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ORIGINAL PAPER

Assessment of left ventricular function by CMR versus MUGA scans in breast cancer patients receiving trastuzumab: a prospective observational study

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Abstract
Little is known about the comparison of multiple-gated acquisition (MUGA) scanning with cardiovascular magnetic resonance (CMR) for serial monitoring of HER2+ breast cancer patients receiving trastuzumab. The association of cardiac biomarkers with CMR left ventricular (LV) function and volume is also not well studied. Our objectives were to compare CMR and MUGA for left ventricular ejection fraction (LVEF) assessment, and to examine the association between changes in brain natriuretic peptide (NT-BNP) and troponin-I and changes in CMR LV function and volume. This prospective longitudinal two-centre cohort study recruited HER2+ breast cancer patients between January 2010 and December 2013. MUGA, CMR, NT-BNP and troponin-I were performed at baseline, 6, 12, and 18 months after trastuzumab initiation. In total, 41 patients (age 51.7 ± 10.8 years) were enrolled. LVEF comparison between MUGA and CMR demonstrated weak agreement (Lin's correlation coefficient r = 0.46, baseline; r = 0.29, 6 months; r = 0.42, 12 months; r = 0.39, 18 months; all $p < 0.05$). Bland–Altman plots demonstrated wide LVEF agreement limits (pooled agreement limits 3.0 ± 6.2). Both modalities demonstrated significant LVEF decline at 6 and 12 months from baseline, concomitant with increased LV volumes on CMR. Changes in NT-BNP correlated with changes in LV diastolic volume at 12 and 18 months ($p < 0.05$), and LV systolic volume at 18 months ($p < 0.05$). Changes in troponin-I did not correlate with changes in LV function or volume at any timepoint. In conclusion, CMR and MUGA LVEF are not interchangeable, warranting selection and utility of one modality for serial monitoring. CMR is useful due to less radiation exposure and accuracy of LV volume measurements. Changes in NT-BNP correlated with changes in LV volumes.

Keywords Breast cancer · Trastuzumab · Cardiotoxicity · Cardiovascular magnetic resonance · MUGA · LVEF

Introduction

Breast cancer continues to be the most common cancer diagnosed in women, with 25% to 30% of cases overexpressing human epidermal growth factor receptor 2 (HER2) [1–3]. Prior to the approval of trastuzumab (Herceptin; Genentech, Inc., San Francisco, CA), this subtype of breast cancer had a relatively poor prognosis, with high risk of recurrence and metastasis [2, 4, 5]. Despite evidence in reduction of disease recurrence and all-cause mortality [6–11], trastuzumab has a

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relatively high incidence of cardiac dysfunction, warranting serial cardiac monitoring [9, 10, 12–15]. Currently, MUGA scanning is used, though it has moderate reproducibility and is operator dependent due to suboptimal spatial resolution and signal-to-noise ratio [16]. Serial MUGA scans also require injection of radiopharmaceuticals through venipuncture, and cumulative radiation exposure can be harmful especially for younger women [17, 18]. Although the echocardiogram (ECHO) is also widely available, it too is operator dependent and subject to several limitations, including poor resolution and reliance on geometric assumptions [16]. CMR has emerged as the reference standard for measurement of ventricular volume and function as it does not depend on geometric assumptions or the shape of the left ventricular (LV) cavity [16]. This, together with excellent spatial resolution and signal-to-noise ratio, allows accurate and reproducible measurements of LV volume and ejection fraction (EF). CMR measurements further have unparalleled intra-observer, inter-observer, and inter-study variability [16, 19, 20]. Despite such benefits, little data exist on the direct comparison between MUGA and CMR for serial monitoring of breast cancer patients receiving trastuzumab. In addition to imaging, population studies have shown that elevated brain natriuretic peptide (BNP) is a biomarker for preclinical systolic dysfunction [21, 22]. Moreover, elevated troponin has been linked to a higher risk of incident heart failure in chemotherapy-treated patients [23–26]. Despite these observations, little is known about the correlation between these biomarkers and LV structure and function by CMR. Therefore, the objectives of this prospective longitudinal study were to compare serial LVEF measurements by CMR and MUGA in breast cancer patients treated with trastuzumab, and to determine the association between changes in biomarker levels (BNP and troponin-I) and changes in cardiac structure and function by CMR.

Materials and methods

From January 2010 to December 2013, women with histologically confirmed diagnosis of invasive breast carcinoma and HER2 overexpression by immunohistochemistry (ICH), fluorescence in situ hybridization (FISH), or dual in situ hybridization (DSH), with planned trastuzumab therapy and baseline LVEF $\geq 50\%$ measured by MUGA, were eligible for participation in this prospective, observational study at the two participating tertiary care institutions (www.clinicaltrials.gov; identifier NCT01022086). Patients were excluded from the study if they had previous treatment with trastuzumab or any other anti-HER2 agent, pre-existing symptomatic heart failure, acute coronary syndrome or coronary revascularization within the past six months, permanent atrial fibrillation, inability to undergo CMR, pregnant and/or nursing, and planned or current treatment of other targeted biological therapies that pose risk of cardiotoxicity.

Ethics approval was obtained from St. Michael's Hospital and Sunnybrook Odette Cancer Centre, and written informed consent was obtained from all patients. Laboratory tests, cardiac imaging, and clinical evaluation were part of the study protocol. The planned duration of trastuzumab therapy was 12 months. All patients underwent study procedures at baseline (prior to the initiation of trastuzumab therapy), and 6, 12, and 18 months following the initiation of therapy. Patients were assessed annually thereafter with cardiac assessments, including a physical examination and assessment by the New York Heart Association (NYHA) Functional Classification.

LVEF measurement by MUGA and CMR was collected within $\pm$ 14-days at 6, 12, and 18 months after therapy initiation. CMR scans were performed with either a 1.5 T scanner (Intera, Phillips Medical Systems, Best, the Netherlands or GE Signa Excite Cv, Milwaukee, WI), using a cardiac coil and retrospective electrocardiographic gating. A standard imaging protocol using validated, commercially available sequences was used [27]. The LV endocardial contours were traced on contiguous short-axis steady-state free precession cine images at end-diastolic phase and end-systolic phase, and summed to calculate the left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV), respectively. LVEF was calculated by (LVEDV − LVESV)/LVEDV × 100%. MUGA scans were performed using a standard clinical protocol. 740 MBq ^{99m}Tc-Pertechnetate (^{99m}Tc O_4^-) was injected intravenously, and blood pool images acquired immediately following tracer administration with the patient in supine position. Planar, ECG-gated images (acquisition matrix 64 × 64, magnification 2.0) were obtained in three views (anterior, left anterior oblique, left lateral) over 10 min. The heart cycle was divided into 32 time bins for acquisition. CMR and MUGA scans were analyzed by two experienced readers, who were blinded to the results of the other imaging technique and all clinical information. The patient and treating medical oncologist were blinded to the results of the CMR.

Biomarker values were measured as per institutional standard biochemistry laboratory commercial assay techniques. High-sensitivity troponin I (hs-TnI) was performed using the Advia Centaur CP TnI-Ultra immunoassay, with a normal reference range of < 0.040 µg/L. Serum N-terminal pro B-type natriuretic peptide (NT-BNP) was performed using the Elecsys proBNP II immunoassay. The normal reference range of NT-BNP in the ambulatory care setting is < 125 ng/L for patients with age < 50 years and < 250 ng/L for ages 50–75. Biomarkers were collected prior to the administration of trastuzumab therapy for that particular cycle.

Medical history and physical exam, including weight and height, routine blood work, Eastern Cooperative Oncology Group (ECOG) performance status, and congestive heart failure (CHF) evaluation, were also performed at each time point during the study. The cardiac evaluation assesses the following symptoms: chest pain, cough, diaphoresis, dyspnea, paroxysmal nocturnal dyspnea, orthopnea, palpitation, pedal edema, and fatigue/decreased exercise tolerance. A New York Heart Classification (NYHA) grade was assigned on the basis of the symptoms present.

Trastuzumab was administered as per standard of care, given every 3 weeks at a loading dose of 8 mg/kg administered as a 90-min infusion and maintenance dose of 6 mg/kg administered as a 30-min infusion up to 18 cycles of therapy (12 months). Chemotherapy treatment was at the discretion of the treating medical oncologist, and consisted of anthracycline or non-anthracycline regimens.

Cardiotoxicity was defined as LVEF decrease $\geq 15\%$ from baseline, or LVEF $< 50\%$ as per MUGA scan and signs and symptoms of CHF (NYHA class III or IV) [28]. Trastuzumab was withheld for 3 weeks for patients who met these criteria, and MUGA scan ($\pm$ echocardiogram) were repeated. A referral to cardiology was also made for management of potential heart failure. If the repeat MUGA scan showed improvement in LVEF after 3 weeks without trastuzumab treatment, trastuzumab was re-initiated with ongoing cardiac monitoring.

Baseline characteristics of the sample were summarized as means and standard deviations (SD) or medians and interquartile ranges (IQR) for continuous variables, and proportions for categorical variables. To compare serial LVEF measurements between CMR and MUGA scans, the Lin's concordance correlation coefficient and 95% confidence interval, and Pearson's correlation coefficient, were estimated at each time point. The Lin coefficient determines how much the two variables being measured are close to the identity (45°) line. Bland–Altman limits of agreement were also calculated, at each time point, and overall, accounting for correlations among repeated measurements [29]. To evaluate changes in LVEF and LV volume measurements, repeated measures analyses were performed under the linear mixed model framework using time as a fixed factor (6, 12, 18, and baseline as the reference category) and the compound symmetry correlation structure. To evaluate the association between changes in biomarker levels and changes in CMR LVEF and LV volume measurements, NT-BNP and troponin-I at each time point were included in the model. To explore the association between LVEF and chemotherapy regimen treated groups (non-anthracycline versus anthracycline), the overall effect of chemotherapy regimen across all time points was tested using a repeated measures model with time and chemotherapy as fixed factors. Lin's concordance correlation and Bland–Altman limits of agreement were estimated using Stata 13 (StataCorp, 2013). All other analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical tests were two-sided and significance was defined as p-values of less than 0.05. No adjustments for multiple comparisons or testing were applied [30].

Results

Between January 2010 and December 2013, 56 patients were screened. Of these patients, 41 patients were consented and enrolled. Table 1 shows the baseline characteristics of the patient population. Of the 41 patients, 10 had cardiovascular risk factors, though none had history of heart failure; 23 patients received anthracycline-based chemotherapy and 19 patients received radiation therapy, with 12 having left-sided treatment.

At baseline, 41 patients were included in the analysis. At 6 months, 38 patients were included in the MUGA analysis, while 35 patients were included in the CMR analysis. At 12 and 18 months, 35 and 33 patients, respectively, were included in both MUGA and CMR analyses. Reasons for incomplete imaging included breast tissue expanders from immediate breast reconstruction ($n=3$ at 6 months; $n=1$ at 12 months; and $n=2$ at 18 months), patient preference to not undergo a scan ($n=2$ for MUGA and $n=1$ for CMR at 12 months; and $n=3$ for MUGA and $n=2$ for CMR at 18 months), or change in treatment plan, resulting in withdrawal ($n=3$ at 6 months; $n=4$ at 12 months; and $n=4$ at 18 months).

LVEF measurements by MUGA and CMR decreased significantly at 6 and 12 months, relative to baseline. There was a recovery in LVEF at 18 months, which was no longer significantly different compared to baseline (Fig. 1).

Table 2 demonstrates the results of a linear mixed model analyses for the mean changes of LVEF, LVEDV, and LVESV by CMR from baseline to 6 months, baseline to 12 months, and baseline to 18 months. There was a significant decrease in LVEF ($p<0.05$) concomitant with increase in LVEDV ($p<0.05$) and LVESV ($p<0.05$) in the comparisons of 6 months versus baseline, and 12 months versus baseline. There was no significant difference between baseline and 18-month LVEF and LV volume measurements.

Analyses for correlation between LVEF values by CMR and MUGA are shown in Table 3. Lin's concordance correlation revealed a weak agreement ($r=0.46$ at baseline; $r=0.29$ at 6 months; $r=0.42$ at 12 months; $r=0.39$ at 18 months; all $p<0.05$). Bland–Altman analyses between MUGA and CMR LVEF are presented in Table 3 and Fig. 2. The pooled Bland–Altman limits of agreement were -15.4% to 9.5%. The limits of agreement were wide at baseline and further increased in range at 6, 12, and 18 months, relative to baseline.

Table 1 Baseline characteristics of study population

Characteristic	N (%)
Age (years)	51.7 ± 10.8[a]
BMI (kg/m^2)	26.8 ± 6.3[a]
Systolic BP (mmHg)	124.6 ± 14.8[a]
Diastolic BP (mmHg)	75.4 ± 8.9[a]
HR (bpm)	79.4 ± 12.8[a]
Cardiovascular risk factors	
Hypertension	10 (24.4)
Smoking[b]	10 (24.4)
Diabetes	4 (9.8)
Hypercholesterolemia	3 (7.3)
Coronary artery disease	1 (2.4)
Antihypertensive medications	10 (24.4)
Tumor profile	
Primary tumor side, left	27 (65.9)
Primary tumor side, right	14 (34.1)
Receptor status	
ER+/PR+	15 (36.6)
ER+/PR−	9 (22.0)
ER−/PR+	3 (7.3)
ER−/PR−	14 (34.1)
Type of surgery	
Breast-conserving surgery	22 (53.7)
Mastectomy	19 (46.3)
Radiation therapy	19 (46.3)
Left-sided	12 (29.3)
Right-sided	3 (7.3)
Bilateral	1 (2.4)
Centre	1 (2.4)
Not reported	2 (4.9)
Anthracycline-based chemotherapy	23 (56.1)
FEC-DH	9 (22.0)
Neoadjuvant AC-Taxol H	5 (12.2)
Neoadjuvant FEC-DH	4 (9.8)
AC-Taxol H	4 (9.8)
Neoadjuvant AC-DH	1 (2.4)
Non-anthracycline chemotherapy	18 (43.9)
TCH	11 (26.8)
Tcyclo-H	6 (14.6)
CMF-H	1 (2.4)
Imaging parameters	
CMR LVEF (%)	60.5 ± 4.3[a]
MUGA LVEF (%)	58.2 ± 5.8[a]
LVEDV (mL)	129.7 ± 24.9[a]
LVESV (mL)	51.5 ± 12.0[a]
Biomarkers	
hs-TnI (ng/mL) (n = 37)	< 0.006 (< 0.006–0.012)[c]
NT-BNP (ng/mL) (n = 39)	57 (33–128)[c]

Table 1 (continued)

AC-DH Doxorubicin, cyclophosphamide, docetaxel, trastuzumab, *AC-Taxol H* doxorubicin, cyclophosphamide, paclitaxel, trastuzumab, *ASA* Acetylsalicylic acid, *BMI* Body mass index, *BP* Blood pressure, *CMF-H* Cyclophosphamide, methotrexate, fluorouracil, trastuzumab, *ER* Estrogen receptor, *FEC-DH* Fluorouracil, epirubicin, cyclophosphamide, docetaxel, trastuzumab, *PR* Progesterone receptor, *TCH* Docetaxel, carboplatin, trastuzumab, *Tcyclo-H* Docetaxel, cyclophosphamide, trastuzumab

[a]Data represented as mean ± SD

[b]Defined as current smoker or remote history of smoking

[c]Data represented as median (interquartile range)

Table 4 demonstrates Spearman correlations between changes in LV structure (LVEDV, LVESV) and function (LVEF) and changes in cardiac biomarkers (hs-TnI and NT-BNP). There was a moderate positive correlation between LVEDV and NT-BNP at 12 and 18 months ($p < 0.05$), and moderate positive correlation between LVESV and NT-BNP at 18 months ($p < 0.05$).

Only one patient had a diagnosis of trastuzumab-induced cardiotoxicity on the basis of MUGA scan at 6 months (LVEF declined from 67% at baseline to 45% at 6 months). Trastuzumab was withheld for one cycle and a cardiology referral was made for further evaluation. As per protocol, MUGA was repeated and ECHO was also performed. In total, three other patients had a drop in LVEF < 50%, with one patient being symptomatic due to concurrent infection. Trastuzumab was not withheld or discontinued for the two other patients on the basis of repeat imaging and clinical decision.

The association between LVEF and chemotherapy regimen treatment (i.e., anthracycline versus non-anthracycline) was analyzed, testing for the overall effect of chemotherapy regimen across all time points. There was no significant association overall for CMR ($p = 0.09$) or MUGA ($p = 0.43$).

Discussion

In this prospective observational study, we demonstrated that serial MUGA versus CMR for LVEF measurements in breast cancer patients receiving trastuzumab is limited by weak agreement, with wide agreement limits at all time points. Both modalities demonstrated a significant LVEF decline at 6 and 12 months from baseline, followed by a recovery to near-baseline values at 18 months. In all patients, CMR further demonstrated a concomitant increase in LV volumes at 6 and 12 months from baseline. There was no signification association between CMR and MUGA LVEF by chemotherapy regimen (i.e., anthracycline versus non-anthracycline).

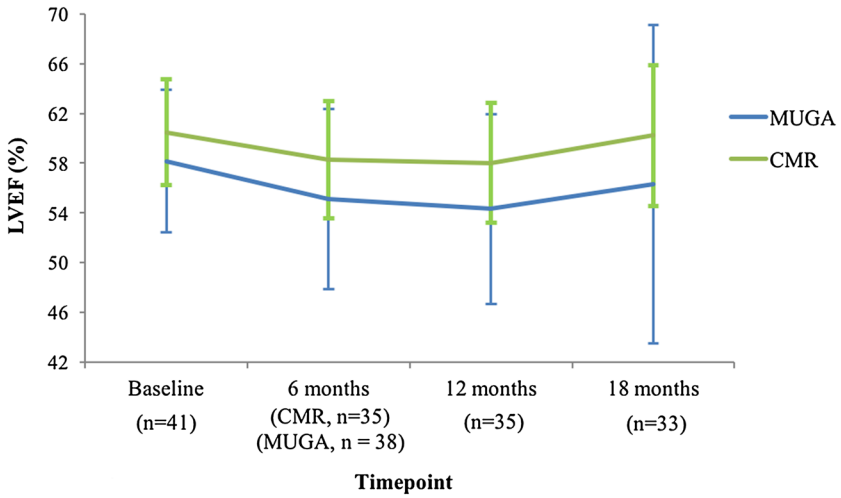

Fig. 1 Temporal measurements of LVEF by CMR and MUGA over 18 months. There were significant changes at 6 and 12 months relative to baseline ($p < 0.05$), but no significant change at 18 months relative to baseline for both modalities ($p = 0.88$ for CMR, $p = 0.80$ for MUGA). Data shown as mean and SD (vertical bars)

Table 2 Estimated mean changes from baseline in LVEF (%) by CMR and LV volume (mL) using linear mixed models

	6 months versus baseline	12 months versus baseline	18 months versus baseline
LVEF (%)			
Mean difference (95% CI)	− 2.1 (− 3.5 to − 0.6)	− 2.2 (− 3.6 to − 0.7)	0.1 (− 1.4 to 1.6)
p-value	0.0060	0.0039	0.88
LVEDV (mL)			
Mean difference (95% CI)	9.8 (4.2 to 15.4)	8.2 (2.6 to 13.8)	2.0 (− 3.7 to 7.7)
p-value	0.0007	0.0045	0.49
LVESV (mL)			
Mean difference (95% CI)	6.7 (3.6 to 9.7)	6.6 (3.6 to 9.7)	0.8 (− 2.4 to 3.9)
p-value	< 0.0001	< 0.0001	0.62

LV left ventricular, *LVEF* left ventricular ejection fraction, *LVEDV* left ventricular end-diastolic volume, *LVESV* left ventricular end-systolic volume

Table 3 Bland–Altman limits of agreement and Lin's concordance correlation coefficient for comparing MUGA LVEF and CMR LVEF measurements (%) at baseline, 6 months, 12 months and 18 months

	Baseline (N = 41)	6 months (N = 38)	12 months (N = 37)	18 months (N = 37)	All time points
Difference MUGA–CMR					
Mean (SD)	− 2.3 (5.1)	− 3.1 (6.8)	− 3.4 (6.8)	− 3.0 (7.8)	− 3.0 (6.2)
95% limits of agreement	− 12.3 to 7.7	− 16.3 to 10.1	− 16.7 to 9.9	− 18.1 to 12.2	− 15.4 to 9.5
Lin's concordance correlation coefficient (95% CI)	0.46 (0.22, 0.64)	0.29 (0.02, 0.53)	0.42 (0.17, 0.62)	0.39 (0.11, 0.62)	
p-value	< 0.001	0.036	0.002	0.008	
Pearson's *r*	0.53	0.36	0.53	0.47	

CMR cardiac MRI, *LVEF* left ventricular ejection fraction, *MUGA* multiple gated acquisition

There was a statistically significant correlation between changes in NT-BNP and changes in LVEDV at 12 and 18 months, and changes in LVESV at 18 months.

To the best of our knowledge, there is only one study that has directly compared MUGA and CMR in breast cancer patients receiving trastuzumab, though many have investigated the role of CMR within the context of cancer chemotherapy. Walker et al. [31] compared the accuracy of MUGA, 2D transthoracic echocardiography (TTE) and real-time three-dimensional TTE (RT3D TTEE) to CMR in assessing LVEF in 50 HER2-overexpressing breast cancer patients. All patients received anthracycline-based therapy with either fluorouracil, epirubicin, and cyclophosphamide (FEC-100) or adriamycin and cyclophosphamide

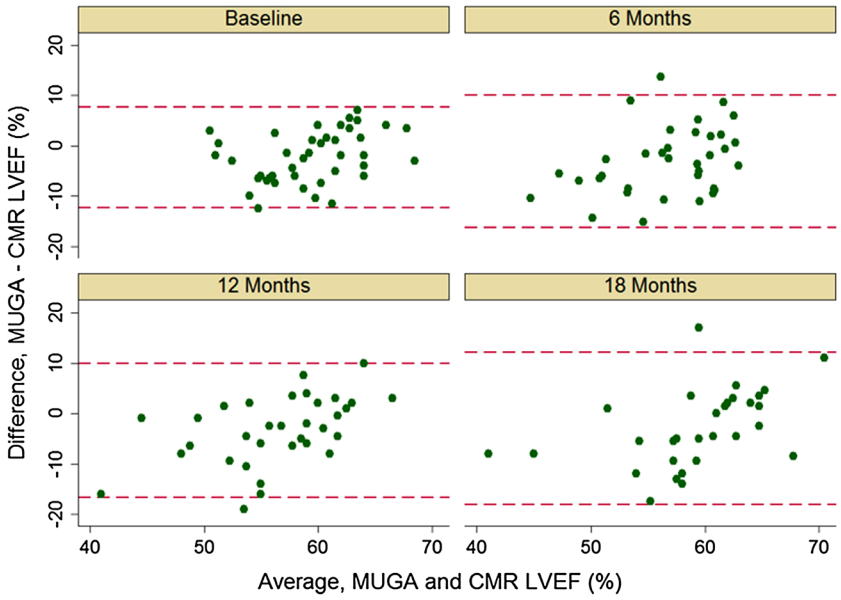

Fig. 2 Bland-Altman plots for assessing agreement between MUGA and CMR LVEF measurements, with dashed lines indicating 95% limits of agreement

Table 4 Spearman correlation coefficients between changes in LV structural and functional parameters and changes in cardiac biomarkers

	LVEF		LVEDV		LVESV	
	Troponin-I	NT-BNP	Troponin-I	NT-BNP	Troponin-I	NT-BNP
6 months versus baseline (N = 34)						
Spearman correlation	− 0.09	0.196	− 0.04	0.23	0.02	0.05
p-value	0.63	0.27	0.81	0.19	0.90	0.76
12 months versus baseline (N = 32)[a]						
Spearman correlation	0.08	0.08	0.09	0.53	− 0.06	0.26
p-value	0.66	0.68	0.65	0.002	0.76	0.16
18 months versus baseline (N = 26)[b]						
Spearman correlation	− 0.32	0.05	0.14	0.56	0.29	0.47
p-value	0.11	0.82	0.50	0.003	0.17	0.02

[a]N = 32 for NT-BNP; N = 31 for Troponin-I

[b]N = 26 for NT-BNP; N = 25 for Troponin-I

LV left ventricular, *LVEF* left ventricular ejection fraction, *LVEDV* left ventricular end-diastolic volume, *LVESV* left ventricular end-systolic volume

(AC), followed thereafter by adjuvant trastuzumab with a taxane chemotherapy. Results demonstrated strong correlation between MUGA and CMR LVEF (r = 0.88 at baseline; r = 0.97 at 6 months; and r = 0.87 at 12 months), with Bland–Altman analyses between MUGA and CMR LVEF reported as − 0.52 ± 5.2 at baseline; − 0.86 ± 4.0 at 6 months; and − 0.3 ± 4.4 at 12 months. The precise reasons for the different results are not entirely clear, although a number of reasons may have contributed to the reported differences. First, we reported the pooled limits of agreement across all time points (accounting for the clustering of data within subjects), while the limits of agreement reported in the study by Walker et al. were calculated at each timepoint only. Important, though, Walker et al. reported the Pearson's r correlation coefficients, while we presented the Lin's concordance coefficients for agreement. It should be noted that correlation and agreement are not the same. We believe that Lin's concordance coefficients are more appropriate for the purposes of our study. In addition, it was not explicitly stated whether the measurements of LVEF by MUGA and CMR were blinded and independent of other tests in the study by Walker et al. In our study, there were two independent readers for CMR and MUGA, who were blinded to both the other test results and the timing of the exam. Finally, CMR is known for its utility in detecting subtle changes in LVEF with higher certainty for the purpose of serial monitoring of breast cancer patients [32]. One study has shown there is consequently a greater chance of detecting subtle changes post-anthracycline treatment by CMR [33]. In our study, only 56.1% of patients

were treated with anthracyclines compared to 100% in the study by Walker et al., thus increasing the chance to detect subtle changes by CMR.

Though many studies have shown elevated troponin-I and BNP are strong predictors of LVEF reduction, to the best of our knowledge, the correlation between these cardiac biomarkers and changes in structure and function in specifically trastuzumab-treated breast cancer patients has not yet been investigated. In an abstract by Grover et al. [33], 29 chemotherapy-naive early stage and metastatic breast cancer patients underwent CMR and ECHO imaging and NT-BNP and hs-TnI measurements at baseline, 1 month and 3 months following the initiation of anthracycline-based chemotherapy. They showed no significant correlation between BNP and changes in LVEDV and LVESV. However, imaging was only done at 1 month and 3 months in comparison to our longer study duration, which demonstrated correlation between changes in LVEDV and NT-BNP at 12 and 18 months, and LVESV and NT-BNP at 18 months. It is plausible that serial biomarkers and imaging have complementary roles in the early detection of trastuzumab-induced cardiotoxicity, which therefore have the potential to identify patients at increased risk of cardiovascular complications in the long term [34, 35]. Further research to investigate the prognostic value of this monitoring strategy is thus necessitated.

Our findings pertaining to increased LV volumes at 6 and 12 months with concomitant decreased LVEF are in accord with published CMR studies, though no study to date has reported results at 18 months or in the context of HER2+ breast cancer patients receiving trastuzumab. Our study also benefitted from rigorous blinding strategies, with independent analysis of CMR and MUGA. Drafts et al. [36] had demonstrated significant increase in LVESV, concomitant with decline in LVEF by 6 months of anthracycline treatment in patients with hematologic or breast malignancies. However, they found that LVEDV remained stable throughout the study, though only 42% of their patients had a diagnosis of breast cancer and the number of patients treated with trastuzumab was not reported. The same group also identified increased LVEDV and LVESV with decreased LVEF at 4 months of anthracycline treatment, though only two patients of the 40 included in the cancer therapy group received trastuzumab concurrently with treatment [37]. Our study extended the previous reports by including assessment at the 18 month time point. Furthermore, the significant increases in both LVEDV and LVESV, and accompanying decline in LVEF, suggest subclinical adverse LV remodelling during trastuzumab treatment.

Unlike MUGA, CMR offers additional parameters (i.e., absolute LV volume parameters) that can be used for clinical decisions. CMR offers an accurate measurement of LV volume, with excellent intra-observer, inter-observer, and inter-study variability [16, 19]. However, its use for serial monitoring in this patient population may be limited due to limitations such as availability, scheduling, and costs, prompting centers to utilize other modalities (e.g., ECHO, MUGA). Furthermore, it is unclear whether early changes in LV structure protend worse clinical outcome in the long term, and whether medications to prevent adverse cardiac remodeling should be routinely used in trastuzumab-treated patients. Certainly larger studies using CMR as an imaging modality could determine the utility of assessing LV structure in the context of oncologic therapy. Further, future cancer clinical trials with newer targeted agents (e.g., immunotherapy, tyrosine kinase inhibitors, anti-angiogenic agents) combined with known cardiotoxic agents, such as anthracyclines, will require cardiac monitoring to detect subtle changes in LVEF. CMR may allow for accurate detection of subtle cardiotoxicity in these early phase trials and can ultimately determine whether close monitoring is required for all subjects in the subsequent phase trials.

Several study limitations should be noted. Though our study is novel with respect to reporting temporal changes over 18 months for CMR, MUGA, and biomarkers, not all patients completed all the study assessments due to breast tissue expanders, a change in treatment decision, or patient preference to forego a scan. Our small sample size also did not allow for stratification of results based on cardiovascular risk factors and other clinical variables, such as stage of patient's disease or hypertension, which can impact temporal changes in LVEF. Moreover, our sample size may have limited definite conclusions regarding the association between LVEF and type of chemotherapy (i.e., anthracycline versus non-anthracycline), as larger clinical trials have suggested there is a greater incidence of trastuzumab-induced cardiotoxicity in patients who were treated with anthracyclines. Finally, clinical outcomes and the precise prognostic value of the LV measurements by CMR versus MUGA, were not assessed in this prospective study.

Conclusions

This small prospective study demonstrated that CMR and MUGA LVEF are not interchangeable in clinical practice with trastuzumab therapy, as evident by the wide Bland–Altman limits of agreement and weak concordance correlation coefficients at all time points. However, CMR presents as a relatively useful modality due to its ability to provide accurate LV volume measurements that are concomitant with LVEF changes. In addition, MUGA has greater cumulative radiation exposure, which can be harmful for younger women. In our small study, changes in NT-BNP was found to correlate with changes in LV volumes in women treated with adjuvant trastuzumab.

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Compliance with ethical standards

Conflict of Interest C. Brezden-Masley has received research grant support and/or honoraria for educational activities and/or served as consultant to Roche.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committees (St. Michael's Hospital and Sunnybrook Odette Cancer Centre) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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