Original article

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Diastolic dysfunction can precede systolic dysfunction on MUGA in cancer patients receiving trastuzumab-based therapy

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Background **Trastuzumab (T) and anthracycline (A)-based chemotherapy is considered the standard of care in human epidermal growth factor receptor-2 + overexpressing breast cancer, but requires monitoring for known cardiotoxicity using left ventricular (LV) ejection fraction (EF) every 3–4 months during treatment. It is not conclusively established whether diastolic dysfunction (DD) precedes LVEF decrease in patients developing trastuzumab-induced cardiotoxicity (TIC).**

Objective **The aim was to elucidate whether DD precedes LVEF decrease in trastuzumab-treated patients being monitored with radionuclide multigated acquisition for TIC.**

Patients and methods **Patients treated with T ± A-based chemotherapy who had undergone multigated acquisition were selected by date range (January 2006–September 2015). Up to four scans were analyzed per patient: (a) pre-A therapy, (b) pre-T therapy, (c) 4 months into T therapy, and (d) at end of T therapy. Baseline referred to the first scan of each patient (i.e. pre-A or pre-T). LV systolic and DD were defined as follows: EF less than 50% or a 10-point decrease from baseline and LV peak filling rate (PFR) less than 2.5 end-diastolic volume/s and time to peak LV filling rates (TPFR) greater than 180 ms, respectively.**

Results **A total of 202 patients were screened for this study, of whom 153 had received A therapy (5.1 ± 4.1 months duration) before T, 192 had 4 months of follow-up data, and 146 had 4 months of follow-up data and beyond (10.5 ± 5.0 months). LVEF decreased with A and T therapy ($P < 0.005$), but remained stable between 4 months and the final exam ($P = 0.26$). In patients with normal diastolic function at baseline (45.5%), PFR decreased with A and T, and DD preceded SD by 73 days on average. In the remaining patients, with abnormal diastolic function at baseline (54.5%), PFR did not change over the course of treatment ($P > 0.1$), nor did TPFR ($P > 0.3$).**

Conclusion **Patients with normal diastolic function at baseline receiving trastuzumab ± anthracycline adjuvant therapy may develop DD before SD, therefore offering an opportunity for early referral to cardiologists to optimize cardiovascular risk factors and manage cardiotoxicity.** ***Nucl Med Commun*** **40:22–29**

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Introduction

Trastuzumab is a humanized monoclonal antibody that is used in the treatment of patients with tumors that overexpress the human epidermal growth factor receptor-2 (HER2). In the 15–20% of patients with breast cancer who overexpress HER2, trastuzumab is administered in conjunction with anthracycline-containing and/or taxane-containing chemotherapy [1,2]. Although treatment with anthracycline chemotherapy and trastuzumab has resulted in improved clinical outcomes, including higher survival rates, these treatments result in an increased risk of cardiotoxicity [1]. The detection of early-onset trastuzumab-induced cardiotoxicity (TIC) is of paramount importance as the early use of cardioprotective drugs (including β-blockers and angiotensin-converting enzyme inhibitors) could potentially decrease the risk of cardiotoxicity and prevent treatment interruption that can minimize the therapeutic effects of the cancer therapy [2,3]. Prophylactic and blanket use of cardioprotective drugs have been tested in small studies (PRADA, MANTICORE,CEECY) with mixed results, may be potentially unsafe (e.g. risk of hypotension, renal failure, drug interaction, etc.) and is not recommended unless warranted by the presence of TIC [4].

In clinical practice, assessment of left ventricular (LV) ejection fraction (EF), a marker of systolic function, using one of the imaging modalities (i.e. echocardiography, radionuclide multigated acquisition (MUGA), or cardiovascular magnetic

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resonance), is used as the main method of detecting cardiotoxicity in cancer patients. In other disease states, such as coronary artery disease (CAD), diabetes, or hypertension, DD of the LV precedes a decrease in EF [5–9]. Similarly, previous studies have shown that diastolic impairment of the LV occurs before deterioration in EF in anthracycline-induced cardiotoxicity [5,6]. Whether abnormalities in diastolic impairment precede systolic function during TIC has not been determined conclusively [10,11]. In a relatively small study, it was shown that diastolic function assessed by echocardiogram was more sensitive than changes in EF for detecting acute cardiotoxicity in patients undergoing concurrent trastuzumab and adjuvant radiotherapy [10]. However, another study carried out by Reuvekamp *et al.* [11] using MUGA reported that abnormalities in diastolic parameters did not occur before systolic dysfunction (SD). To resolve these conflicting conclusions, we sought to independently evaluate changes in MUGA [which has excellent reproducibility for diastolic dysfunction (DD)]-derived diastolic and systolic function parameters at serial intervals in a large registry of breast cancer patients treated with trastuzumab. We evaluated the average time to onset of SD and DD in this patient population.

Patients and methods

Patient recruitment

The Institutional Research Ethics Board of the Ottawa Hospital approved this retrospective observational study. Patients diagnosed with HER2-positive breast cancer and who had a MUGA scan before trastuzumab administration were selected from The Ottawa Hospital electronic medical records systems between the dates of January 2006 and March 2016. Search terms included MUGA scan and associated reports containing the word 'Herceptin'. Patients with anthracycline and nonanthracycline chemotherapy were included, and diverse risk factors were considered such as the history of cardiac disease, chemotherapy regimen, and disease stage. Patients were screened to include only those having 2 or more MUGA scans. Up to 4 MUGA scans were analyzed for each patient including the following four time-points: 'pre-anthracycline' – before anthracycline therapy, 'pretrastuzumab' – before commencement of trastuzumab and after anthracycline therapy if applicable, '4 months follow-up' – first follow-up scan after pretrastuzumab scan, and 'final' – last MUGA at end of therapy. The 'baseline' time-point referred to the first MUGA scan available for each patient (i.e. preanthracycline or pretrastuzumab). Thereby, patient history and relevant MUGA scans of these patients were collected and analyzed. Demographics, clinical history, cardiovascular risk factors, and cancer therapy data were tabulated per patient on the basis of institutional patient records as part of routine clinical workup.

The number of cardiovascular risk factors were counted for each patient including diabetes, dyslipidemia, hypertension, smoking (current or past), history of CAD, family history of CAD, and obesity (BMI $> 30\,kg/m^2$). Similarly, the Morise risk score of cardiac death or myocardial infarction was calculated, excluding estrogen status in women, which was not consistently available, and was stratified into low-risk, medium-risk, and high-risk groups [12].

Patient therapy

All breast cancer patients (early stage and metastatic) were treated as per the recommendations of their primary oncologist. Patients with early-stage breast cancer received adjuvant chemotherapy with anthracycline ± taxane-based chemotherapy and trastuzumab. Patients with metastatic breast cancer received various first-line chemotherapy regimens including taxanes, capecitabine, FEC (fluorouracil, epirubucin, cyclophosphamide), TCH (taxotere, carboplatin,trastuzumab), CMF (cyclophosphamide, methotrexate, fluorouracil), and FAC (fluorouracil, doxorubicin, cyclophosphamide, and other HER2 targeted agents including pertuzumab). Several patients with metastatic breast cancer received second-line HER2 targeted therapy with T-DM1 (trastuzumab, emtansine).

All patients in this study were tracked for TIC with MUGA imaging. Patients with early-stage cancer had 3–4 MUGA scans in total over 1 year (17 cycles) of herceptin. Trastuzumab in the metastatic setting was continued until disease progression or toxicity, including cardiotoxicity (LVEF $< 50\%$). Hence, the number of scans per patient varied, and the last MUGA scan was considered for this study.

Multigated acquisition

All MUGA scans were acquired based on our routine clinical protocol, which consists of red blood cell labeling using 925 MBq of ^{99m}Tc using either the *in-vivo* or *in-vitro* methods depending on intravenous access. Images were acquired using Philips BrightView gamma cameras (Philips Healthcare, Milpitas, California, USA) with a single head planar acquisition in the left anterior oblique orientation. Technologists were instructed to tweak the angle to obtain optimal separation between left and right ventricles, and typically reproduced the projection angle utilized in previous MUGA scans. Image acquisitions targeted six million counts with 25 min maximum acquisition time using a 140 keV ± 10% energy window, a 2.2 zoom factor, and a cardiac high-resolution collimator. Images had 24 cardiac phases and 128×128 pixels. Electrocardiogram triggering had a 30% beat rejection window (± 15%).

Images were processed using Hermes Hybrid Viewer 2.6 (Hermes Medical Solutions, Stockholm, Sweden). The parameters that describe ventricular function were extracted from the phase–activity curve, which was obtained by semiautomatically drawn multiple regions of interest at each frame, which were edited to exclude overlapping atrial counts. A corresponding background time–activity curve was sampled using a region of interest manually located distally outward from the blood pool

at a region with minimal activity. Systolic and diastolic function parameters were calculated automatically from the background activity-corrected time–activity curves as described previously [13].

LVEF was calculated to assess LV systolic function, whereas LV peak filling rate (PFR) and time to peak filling rate (TPFR) were calculated to assess LV diastolic function [14]. LV SD was defined as EF less than 50% or a 10-point decrease from baseline as per the currently accepted clinical definition of TIC [15]. DD was defined as PFR less than 2.5 end-diastolic volume per s (EDV/s) or TPFR greater than 180 ms [11,13,16].

Because we were interested in the incremental value of DD over SD (current practice) for detecting TIC, we evaluated the proportion of patients in whom DD preceded SD versus those in whom DD was concurrent with or after SD.

Statistical analysis

Summary statistics are reported as mean ± one SD for continuous variables and as percent prevalence for dichotomous variables. Population means were compared using an unpaired Student's *t*-test. Changes between time-points were compared using a paired Student's *t*-test to account for the absence of data for some patients at certain time-points (e.g. no anthracycline treatment or short follow-up times); hence, each patient was their own control in assessing changes between time-points. Percent prevalences were compared using a two-proportions *Z*-test. The relationship between diastolic function and systolic function parameters, and their change, was tested using the Pearson correlation test. To track changes in cardiac function over the course of therapy, mean ± SD were plotted for EF, PFR, and TPFR at each time-point for all patients combined and for dichotomous groups as shown in Fig. 1. *P* values less than 0.05 were considered significant. Kaplan–Meier survival curves with 95% confidence intervals were used to visualize the increasing prevalence of SD and DD in the population using the first onset of the respective dysfunction and censoring if dysfunction did not occur by the final time-point. The median time difference between the equal prevalence of SD and the prevalence of DD was used to estimate the early-onset of DD compared with SD. All analyses were carried out in Matlab 2015a (MathWorks, Natick, Massachusetts, USA).

Results

In this study, 202 patients were included. Patient demographics, cardiovascular risk factors, cancer characteristics, therapy parameters, and MUGA parameters are summarized in Table 1. The number of MUGA scans varied between patients on the basis of disease stage, patient response to therapy, and presumed development of cardiotoxicity. Of the 202 patients, 136 patients had received a MUGA scan preanthracycline therapy (5.1 ± 4.1 months duration), 192 had 4 months of follow-up after trastuzumab commencement (4.2 ± 2.5 months), and 146 had 4 months of follow-up after trastuzumab commencement and beyond (10.5 ± 5.0 months).

PFR and EF were correlated moderately [17] ($r = 0.63$, $P < 0.0001$) and TPFR was correlated weakly with EF ($r = -0.14$, $P < 0.001$). Changes from baseline PFR were correlated moderately with changes in EF ($r = 0.51$, $P < 0.0001$), but changes in TPFR did not correlate with changes in EF ($P = 0.1$).

Changes in cardiac function parameters

The average EF decreased over the course of anthracycline therapy ($P < 0.001$) and during the first 4 months of trastuzumab therapy ($P < 0.0001$), but leveled off afterwards ($P = 0.3$) as shown in Fig. 1. As summarized in Table 2, SD (EF < 50% or 10 points decrease in EF) was detected in 105 (52%) of patients at any time (before or after chemotherapy), with 18 individuals (8.8%) having abnormal EF at baseline.

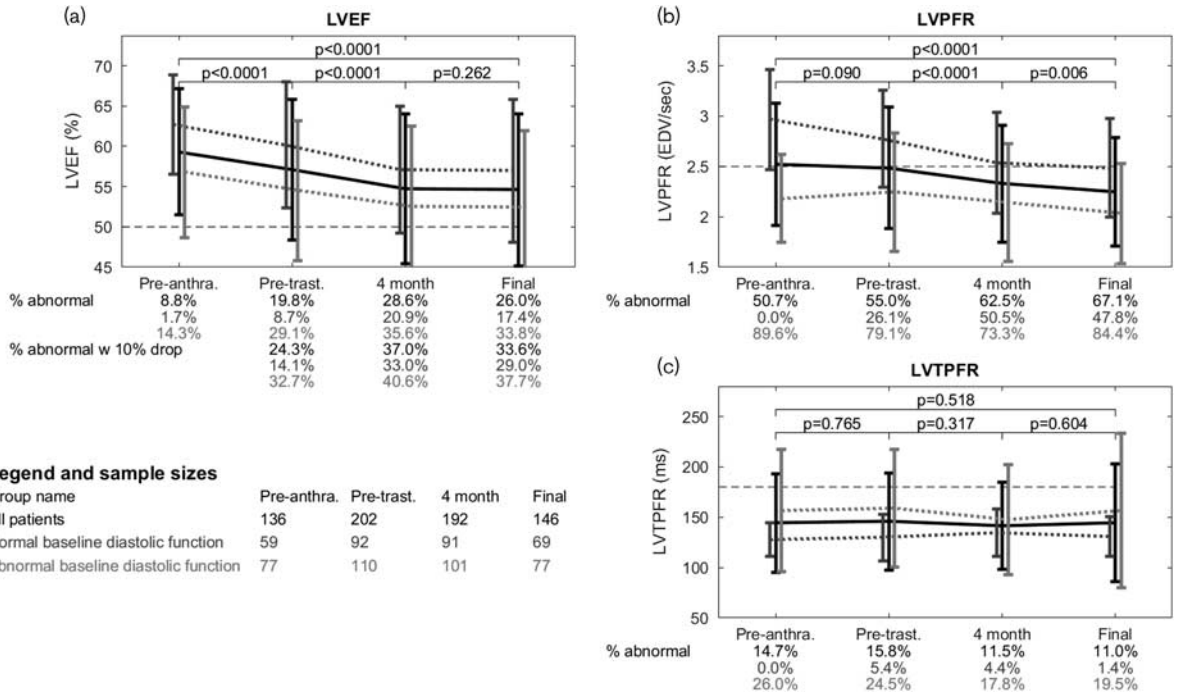
PFR did not change significantly over the course of anthracycline use ($P = 0.09$), but did persistently decline over the course of trastuzumab therapy ($P < 0.006$, Fig. 1). No significant changes in the mean TPFR were observed over the course of therapy ($P > 0.3$). A total of 110 (54.5%) patients had abnormal diastolic function at baseline and an additional 64 (31.6%) developed DD during therapy. Among those having DD at any time-point, 164 (94.3%) patients had abnormal PFR (< 2.5 EDV/s) and 59 (33.9%) patients had abnormal TPFR (>180 ms), with 43 (24.7%) patients having both abnormal PFR and TPFR (Table 2).

Baseline diastolic function

Roughly half of the patients in our study (54.5%) had DD at baseline by the study's definitions (Table 1). Not surprisingly, these patients were older ($P < 0.001$) and had a higher prevalence of hypertension ($P = 0.02$), which leads to a greater number of clinical risk factors ($P = 0.05$) and higher prevalence of medium versus low risk of cardiovascular events on the basis of the Morise risk score ($P = 0.005$). No patient was classified to severe risk on the basis of the Morise risk score. They also tended ($P = 0.05$) to have a lower incidence of right-only breast cancer and these patients were more frequently treated with anthracycline ($P = 0.002$). They had lower average EF values than those with normal baseline diastolic function (56.3 ± 7.8 vs. 62.5 ± 7.2%, $P < 0.001$, Table 1), but these decreased at a similar rate with therapy (Fig. 1).

The mean PFR did not change significantly in those with DD at baseline ($P = 0.1$), but in those with normal baseline diastolic function, PFR decreased up to 4 months of follow-up (Fig. 1). Although TPFR was greater in abnormal versus normal baseline diastolic function patients (159 ± 63 vs. 127 ± 17, $P < 0.001$), there were no significant changes in TPFR over time ($P > 0.2$).

Fig. 1



Average (a) ejection fraction, (b) peak filling rate, and (c) time to peak filling rate values by time-point for all patients (black) and those with normal (dark grey) and abnormal (light grey) diastolic function at baseline. The error bars indicate one SD. *P* values correspond to changes in the mean values for all patients using a paired *t*-test. LVEF, left ventricular ejection fraction; LVPFR, left ventricular peak filling rate; LVTPER, left ventricular time to peak filling rate.

DD versus SD in patients with normal diastolic function at baseline

Of the 92 patients with normal diastolic function at baseline, 66 (72%) developed DD or SD over the course of the study; of these, 33 (50%) developed DD before the presence of SD (Table 2) and 12 (18%) developed SD within the follow-up period. The prevalence of SD and DD over time in these patients is shown in Fig. 2, showing that DD preceded SD by 73 days on average on the basis of the time lag to reach equal percent prevalence. Minimal overlap between the 95% confidence intervals (thin dotted lines) supports statistically significant differences between the rates at which DD and SD present.

Other cohorts

Three additional subgroups were examined to elucidate interactions of disease stage, radiation treatment, and SD with cardiac function. Patients with metastatic cancer had significantly lower EF at all time-points and post-baseline PFR compared with patients with early-stage cancer (Fig. 3). Nevertheless, similar time to dysfunction results were derived for the metastatic versus nonmetastatic subgroups with DD preceding SD by 61 versus 73 days, respectively. Although patients who received left-sided radiation therapy had slightly higher EF values at baseline than patients who did not receive left-sided radiation therapy (4% mean difference, $P < 0.01$), no significant differences in EF values at other time-points were noted between the two groups.

Patients who developed SD at any time-point had lower PFR values overall and their PFR decreased much more markedly. Although small differences in DD prevalence existed at baseline (58 and 42% for SD and no-SD, respectively, $P = 0.02$), markedly different DD prevalence was present at the final follow-up (86 vs. 45%, $P < 0.0001$).

Discussion

Our study investigated whether DD precedes SD and can then be utilized for the early detection of cardiotoxicity. Early detection of cardiotoxicity is essential for the prevention and treatment of cardiac dysfunction in breast cancer patients who are undergoing chemotherapy so that they may continue their course of treatment for optimal outcomes.

Diastolic function parameters

Clinically, PFR and TPFR are not reported at our center and therefore did not influence patient management in this study. Using existing definitions of LV dysfunction using MUGA imaging, we discovered a much higher prevalence of DD (54.5%) than SD at baseline (8.8%)

Table 1 Demographics and clinical characteristics of a study population with normal ($n = 92$) and abnormal ($n = 110$) diastolic function at baseline

	All (%)	Normal diastolic function (%)	Abnormal diastolic function (%)	*P* value
Demographics				
N at pretrastuzumab	202	92	110	
Age (years)	61.2 ± 11.6	57.9 ± 12.0	64.0 ± 10.6	< 0.001
BMI (kg/m^2)	27.5 ± 6.4	27.6 ± 7.0	27.4 ± 5.9	0.82
Sex (female)	98.5	98.9	98.2	NA
Cardiovascular risk factors				
Obesity	27.3	27.5	27.1	0.95
Hypertension	29.0	20.9	35.8	0.02
Diabetes	9.0	6.6	10.9	0.29
Dyslipidemia	8.0	7.7	8.2	0.90
Smoker	6.0	5.5	6.4	0.78
Ex-smoker	23.5	25.3	22.0	0.59
Use of AT blockers	17.5	13.2%	21.1%	0.14
Use of β-blockers	8.0	6.6	9.2	0.50
Prior CAD	0.5	0.0	0.9	NA
Family history of CAD	2.0	2.2	1.8	NA
Number of risk factors	1.4 ± 1.3	1.2 ± 1.4	1.6 ± 1.3	0.05
Morise risk score				
Low (0–8)	55.4	66.3	46.4	0.005
Medium (9–15)	44.6	33.7	53.6	0.005
High (>15)	0	0	0	NA
Cancer characteristics				
Early-stage breast cancer	77.4	80.0	75.2	0.42
Metastatic breast cancer	22.6	20.0	24.8	0.42
Location				
Right breast	36.1	43.5	30.0	0.05
Left breast	38.1	34.8	40.9	0.37
Both breasts	24.3	19.6	28.2	0.16
Therapy				
History of adjuvant anthracycline	73.3	84.3	64.2	0.002
History of adjuvant nonanthracycline	57.9	62.9	53.8	0.20
Second-line chemotherapy	14.9	14.1	15.5	0.79
Left radiation therapy	39.6	39.3	39.8	0.94
Right radiation therapy	43.1	46.1	40.7	0.45
MUGA data (baseline)				
Heart rate (beats/min)	74.3 ± 11.9	75.0 ± 12.7	73.7 ± 11.2	0.42
Systolic function				
EF (%)	59.1 ± 8.1	62.5 ± 7.2	56.3 ± 7.8	< 0.001
Diastolic function				
PFR (EDV/s)	2.5 ± 0.6	3.0 ± 0.4	2.2 ± 0.4	< 0.001
TPFR (ms)	145 ± 50	127 ± 17	159 ± 63	< 0.001
MUGA timing				
Preanthracycline – pretrastuzumab (days)	−153 ± 124 ($n = 136$)	−150 ± 90 ($n = 59$)	−156 ± 146 ($n = 77$)	0.76
4 months – pretrastuzumab (days)	126 ± 75 ($n = 192$)	126 ± 68 ($n = 91$)	126 ± 81 ($n = 101$)	0.98
Final – pretrastuzumab (days)	317 ± 151 ($n = 146$)	313 ± 164 ($n = 69$)	320 ± 139 ($n = 77$)	0.79

AT, angiotensin; CAD, coronary artery disease; EDV, end-diastolic volume; EF, ejection fraction; MUGA, multigated angiography; PFR, peak filling rate; TPFR, time to peak filling rate.

Table 2 Frequency of systolic dysfunction and diastolic dysfunction at any time-point

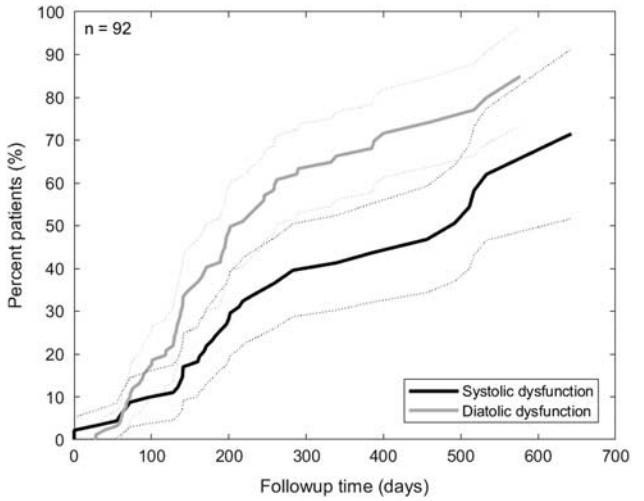
Parameters	All (%)	Normal baseline diastolic function (%)	Abnormal baseline diastolic function (%)	*P* value
N (%)	202	92 (45.5)	110 (54.5)	
SD	52.0	43.5	59.1	0.027
DD	86.1	69.6	100	NA
Abnormal PFR	94.3	92.2	95.5	NA
Abnormal TPFR	33.9	15.6	44.5	< 0.001
Abnormal PFR and TPFR	24.7	6.3	35.5	NA
DD or SD	87.1	71.7	100	NA
DD before SD	71.0	50.0	83.6	< 0.001
DD after or concurrent SD	29.0	50.0	16.4	< 0.001
DD followed by SD	52.4	18.4	72.3	< 0.001

DD, diastolic dysfunction; PFR, peak filling rate; SD, systolic dysfunction; TPFR, time to peak filling rate.

(Fig. 1). In the cohort of patients with DD at baseline, there was no significant decrease in PFR with therapy, indicating no further damage, whereas in the cohort of patients with normal diastolic function at baseline, there was a continuous decrease in PFR over the course of chemotherapy consistent with cardiotoxicity (Fig. 1). In

both cohorts, EF decreased over the course of therapy at a similar rate, with lower baseline EF values in the abnormal baseline diastolic function cohort. In patients with normal baseline diastolic function, DD developed at a faster rate than SD (Fig. 2), with DD preceding SD by an average of 73 days. Nevertheless, only 50% of patients in this group developed DD before SD (Table 2). These findings indicate that although diastolic function parameters (PFR) may indeed be an earlier marker of cardiotoxicity than systolic function parameters (EF) in some patients, not all patients who develop SD show antecedent DD detectable by MUGA.

Fig. 2

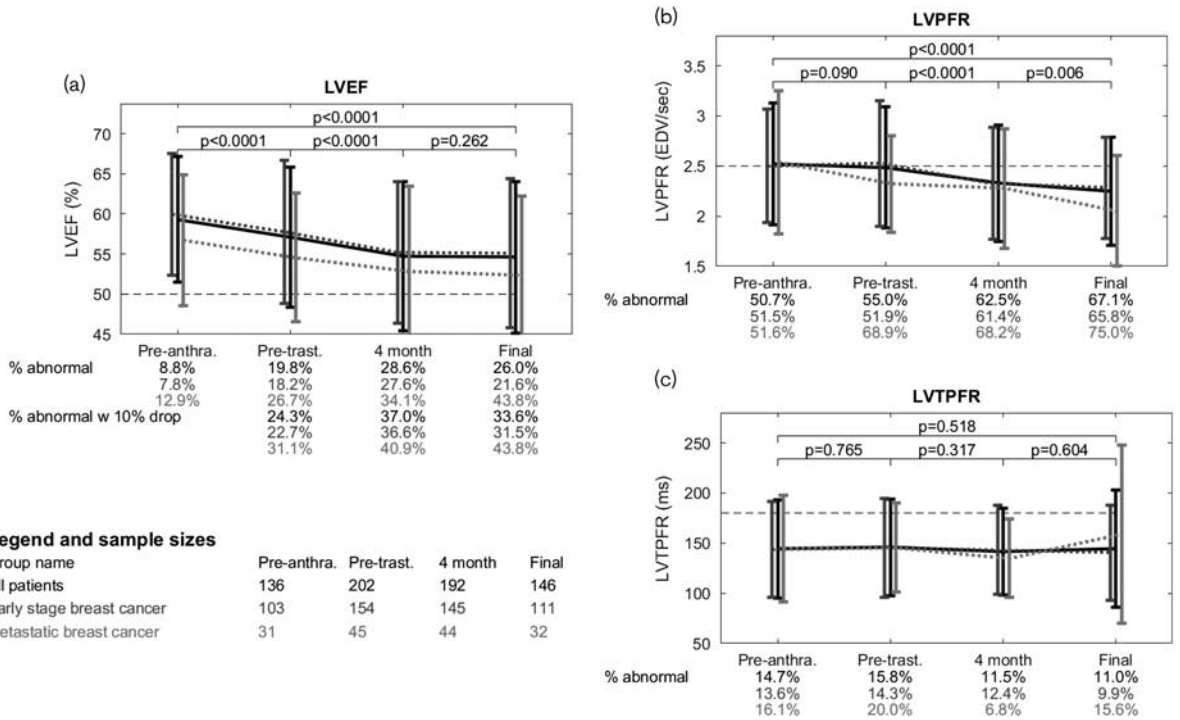


Kaplan–Meier curves for the presence of systolic and diastolic dysfunction in the cohort of patients with normal diastolic function at baseline ($n = 92$). Dotted lines indicate 95% confidence intervals.

PFR correlated moderately with EF ($r = 0.63$), supporting the notion that the two parameters are partly redundant. TPFR, however, had almost no correlation with EF ($r = -0.14$), but also did not significantly change over the course of treatment (Figs 1 and 3) and therefore may not be as useful to monitor early TIC as PFR. Our results are in line with the study carried out by Cochet *et al.* [18], which showed that the presence of DD without SD in HER2-positive breast cancer patients undergoing trastuzumab chemotherapy is an independent predictor of TIC.

EF decreased at similar rates in both subgroups of normal and abnormal baseline diastolic function (Fig. 1), whereas PFR decreased at a significant rate after anthracycline administration and at the beginning of trastuzumab administration. The difference between EF and PFR

Fig. 3



Average (a) ejection fraction, (b) peak filling rate, and (c) time to peak filling rate values by time-point for all patients (black) and those with early (dark grey) and metastatic (light grey) disease at baseline. The error bars indicate one standard deviation. *P* values correspond to changes in the mean values for all patients using a paired *t*-test. LVEF, left ventricular ejection fraction.

rates of decline could be attributed to the lower sensitivity of EF in detecting small changes in LV contractility [19].

The results of our study are similar to those in the smaller study by Reuvekamp *et al.* [11], but our conclusions differ. Even though the two studies used very similar methodology, we measured a higher prevalence of DD at any time-point (86 vs. 58%, $P < 0.001$). Nevertheless, using the same data analysis methods as Reuvekamp *et al.* [11], we obtained similar analysis results (Table 3), with DD preceding SD in 52% (compared with 54%, $P = 0.86$) of the patients who had both SD and DD (at any time-point). They concluded that trastuzumab-induced SD and DD do not occur in a certain order because they found that of the 24 (31%) patients who developed DD and SD, 13 (54%) patients had DD before SD and 11 (46%) had DD after or concurrent with SD. The difference in our conclusions could be partly attributed to our analysis methods. Although they considered only patients who had developed both SD and DD for evaluating their order, we included patients who had developed either dysfunction. A further difference is that our conclusion is based on a subset of 92 patients who had normal diastolic function at baseline. Consequently, we analyzed the order of dysfunction type in 66 (vs. 29) patients. Similar to Reuvekamp *et al.* [11], we found a roughly even split between DD preceding SD and DD following or concurrent with SD (Table 2), but when we included analysis of dysfunction prevalence as a function of time using Kaplan–Meier curves (Fig. 2), we observed that DD tended to precede SD by an average of 73 days.

Other patient subsets

Cancer stage, hypertension, and smoking history did not have a clear interaction with the onset of SD or DD. In some studies, the correlation between trastuzumab and cardiotoxicity was assumed in patients with any of those risk factors [10,20–22]. Our study showed that patients with metastatic cancer had lower EF and PFR compared with patients with early stage cancer (Fig. 3), likely because of comorbidities at baseline. Both populations had a similar rate of decrease of EF, but patients with metastatic disease showed a more pronounced decrease in PFR, which may be a consequence of anthracycline and trastuzumab therapy for more than one year, which increased patients' risk of developing cardiotoxicity [21]. Further, comparison between patients who were left-sided radiation treatment naïve and those who had received radiation treatment indicated that the latter subgroup showed a slightly lower rate of EF and PFR change, but this was not statistically significant. Thus, this finding suggests that modern radiation therapy delivery is not a significant contributor to TIC, as reported previously by others [23–25].

Table 3 Systolic dysfunction and diastolic dysfunction prevalence in comparison with Reuvenkamp *et al.* [11]

Parameters	This study (%)	Reuvenkamp *et al.* [11] (%)	*P* value
N	202	77	
SD	52	47	0.46
DD	86	58	< 0.001
Abnormal PFR	94	87	0.11
Abnormal TPFR	34	58	0.003
Abnormal PFR and TPFR	25	42	0.025
DD and SD	51	31	0.003
DD before SD	52	54	0.86
DD after or concurrent SD	48	46	0.86

DD, diastolic dysfunction; PFR, peak filling rate; SD, systolic dysfunction; TPFR, time to peak filling rate.

Other imaging modalities

Other noninvasive techniques such as echocardiography or cardiovascular magnetic resonance can also be used to assess DD in these patients. Although echocardiography utilizes tissue and pulse Doppler methods to evaluate tissue velocities and LV filling pressure, cardiovascular magnetic resonance uses the cine-phase contrast technique to interrogate inflow through the mitral valve and pulmonary veins for evaluation of DD. Previous echocardiography studies have provided preliminary evidence in favor of DD preceding LVEF decrease in patients receiving anthracycline, but more studies are needed before it can be accepted as a useful measure in guidelines [5,10,19]. Higher operation costs and lower availability have limited the use of cardiovascular magnetic resonance and consequently also studies evaluating DD in this group of patients.

Limitations

This study used imaging time-points associated with the phase of treatment, resulting in varying time intervals between imaging sessions. Consequently, not all available imaging time-point data were considered and may have caused some loss of precision with respect to the first onset of DD and SD. Hence, follow-up studies are required to more accurately and precisely characterize the value of DD as an early predictor of cardiotoxicity over SD alone.

As mentioned, we used existing criteria to define DD, which may not accurately represent our patient cohort, and may have caused an increased prevalence and earlier detection of DD in this study. Nevertheless, these criteria are well established in the literature, and their modification would prevent comparison to existing literature.

In this study, we utilized gated images at cardiac rest state with 24 frames/cycle (acceptable as per the American Society of Nuclear Cardiology guidelines [13] and a widely used method for measuring LVEF in the cancer chemotherapy population). Increasing the number of gates/cycle could potentially improve the precision of diastolic function measurements, enabling the detection of smaller

PFR changes and with greater confidence – especially in cases with elevated heart rates. Nevertheless, we could not test this hypothesis with the data available to us.

Finally, our study included a heterogenous population of patients undergoing various therapy regiments. However, our inclusion criteria allowed us to study a nonbiased, clinically representative sample population, where we were able to investigate whether DD preceded SD irrespective of clinically indicated (on the grounds of SD and end of trastuzumab therapy) follow-up censorship.

Conclusion

Patients receiving trastuzumab ± anthracycline adjuvant therapy may develop DD before SD, therefore offering an opportunity for early referral to cardiologists. Further studies are warranted to evaluate the long-term clinical implications of DD in patients who have completed anthracycline and trastuzumab-based chemotherapy.

Acknowledgements

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Conflicts of interest

Ran Klein is a consultant with Jubilant DRAXimage and has received grant funding from industry partnership programs including GE Healthcare, Jubilant DRAXimage, Shelley Medical Solutions, and Hermes Medical Solutions. Ran Klein receives revenues from the rubidium generator technology licensed to Jubilant DRAXimage and revenue shares from the sale of FlowQuant. Susan Dent sits on advisory boards for Hoffman La Roche and has received honoraria from Pfizer and Novartis; not related to topic in this manuscript. Girish Dwivedi reports two paid lectures from Astra Zeneca and Amgen not related to the topic in the manuscript. For the remaining authors, there are no conflicts of interest.

References

1 Rochette L, Guenancia C, Gudjoncik A, Hachet O, Zeller M, Cottin Y, *et al.* Anthracyclines/trastuzumab: new aspects of cardiotoxicity and molecular mechanisms. *Trends Pharmacol Sci* 2015; **3**:326–348.
2 Viani GA, Afonso SL, Stefano EJ, De Fendi LI, Soares FV. Adjuvant trastuzumab in the treatment of her-2-positive early breast cancer: a meta-analysis of published randomized trials. *BMC Cancer* 2007; **7**:153.
3 Janbabai G, Nabati M, Faghihinia M, Azizi S, Borhani S, Yazdani J. Effect of enalapril on preventing anthracycline-induced cardiomyopathy. *Cardiovasc Toxicol* 2017; **17**:130–139.
4 Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, *et al.* 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur Heart J* 2016; **37**:2768–2801.
5 Lee BH, Goodenday LS, Muswick GJ, Yasnoff WA, Leighton RF, Skeel RT. Alterations in left ventricular diastolic function with doxorubicin therapy. *J Am Coll Cardiol* 1987; **9**:184–188.
6 Marchandise B, Schroeder E, Bosly A, Doyen C, Weynants P, Kremer R, *et al.* Early detection of doxorubicin cardiotoxicity: interest of Doppler echocardiographic analysis of left ventricular filling dynamics. *Am Heart J* 1989; **118**:92–98.
7 Cottin Y, Touzery C, Coudert B, Gilles A, Walker P, Massing JL, *et al.* Impairment of diastolic function during short-term anthracycline chemotherapy. *Br Heart J* 1995; **73**:61–64.
8 Redfield MM, Jacobsen SJ, Burnett JC, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA* 2003; **289**:194–202.
9 Bonow RO, Bacharach SL, Green MV, Kent KM, Rosing DR, Lipson LC, *et al.* Impaired left ventricular diastolic filling in patients with coronary artery disease: assessment with radionuclide angiography. *Circulation* 1981; **64**:315–323.
10 Cao L, Cai G, Chang C, Miao A-Y, Yu X-L, Yang Z-Z, *et al.* Diastolic dysfunction occurs early in HER2-positive breast cancer patients treated concurrently with radiation therapy and trastuzumab. *Oncologist* 2015; **20**:605–614.
11 Reuvekamp EJ, Bulten BF, Nieuwenhuis AA, Meekes MRA, de Haan AFJ, Tol J, *et al.* Does diastolic dysfunction precede systolic dysfunction in trastuzumab-induced cardiotoxicity? Assessment with multigated radionuclide angiography (MUGA). *J Nucl Cardiol* 2016; **23**:824–832.
12 Morise A, Evans M, Jalisi F, Shetty R, Stauffer M. A pretest prognostic score to assess patients undergoing exercise or pharmacological stress testing. *Heart* 2005; **93**:200–204.
13 Corbett JR, Akinboboye OO, Bacharach SL, Borer JS, Botvinick EH, DePuey EG, *et al.* Equilibrium radionuclide angiocardiography. *J Nucl Cardiol Off Publ Am Soc Nucl Cardiol* 2006; **13**:e56–e79.
14 Perik PJ, de Vries EGE, Gietema JA, van der Graaf WTA, Smilde TDJ, Sleijfer DT, *et al.* Serum HER2 levels are increased in patients with chronic heart failure. *Eur J Heart Fail* 2007; **9**:173–177.
15 Mitani I, Jain D, Joska TM, Burtness B, Zaret BL. Doxorubicin cardiotoxicity: prevention of congestive heart failure with serial cardiac function monitoring with equilibrium radionuclide angiocardiography in the current era. *J Nucl Cardiol Off Publ Am Soc Nucl Cardiol* 2003; **10**:132–139.
16 Mitra D, Basu S. Equilibrium radionuclide angiocardiography: its usefulness in current practice and potential future applications. *World J Radiol* 2012; **4**:421–430.
17 Taylor R. Interpretation of the correlation coefficient: a basic review. *J Diagn Med Sonogr* 1990; **6**:35–39.
18 Cochet H, Bullier E, Gerbaud E, Durieux M, Godbert Y, Lederlin M, *et al.* Absolute quantification of left ventricular global and regional function at nuclear MPI using ultrafast CZT SPECT: initial validation versus cardiac MR. *J Nucl Med* 2013; **54**:556–563.
19 Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, *et al.* Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr* 2014; **27**:911–939.
20 Leung HWC, Chan ALF. Trastuzumab-induced cardiotoxicity in elderly women with HER-2-positive breast cancer: a meta-analysis of real-world data. *Expert Opin Drug Saf* 2015; **14**:1661–1671.
21 Chen T, Xu T, Li Y, Liang C, Chen J, Lu Y, *et al.* Risk of cardiac dysfunction with trastuzumab in breast cancer patients: a meta-analysis. *Cancer Treat Rev* 2011; **37**:312–320.
22 Serrano C, Cortés J, De Mattos-Arruda L, Bellet M, Gómez P, Saura C, *et al.* Trastuzumab-related cardiotoxicity in the elderly: a role for cardiovascular risk factors. *Ann Oncol Off J Eur Soc Med Oncol* 2012; **23**:897–902.
23 Wadhwa D, Fallah-Rad N, Grenier D, Krahn M, Fang T, Ahmadie R, *et al.* Trastuzumab mediated cardiotoxicity in the setting of adjuvant chemotherapy for breast cancer: a retrospective study. *Breast Cancer Res Treat* 2009; **117**:357–364.
24 Tan-Chiu E, Yothers G, Romond E, Geyer CE, Ewer M, Keefe D, *et al.* Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *J Clin Oncol Off J Am Soc Clin Oncol* 2005; **23**:7811–7819.
25 Guglin M, Hartlage G, Reynolds C, Chen R, Patel V. Trastuzumab-induced cardiomyopathy: not as benign as it looks? A retrospective study. *J Card Fail* 2009; **15**:651–657.