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

Short title: Right heart function in chemotherapy patients


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Word Count: 2947

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Keywords: Right heart function; chemotherapy; cardiotoxicity; echocardiography
ABBREVIATIONS

ASE: American Society of Echocardiography
RAA: Right Atrial Area
RV: Right Ventricle
RV FAC: Right Ventricular Fractional Area Change
RV LSFW Right Ventricular Longitudinal-Strain of the Free Wall
LV: Left Ventricle
LVEF: Left Ventricular Ejection Fraction
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. Animal studies however, 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 to 65.4) to 57.4% (95% CI: 54.0 to 60.9) (p=0.04). During the same time period, the mean RAA increased from 12.1 cm\(^2\) (95% CI: 11.1 to 13.0 cm\(^2\)) to 13.8 cm\(^2\) (95% CI: 12.7 to 14.9 cm\(^2\)) (P = 0.02), mean RV FAC decreased (P = 0.01) from 48.3% (95% CI: 44.8 to 51.74) to 42.1% (95% CI: 38.5 to 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.
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 which can occur years after completion of chemotherapy. The clinical impact of this latent toxicity can be significant. A study 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]. While a number of studies have reported on the adverse impact of anthracycline based agents on left ventricular (LV) systolic and diastolic function, limited data exists on the impact on right ventricular (RV) function. Preliminary human and animal studies have suggested the detrimental toxic effect of doxorubicin provokes global cardiac injury that extends to both the left and right ventricles [3-5]. 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 and who had at least 2 echocardiograms performed at least 3 months apart. The majority of patients (i.e. 80%) had undergone echocardiogram prior to 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 performed 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. Parameters of cardiac structure and function were measured as per ASE guidelines [9-10].

Right atrial area [RAA] measurements were performed in the apical 4-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 4-chamber view using the percentage change in the RV end-diastolic and end-systolic areas.

RV longitudinal-strain of the free wall (RV LSFW) was measured offline using speckle tracking method and dedicated TomTec [TomTec Imaging Systems, Unterschleissheim, Germany]
software. 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 systolic longitudinal strain. Longitudinal strain (LS) of the RV free wall was measured as the average of 3 segmental strain values (base, mid, and apex) (Figure 1).

Images were reviewed and analyzed offline by 2 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 intraclass 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 +/- standard deviation 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 to 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 non-smokers and had no history of hypertension or hyperlipidemia. A total of 15 patients received doxorubicin-based
chemotherapy (doxorubicin/cyclophosphamide every 3 weeks x 4 cycles +/-paclitaxel). The mean total dose of doxorubicin was 232 mg/m2 (95 % CI: 214.84-249.16 mg/m2). A total of 34 patients received epirubicin containing chemotherapy (fluorouracil/epirubicin/cyclophosphamide every 3 weeks x 3 +/- docetaxel). The average total dose of epirubicin was 294.12 mg/m2 (95 % CI: 285.78-302.46 mg/m2).

**Echocardiographic variables (Table 2)**

The average LV ejection fraction (LVEF) decreased from 62.2% (95% CI: 59.1 to 65.4) at their first echocardiogram to 57.4% (95% CI: 54.0 to 60.9) on follow-up echocardiogram (p=0.04). 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 cm² (95% CI: 11.1 to 13.0 cm2) to 13.8 cm² on follow-up echocardiogram (95% CI: 12.7 to 14.9 cm2) (P = 0.02).

Mean RV FAC significantly decreased from 48.3% (95% CI: 44.8 to 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**

While 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 evident in breast cancer patients receiving anthracycline based chemotherapy using myocardial deformation parameters (RV LSFW), an important marker of subclinical dysfunction described 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, 11-13].

Despite improvement 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 a robust predictor of heart failure, sudden death, stroke, and mortality in patients with right and left heart conditions [16-18]. 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 [19-22]. 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 non-geometrical 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 to the thicker muscular LV, although data to support this premise is limited. Prospective non-human 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 are unable to determine if the RV is more sensitive to the cardiotoxic effects.

RV cardiotoxicity as a result of chemotherapy is not been adequately studied and previous studies have revealed divergent results. No change in RV myocardial performance index was noted by Belham et al. when patients were evaluated following low-dose anthracycline administration [27]. Similarly, Cottin et al. reported no alterations in the RV function at 1 and 12 months after anthracycline therapy using multiple gated 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 37 patient study [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 the cardio-oncologic patient [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 for identify cardiotoxicity prior to current LV parameters. To determine the impact of these RV parameters on patient prognosis, a larger prospective multicentre 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 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
SD is on the advisory board and receives honoraria from Hoffman-La Roche, Amgen; Eisai; and Pfizer. No other conflicts of interest for any other authors.

FUNDING

Dr. Girish Dwivedi is supported by a CIHR salary support award.

Ethics statement

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


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area change to predict death, heart failure, and stroke following myocardial infarction (from the VALIANT ECHO Study). Am J Cardiol 2008;101:607-12.


Figure Legends

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N= 49</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.4 ± 3.3 (50.1-56.7)</td>
</tr>
<tr>
<td>Women</td>
<td>48 (98.0%)</td>
</tr>
<tr>
<td>Body mass index (kg/m2)</td>
<td>25.9 ± 1.3 (24.6-27.2)</td>
</tr>
</tbody>
</table>

**Cardiac risk factors**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker/ex-smoker</td>
<td>21 (42.9%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (24.5%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>7 (14.3%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7 (14.3%)</td>
</tr>
<tr>
<td>Family History of coronary artery disease</td>
<td>2 (4.1%)</td>
</tr>
</tbody>
</table>

**Cardiac History**

<table>
<thead>
<tr>
<th>History</th>
<th>Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior coronary artery disease</td>
<td>2 (4.1%)</td>
</tr>
</tbody>
</table>
TABLE 2: ECHOCARDIOGRAPHY PARAMETERS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF</td>
<td>62.2% (95% CI: 59.1 to 65.4)</td>
<td>57.4% (95% CI: 54.0 to 60.9)</td>
<td>P=0.04</td>
</tr>
<tr>
<td>LV GLS</td>
<td>-15.4 (95% CI: -16.3 to -14.5)</td>
<td>-12.8 (95% CI: -13.8 to -11.9)</td>
<td>P=&lt;0.0001</td>
</tr>
<tr>
<td>LV Diastole (cm)</td>
<td>4.6 (95% CI: 4.5 to 4.7)</td>
<td>4.9 (95% CI: 4.8 to 5.1)</td>
<td>P = &lt;0.0001</td>
</tr>
<tr>
<td>LV Systole (cm)</td>
<td>3.0 (95% CI: 2.9 to 3.2)</td>
<td>4.0 (95% CI: 2.9 to 5.1)</td>
<td>P = 0.10</td>
</tr>
<tr>
<td>IV Septum (cm)</td>
<td>0.84 (95% CI: 0.80 to 0.89)</td>
<td>0.84 (95% CI: 0.80 to 0.87)</td>
<td>P = 0.75</td>
</tr>
<tr>
<td>Posterior Wall (cm)</td>
<td>0.87 (95% CI: 0.83 to 0.91)</td>
<td>0.87 (95% CI: 0.83 to 0.90)</td>
<td>P = 0.96</td>
</tr>
<tr>
<td>Fractional Shortening (%)</td>
<td>33.9 (95% CI: 31.8 to 36.0)</td>
<td>30.3 (95% CI: 27.8 to 32.7)</td>
<td>P = 0.003</td>
</tr>
<tr>
<td>Mitral Valve E Max Velocity (cm/s)</td>
<td>74.9 (95% CI: 70.7 to 79.2)</td>
<td>73.8 (95% CI: 69.0 to 78.6)</td>
<td>P = 0.60</td>
</tr>
<tr>
<td>Mitral Valve A Max Velocity (cm/s)</td>
<td>71.1 (95% CI: 64.6 to 77.7)</td>
<td>73.8 (95% CI: 68.4 to 79.1)</td>
<td>P = 0.20</td>
</tr>
<tr>
<td>Mitral Valve E/A</td>
<td>1.14 (95% CI: 1.02 to 1.30)</td>
<td>1.08 (95% CI: 0.95 to 1.21)</td>
<td>P = 0.15</td>
</tr>
<tr>
<td>Left atrium (cm)</td>
<td>3.3 (95% CI: 3.1 to 3.5)</td>
<td>3.4 (95% CI: 3.2 to 3.5)</td>
<td>P = 0.12</td>
</tr>
<tr>
<td>Aortic Root (cm)</td>
<td>2.8 (95% CI: 2.6 to 2.9)</td>
<td>2.9 (95% CI: 2.7 to 3.0)</td>
<td>P = 0.14</td>
</tr>
<tr>
<td>RV FAC</td>
<td>48.3% (95% CI: 44.8 to 51.7)</td>
<td>42.1% (95% CI: 38.5 to 45.6%)</td>
<td>P = 0.01</td>
</tr>
<tr>
<td>RAA</td>
<td>12.7cm2 (95% CI: 11.1 to 13.1cm2)</td>
<td>13.8 cm2 (95% CI: 12.7 to 14.9cm2)</td>
<td>P = 0.02</td>
</tr>
<tr>
<td>LS RVFW</td>
<td>-16.2% (95% CI: -18.1 to -14.4%)</td>
<td>-13.8% (95% CI: -15.1 to -12.5%)</td>
<td>P = 0.04</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>83 (95% CI: 74 to 92)</td>
<td>79 (95% CI: 74 to 84)</td>
<td>P = 0.32</td>
</tr>
</tbody>
</table>

LVEF= LV ejection fraction; LV GLS= longitudinal strain of the LV; RV FAC=Right ventricular fractional area change; RAA=right atrial area; LS RVFW=longitudinal strain of the RV free-wall
Figure 1

A

B

173x79mm (150 x 150 DPI)