosis in conditions that have typically been regarded as largely related to LV pathologies, including congestive heart failure and coronary artery disease (6, 7, 11, 12, 13). Despite advancement in echocardiographic techniques, the assessment of the right ventricle by conventional two-dimensional echocardiography remains challenging due to its complex shape and systolic mechanics (9).

Right atrial assessment is of clinical importance as its enlargement can reflect abnormalities in RV function, and right atrial enlargement has been shown to be strongly associated with adverse clinical outcomes (14, 15). We measured RAA in our study as it is considered an accurate and reliable technique for evaluating right atrial size (9, 14).

Of the many different echocardiographic indices of RV function, RVFAC is the most commonly used two-dimensional method to assess RV function (9). It is considered to be a robust predictor of heart failure, sudden death, stroke and mortality in patients with right and left heart conditions (16, 17, 18). However, like LVEF, RVFAC change may be a late manifestation of RV dysfunction. In the setting of cardiotoxicity from cancer therapy, early detection of subclinical cardiotoxicity is desirable to permit modification of cancer treatment or optimization of cardiac function.

Deformation imaging (strain or strain rate imaging) was initially developed to measure LV mechanics. However, recent studies have established its usefulness for the assessment of the RV in disease states where RV function can be adversely affected (19, 20, 21, 22). As the bulk of RV muscle fibers run longitudinally, longitudinal shortening assessed by strain imaging has the potential to reveal early stages of myocardial dysfunction not evident on routine RV parameters (23). Similar to LV strain, RV assessment by speckle-tracking method allows the assessment in a nongeometrical manner, relatively independent of tethering or translational motion (24, 25). Importantly, strain-based assessment is less affected by loading conditions, which may be particularly important in patients receiving chemotherapy, who are prone to changing fluid and weight status during the course of therapy. These factors suggest that deformation imaging of the RV using speckle-tracking echocardiography may be a promising modality for detection of subclinical cardiotoxicity during cancer therapy.

### Mechanism of right heart abnormalities

In our study we found that RAA, RVFAC and RV LSFw (in addition to LVEF) were adversely affected by anthracycline-based chemotherapy. Previous histological studies have indicated that cardiotoxic damage is more prominent in the sub-endocardial part of the cardiac walls (26). Intuitively, a thinner RV may be more sensitive to the toxic effects of chemotherapy compared with the thicker muscular LV, although data to support this

premise are limited. Prospective nonhuman studies with histological analysis to test whether the right ventricle is involved at an earlier time than the left ventricle would lend support to this hypothesis. We have identified both LV and RV dysfunction in our patients, but we are unable to determine if the RV is more sensitive to the cardiotoxic effects.

RV cardiotoxicity as a result of chemotherapy has not been adequately studied and previous studies have revealed divergent results. Belham *et al.* observed no change in RV myocardial performance index when patients were evaluated following administration of low-dose anthracycline (27). Similarly, Cottin *et al.* reported no alterations in the RV function at 1 and 12 months after anthracycline therapy using multiplexed acquisitions (28). However, Yildirim *et al.* reported abnormalities in the RV tissue Doppler velocities at rest and during dobutamine stress echocardiography following anthracycline administration (29) and Tanindi *et al.* reported a decrease in the RVFAC during chemotherapy in a study carried out in 37 patients (3). Our results reveal similar findings and add to the growing evidence by demonstrating abnormalities in RV function using deformation imaging – an important technique to identify subclinical LV dysfunction that has been incorporated into the most recent multimodality imaging guidelines to assess cardio-oncologic patients (8).

### Limitations

Because of the retrospective aspect of this study we were unable to evaluate the utility of RV tissue Doppler and tricuspid annular plane septal excursion measurements as they were not systematically recorded. Another limitation of the study is the absence of cardiac biomarkers as they were not collected. Due to the limited number of patients in our study, we were unable to determine if the RV functional impairment was independent of or preceded a fall in LV function. However, this study clearly demonstrates, using multiple measures, that the RV may be adversely impacted by anthracycline-based chemotherapy regimens. Further studies will be required to evaluate the potential of RV parameters to identify cardiotoxicity before the current LV parameters. To determine the impact of these RV parameters on patient prognosis, a larger prospective multicenter study with a more objective comparison method, such as cardiac magnetic resonance imaging, will be needed to confirm these correlations and the clinical impacts of our results.

### Conclusions

Our pilot study confirms that the right side of the heart is adversely affected in breast cancer patients undergoing anthracycline-based chemotherapy. Future work should be conducted to determine if right heart dysfunction precedes left heart abnormalities, potentially permitting earlier detection and possible intervention strategies to prevent chemotherapy-induced cardiac dysfunction in this population.

#### Declaration of interest

S D is on the advisory board and receives honoraria from Hoffman-La Roche, Amgen; Eisai; and Pfizer. There are no other conflicts of interest for any other authors.

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#### Ethics statement

The study was approved by Ottawa Health Science Network-REB (OHSN-REB).

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