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ORIGINAL PAPER

Early diastolic strain rate measurements by cardiac MRI in breast cancer patients treated with trastuzumab: a longitudinal study

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Abstract
We evaluated temporal changes in early diastolic strain rates by cardiovascular magnetic resonance (CMR) as an early detector of trastuzumab-induced ventricular dysfunction. We conducted a prospective, multi-centre, longitudinal observational study of 41 trastuzumab-treated breast cancer women who underwent serial CMR (baseline, 6, 12, and 18 months). Two blinded readers independently measured left ventricular ejection fraction (LVEF), peak systolic strain parameters (global longitudinal strain [GLS] and global circumferential strain [GCS]), and early diastolic strain rate parameters (global longitudinal diastolic strain rate [GLSR-E], global circumferential diastolic strain rate [GCSR-E], and global radial diastolic strain rate [GRSR-E]), by feature tracking (FT-CMR) using CMR42. There was a significant decline in peak systolic strain GLS and GCS at 6 months ($p=0.024$ and $p<0.001$, respectively) and 12 months ($p=0.002$ and $p<0.001$, respectively), followed by recovery at 18 months, which paralleled decline in LVEF at 6 months ($p=0.034$) and 12 months ($p=0.012$). Conversely, early diastolic strain rates GLSR-E and GCSR-E did not significantly change over 18 months ($p>0.10$), while GRSR-E was marginally significant at 12 months ($p=0.021$). There was no significant correlation between changes at 6 months in LVEF and GLSR-E or GRSR-E ($p>0.10$), and a marginally significant weak correlation between LVEF and GCSR-E ($p=0.046$). Among trastuzumab-treated patients without overt cardiotoxicity, there was no consistent temporal change in FT-CMR-derived diastolic strain rate parameters up to 18 months, in contrast to decline in systolic strain and LVEF. Systolic strains by FT-CMR are likely more useful than diastolic strain rates for monitoring subclinical trastuzumab-related myocardial dysfunction.
ClinicalTrials.gov identifier NCT01022086.

Keywords Breast cancer · Trastuzumab · Cardiotoxicity · Cardiovascular magnetic resonance · Subclinical ventricular dysfunction · Ventricular function · LVEF · LV peak systolic strain · LV early diastolic strain rate

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Introduction

Trastuzumab is an antibody against human epidermal growth factor receptor 2 (HER2) [1], known to cause type II cardiotoxicity, ranging from asymptomatic decline in left ventricular ejection fraction (LVEF) to symptomatic heart failure (HF) [2–4]. Currently, radionuclide ventriculography and echocardiography are imaging modalities used for baseline and serial monitoring of ventricular function [5]. However, measurable reduction in LVEF represents late LV dysfunction [6]. With improving imaging techniques, earlier detection of cardiac injury prior to appreciable change in LVEF would allow timely initiation of cardioprotective treatments to potentially reverse cardiac abnormalities. Optimization of cardiovascular-related risk would also allow for greater tolerability and trastuzumab therapy completion to prevent cancer recurrence.

Recently, cardiovascular magnetic resonance (CMR) imaging has emerged as an important modality for a variety of cardiovascular indications [7]. Due to the volumetric assessment, CMR is the gold standard for measuring LV volumes and function with high reproducibility, accuracy, and minimal risk. The utility of CMR extends beyond routine LVEF measurement, as it provides additional systolic and diastolic parameters. Indeed, LV strain has emerged as a sensitive marker of subclinical LV dysfunction, and its role in providing prognostic assessment over traditional LVEF is being established in a variety of cardiac conditions [8].

While emerging data support LV peak systolic strain as an early marker of cardiotoxicity prior to a significant reduction in LVEF [9–12], little is known regarding the utility of diastolic strain rate. In practice, diastolic strain rate parameters are readily available with LV systolic strain using feature tracking CMR (FT-CMR) which does not require additional MRI sequences, highlighting its potential wide applicability to detect subclinical myocardial changes. In various clinical disease states including anthracycline-induced cardiotoxicity, diastolic dysfunction may precede, or occur concurrently with systolic dysfunction [13–16]. Nevertheless, there is a paucity of data on whether diastolic dysfunction develops prior to or concurrently with trastuzumab-related systolic dysfunction.

Accordingly, in a cohort of breast cancer patients treated with trastuzumab, we evaluated the temporal changes in early diastolic strain rate parameters to assess their utility in detecting subclinical trastuzumab-related myocardial injury.

Materials and methods

Study design

We conducted a prospective cohort study of newly diagnosed HER2 + breast cancer patients in two tertiary care centers between December 2009 and December 2013 (ClinicalTrials.gov identifier NCT01022086), as previously described in detail [17, 18]. Briefly, Research Ethics Board approval was obtained from St. Michael's Hospital and Sunnybrook Odette Cancer Center. All study participants provided written informed consent. The inclusion criteria were: ≥ 18 years old, Eastern Cooperative Oncology Group (ECOG) performance status 0–2, histologically confirmed diagnosis of invasive breast carcinoma with HER2 overexpression, planned treatment with trastuzumab adjuvant chemotherapy, baseline LVEF > 50% by radionuclide ventriculography. The exclusion criteria were: previous treatment with trastuzumab or another anti-HER2 agent (e.g., lapatinib, pertuzumab), pre-existing symptomatic HF (New York Heart Association Class III or IV), acute coronary syndrome within the last 6 months, permanent atrial fibrillation, and contraindications to undergo MRI. As per standard of care, all patients received 18 cycles (12 months) of adjuvant trastuzumab, along with anthracycline- or non-anthracycline- based chemotherapy at the discretion of the treating oncologist. All enrolled women underwent serial radionuclide ventriculography for monitoring of LVEF every 3 months, as per standard of care. In the event of cardiotoxicity, trastuzumab treatment was withheld for 3 weeks, with re-initiation of trastuzumab if the subsequent radionuclide ventriculography scan showed improvement in LVEF, in accordance with contemporary guidelines [19].

Data collection

The demographic characteristics, vital signs, tumor characteristics and stage, chemotherapy and radiotherapy regimen, type of surgery and cardiovascular risk factors were collected at baseline in a standardized manner. Serum N-terminal pro brain natriuretic peptide (NT-proBNP) (Roche Diagnostics GmbH, Manheim, Germany) and high-sensitivity troponin I (hs-TnI) were measured as biomarkers at baseline, 6, 12, and 18 months.

CMR image processing

Baseline CMR was performed prior to initiation of trastuzumab, followed by serial CMR performed at 6, 12, and 18 months post-initiation. All CMR examinations were performed with a 1.5 T scanner (Intera, Philips Medical Systems, Best, the Netherlands, or a GE Signa Excite Cv, Milwaukee, WI) using a cardiac coil and retrospective electrocardiographic gating. Standard protocols using validated, commercially available sequences were used. Images were obtained with breath-hold at end-expiration. Typical steady-state free precession sequence (SSFP) parameters used were as follows: repetition time 4 ms, time to echo 2 ms, slice thickness 8 mm, field of view 320–330 × 320–330 mm, matrix size 256 × 196, temporal resolution of < 40 ms (depending on the heart rate), 25 frames per cardiac cycle, and flip angle 50 degrees.

Prior to image processing, all CMR studies were de-identified and assigned a unique identification code. CMR studies were analyzed with commercially available CMR42 software (Circle Cardiovascular, Calgary, Alberta, Canada). A single experienced blinded reader measured LVEF and a second blinded experienced reader independently performed LV strain and strain rate analysis (both readers were blinded to clinical data and time point of CMR).

Left ventricular end-diastolic volumes (LVEDV) and left ventricular end-systolic volumes (LVESV) were measured using the short-axis stack by tracing endocardial contours during end-diastole and end-systole, using the blood volume method, including papillary muscles and trabeculations. LVEF was calculated as (LVEDV − LVESV)/LVEDV × 100%.

Myocardial deformation (strain) imaging was performed using FT-CMR according to previously published methods [20, 21]. Briefly, endocardial and epicardial borders were manually drawn in the end-diastolic frame, which were then automatically propagated (tracked) throughout the cardiac cycle by matching anatomical structures. The peak systolic strain and early diastolic strain rate were computed according to distance moved between frames. Systolic strain is the percent change in length relative to baseline length (Langrangian strain); a positive strain implies elongation while negative strain implies shortening [22]. The systolic strain parameters calculated were global longitudinal strain (GLS), global circumferential strain (GCS), and global radial strain (GRS). Early diastolic strain rate is the slope (i.e., speed) of myocardial deformation during early diastole, reflective of LV relaxation and diastolic function [22]. The early diastolic strain rates calculated were global longitudinal strain rate (GLSR-E), global circumferential strain rate (GCSR-E), and global radial strain rate (GRSR-E). Multiple 2D long-axis cine images (2, 3, and 4-chamber views) were tracked to derive longitudinal strain and strain rate, while short-axis cine images were used to derive circumferential and radial strain and strain rate. Strain and strain rates were obtained for each segment and the global values were defined as the mean of all segmental values. For the baseline early diastolic strain values computed for our cohort, 90%, 72.5%, and 30% of measured GLSR-E, GCSR-E, and GRSR-E values were within the published normal ranges, respectively [23].

Statistical analysis

Continuous data are expressed in mean with standard deviation or median with interquartile range (IQR), as appropriate. Mixed linear models were used to evaluate temporal changes in the strain and strain rate over time, with Sidak adjustment for multiple pairwise comparisons of the three time points (6, 12, 18 months) with baseline. We evaluated interaction with anthracycline use in a separate mixed linear model. The relationships between change in early diastolic strain rate parameters with changes in systolic strain, LVEF, LVESV, and LVEDV at 6 months were examined using the non-parametric Spearman's correlation. The relationships between changes in early diastolic strain rate parameters and changes in NT-proBNP and hs-TnI at 6 months were similarly evaluated by Spearman's (or Kendall tau-b [τ]) correlation.

Statistical significance was defined as a two-sided p value < 0.05. All data were analyzed using SPSS version 22 (IBM Corp., Armonk, NY).

Results

The baseline characteristics of the 40 patients enrolled in this longitudinal study are shown in Table 1. Of the 40 early breast cancer patients (mean age 52), 23 received anthracycline-based chemotherapy, and FT-CMR-derived early diastolic strain rate measurements were available for 40 patients at baseline, 35 at 6 months, 34 at 12 months, and 33 patients at 18 months. Incomplete CMR for all patients were due to use of breast tissue expanders, change in treatment plan, or non-compliance due to patient choice. One patient experienced cardiotoxicity with LVEF reduction measured by radionuclide ventriculography, for whom trastuzumab was withheld and resumed after 1 cycle. During the study, no patient developed new clinical HF or died.

The temporal measurements of early diastolic strain rate parameters GLSR-E, GCSR-E, and GRSR-E during follow-up are shown in Figs. 1, 2, 3, respectively. The intra-class correlation coefficients for GLSR-E, GCSR-E, and GRSR-E were 0.90, 0.51, and 0.29, respectively, suggesting that reproducibility was best for GLSR-E and worst for GRSR-E. Compared to baseline, GLSR-E and GCSR-E did not significantly differ between the 4 time points (baseline, 6, 12, and 18 months), while GRSR-E was only marginally significant over time. By pairwise comparison with baseline, GRSR-E had a significantly positive change (i.e., less negative, or slower relaxation) at 12 months ($p = 0.021$), while no difference was observed at 6 or 18 months.

In contrast, there were significant changes in systolic strain parameters GLS and GCS, and LVEF.

When compared to baseline, GLS and GCS decreased significantly at 6 months ($p = 0.024$ and $p < 0.001$, respectively) and 12 months ($p = 0.002$ and $p < 0.001$, respectively), with no significant difference at 18 months, supporting the notion that trastuzumab-related myocardial injury may be reversible. Correspondingly, a significant decline in LVEF at 6 months (58.4%, 95% confidence interval [CI]

Table 1 Baseline characteristics of women treated with trastuzumab (n = 40)

Characteristic	
Age, years, mean (s.d.)	52 (11)
BMI, kg/m^2, mean (s.d.)	27 (6)
Cardiovascular risk factors, n (%)	
Coronary heart disease	1 (2%)
Hypertension	10 (24%)
Diabetes	4 (10%)
Dyslipidemia	3 (8%)
Current smoking	10 (24%)
Cardiovascular medications, n (%)	
Beta-blockers	3 (9%)
ACE Inhibitors	3 (9%)
Breast cancer stage, n (%)	
Early	27 (66%)
Locally invasive	13 (32%)
Metastatic	0 (0%)
Surgical intervention, n (%)	
Lumpectomy	21 (51%)
Mastectomy	19 (46%)
Both	1 (2%)
Radiation therapy (left-sided), n (%)	12 (32%)
Anthracycline-based chemotherapy, n (%)	23 (56%)
Blood pressure, mean (s.d.)	
Systolic blood pressure, mmHg	125 (15)
Diastolic blood pressure, mmHg	75 (9)
Heart rate at baseline, bpm, mean (s.d.)	79 (13)
Heart rate during CMR, bpm, median (range)	73 (48–107)
Cardiac biomarkers, median (IQR)	
Nt-pro brain natriuretic peptide, ng/mL	57 (33–128)
High-sensitivity Troponin-I, ng/mL	< 0.006 (< 0.006–0.012)
Cardiac magnetic resonance parameters, mean (s.d.)	
LVEDV (mL)	130 (25)
LVESV (mL)	51 (12)
LVEF (%)	60.4 (4.3)
GLS (%)	− 20.0 (2.7)
GCS (%)	− 20.9 (2.5)
GRS (%)	38.6 (7.7)
GLSR-E (1/s)	1.01 (0.36)
GCSR-E (1/s)	1.10 (0.35)
GRSR-E (1/s)	− 2.53 (0.83)

ACE angiotensin converting enzyme, *BMI* body mass index, *GLS* global longitudinal strain, *GCS* global circumferential strain, *GRS* global radial strain, *GLSR-E* early diastolic global longitudinal strain rate, *GCSR-E* early diastolic global circumferential strain rate, *GRSR-E* early diastolic global radial strain rate, *IQR* interquartile range, *LVEF* left ventricular ejection fraction, *LVESV* left ventricular end-systolic volume, *LVESV* left ventricular end-diastolic volume, *s.d.* standard deviation

56.7–60.0%, p = 0.034) and 12 months (57.9%, 95% CI 56.4–59.7%, p = 0.012) were observed, but not at 18 months (60.2%, 95% CI 58.2–62.2%, p = 0.93). Furthermore, we observed significant changes in LVEDV (p = 0.004) and LVESV (p < 0.001) during the 18-month study period. Compared to baseline, both LVEDV and LVESV significantly increased at 6 months (p = 0.024 and 0.001, respectively) and 12 months (p = 0.046 and 0.001, respectively).

We examined the correlations between peak systolic strain and early diastolic strain rate parameters. At baseline, GLSR-E and GRSR-E correlated with GLS, GCS, and GRS, while GCSR-E only correlated with GCS (Table 2). The

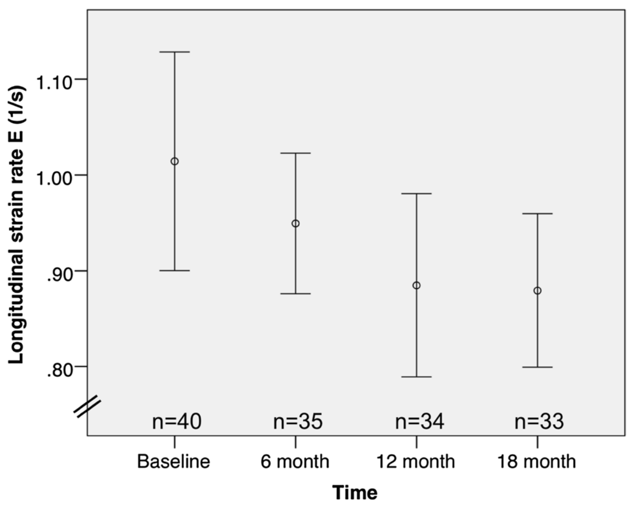

Fig. 1 Comparison of early diastolic global longitudinal strain rate (GLSR-E) measured across four time points (baseline, 6, 12, 18 months after trastuzumab initiation). Data are shown as mean with 95% confidence interval. p value for overall temporal differences in GLSR-E was 0.11

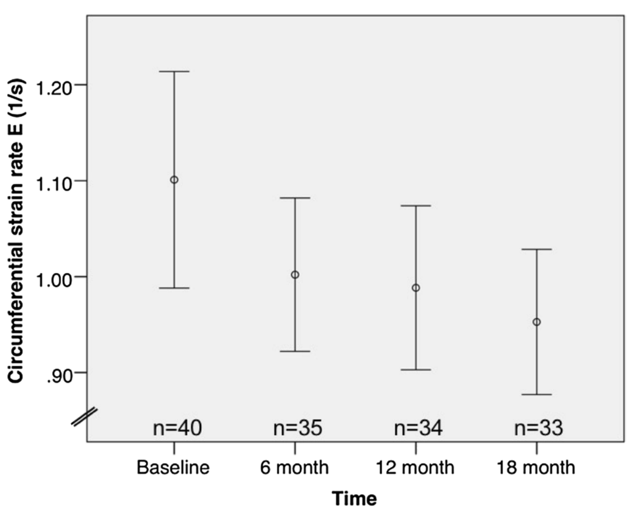

Fig. 2 Comparison of early diastolic global circumferential strain rate (GCSR-E) measured across four time points (baseline, 6, 12, 18 months after trastuzumab initiation). Data are shown as mean with 95% confidence interval. p value for overall temporal differences in GCSR-E was 0.13

changes between baseline and 6 months in early diastolic strain rate parameters GLSR-E, GCSR-E, and GRSR-E did not consistently correlate with changes in GLS, GCS, or GRS (Table 3). There was a significant correlation between 6-month change in GLSR-E with GRS, 6-month change in GRSR-E with GLS and GRS, and 6-month change in GCSR-E with GCS. There was no significant interaction between anthracycline use and 6-month change in GLSR-E ($p=0.79$), GCSR-E ($p=0.78$), or GRSR-E ($p=0.60$).

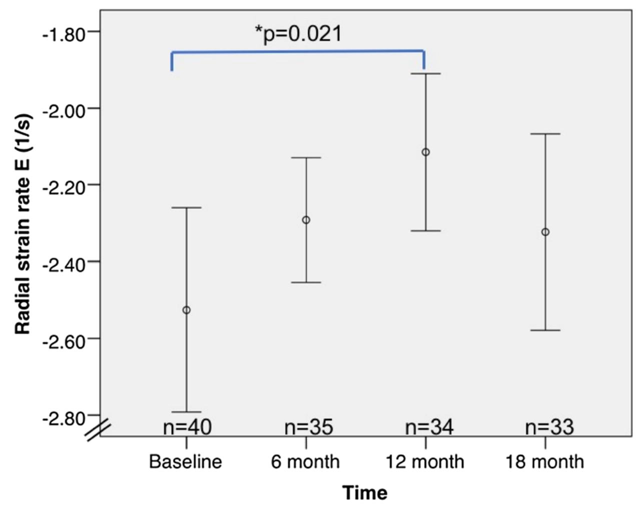

Fig. 3 Comparison of early diastolic global radial strain rate (GRSR-E) measured across four time points (baseline, 6, 12, 18 months after trastuzumab initiation). Data are shown as mean with 95% confidence interval. p value for overall temporal differences in GRSR-E was 0.044. p value refers to the adjusted (Sidak) pairwise comparison of 12-month with baseline; other pairwise comparisons were not significant

At baseline, GLSR-E and GRSR-E did not correlate with LVEF ($p=0.15$, $p=0.062$), but GCSR-E did (Spearman's correlation coefficient 0.49, $p=0.002$) (Table 2). Between baseline and 6 months, no significant relationship existed between changes in LVEF and GLSR-E ($p=0.95$) or GRSR-E ($p=0.12$), while a marginally significant weak correlation between LVEF and GCSR-E (Spearman's correlation coefficient 0.34, $p=0.046$) was observed (Table 3).

Compared to baseline, GLSR-E, GCSR-E, and GRSR-E correlated with LVESV, while only GLSR-E and GCSR-E correlated with LVEDV (Table 2). However, the 6-month changes in early diastolic strain rate parameters did not correlate with the corresponding 6-month changes in LVESV or LVEDV (Table 3).

There was no significant correlation between change in NT-proBNP and change in early diastolic strain rate parameters at 6 months (GLSR-E $\tau=-0.19$, $p=0.31$; GCSR-E $\tau=0.026$, $p=0.89$; GRSR-E $\tau=-0.033$, $p=0.86$). Likewise, there was no significant correlation between change in hs-TnI and changes in diastolic strain parameters at 6 months (GLSR-E $\tau=0.068$, $p=0.72$; GCSR-E $\tau=0.044$, $p=0.82$; GRSR-E $\tau=-0.15$, $p=0.44$).

Ancillary analysis

We compared the change in early diastolic strain rate parameters with changes in LVEF, LVEDV, LVESV, and cardiac biomarkers between 6 to 12 months, and between 12 to 18 months, respectively. In contrast to the changes between

Table 2 Spearman's correlation coefficients between early diastolic strain rates and systolic strains, left ventricular ejection fraction, and volumes at baseline

	GLS	GCS	GRS	LVEF	LVESV	LVEDV
GLSR-E	−0.56 ($p<0.001$)	−0.48 ($p=0.002$)	−0.52 (<0.001)	0.23 ($p=0.15$)	−0.40 ($p=0.011$)	−0.33 ($p=0.039$)
GRSR-E	0.49 ($p<0.001$)	0.34 ($p=0.036$)	−0.59 (<0.001)	−0.30 ($p=0.062$)	−0.32 ($p=0.042$)	0.22 ($p=0.18$)
GCSR-E	−0.22 ($p=0.17$)	−0.54 (<0.001)	0.18 ($p=0.28$)	0.49 ($p=0.002$)	−0.50 ($p<0.001$)	−0.36 ($p=0.026$)

GLS global longitudinal strain, *GCS* global circumferential strain, *GRS* global radial strain, *GLSR-E* early diastolic global longitudinal strain rate, *GCSR-E* early diastolic global circumferential strain rate, *GRSR-E* early diastolic global radial strain rate, *LVEF* left ventricular ejection fraction, *LVESV* left ventricular end-systolic volume, *LVEDV* left ventricular end-diastolic volume

Table 3 Spearman's correlation coefficients between changes (from baseline to 6 months) in early diastolic strain rates and systolic strains, left ventricular ejection fraction, and volumes

	GLS	GCS	GRS	LVEF	LVESV	LVEDV
GLSR-E	−0.25 ($p=0.15$)	−0.091 ($p=0.61$)	0.34 ($p=0.048$)	−0.012 ($p=0.95$)	0.084 ($p=0.63$)	0.20 ($p=0.25$)
GRSR-E	0.46 ($p<0.001$)	0.17 ($p=0.35$)	−0.60 ($p<0.001$)	−0.27 ($p=0.12$)	0.19 ($p=0.29$)	−0.058 ($p=0.74$)
GCSR-E	−0.014 ($p=0.94$)	−0.43 ($p=0.011$)	0.051 ($p=0.78$)	0.34 ($p=0.003$)	−0.25 ($p=0.15$)	0.037 ($p=0.83$)

GLS global longitudinal strain, *GCS* global circumferential strain, *GRS* global radial strain, *GLSR-E* early diastolic global longitudinal strain rate, *GCSR-E* early diastolic global circumferential strain rate, *GRSR-E* early diastolic global radial strain rate, *LVEF* left ventricular ejection fraction, *LVESV* left ventricular end-systolic volume, *LVEDV* left ventricular end-diastolic volume

baseline and 6 months, we found that the changes between 6 and 12 months in all three early diastolic strain rate parameters were significantly correlated with changes in LVEF and LVESV during the same timeframe, while no significant correlation was observed in the changes between 12 and 18 months (Supplementary Tables 1 and 2). No significant correlation between changes in cardiac biomarkers and early diastolic strain rate parameters was observed between these timeframes (Supplementary Tables 1 and 2).

Discussion

In this prospective longitudinal study, we investigated whether temporal changes in myocardial diastolic strain rate measured by FT-CMR preceded or coincided with impairment in systolic function in a cohort of trastuzumab-treated early breast cancer patients. To the best of our knowledge, this is the first FT-CMR study to examine longitudinal changes in LV early diastolic strain rates as a surrogate of diastolic function in trastuzumab-treated patients. During the 18-month follow-up, there were no consistent significant changes in early diastolic strain rates. The temporal relationships between early diastolic strain rates and systolic strains were also not consistent. Furthermore, diastolic strain parameters showed weak correlation with LVEF. These findings are in contrast to the significant temporal change in peak systolic strain and LVEF at 6 and 12 months. Taken together, our results suggest that diastolic strain rate is likely not a clinically sensitive tool, while peak systolic strain and LVEF are more useful to detect early myocardial injury in trastuzumab treated patients.

In hopes of identifying subclinical cardiac dysfunction prior to development of LVEF reduction or clinical HF, imaging derived systolic and diastolic indices have been proposed for monitoring cardiotoxicity. Diastolic dysfunction may precede systolic dysfunction, providing an early marker of cardiotoxicity and HF with relatively preserved systolic function. It has been previously shown that LV diastolic impairment occurs prior to reduction in LVEF for anthracycline-related cardiotoxicity [13, 16]; however, these findings have not been consistently demonstrated for trastuzumab [24, 25]. Optimal imaging parameters for detecting subclinical trastuzumab-related cardiotoxicity remain elusive. Recently, myocardial deformation indices using strain and strain rate have been increasingly recognized as early markers of myocardial injury for detection of subclinical cardiotoxicity [11].

CMR with myocardial tagging is currently the reference standard technique for myocardial deformation [26]. Quantification of strain and strain rate can be measured by harmonic phase analysis (HARP) and spatial modulation of magnetisation (SPAMM) [27, 28], which has allowed detection of subclinical changes in LV function even in asymptomatic subjects without known cardiovascular disease [29]. However, myocardial tagging and its post-processing analyses are cumbersome and time consuming, limiting its practical use outside of the research setting, hence prompting development of novel myocardial deformation methodologies with broader clinical accessibility and applicability. The novel FT-CMR technique for measuring strain using SSFP sequence, unlike myocardial tagging, requires no additional sequences as the cine images required are part of the routine LV study protocol, allowing for rapid acquisition and post-processing. Although studies have validated FT-CMR against myocardial tagging using HARP and SPAMM for systolic and diastolic strain, its accuracy may be inferior compared to myocardial tagging and is likely less robust than tagging modalities [30–32]. However, the ability to quantify strain from SSFP cine images using novel FT-CMR with practicality, ease of acquisition, and reduced analysis time is enticing for its potential implementation into clinical practice. For these reasons, whether FT-derived diastolic strain rates can be useful in the monitoring of trastuzumab cardiotoxicity is a novel and clinically relevant question examined in this study.

The advantage of strain and strain rate over LVEF is that they are less sensitive to preload and afterload changes. Indeed, prior studies using echocardiography-derived strain have shown its value as a predictor of trastuzumab-related cardiotoxicity [33–35]. Of the strain parameters measured by speckled tracking echocardiogram, consensus recommendation favoured use of GLS as the strain parameter for early detection of subclinical LV dysfunction [36]. Although echocardiography is more accessible for strain imaging, its limitations include lower reproducibility and reliability. CMR is a well-established modality for measuring myocardial strain that overcomes some limitations of echocardiography. While a few studies demonstrated deterioration in systolic strain by myocardial tagging CMR in trastuzumab-treated patients [37, 38], there are limited data on myocardial deformation as measured by the novel technique FT-CMR in this patient population.

Given the advantages of FT-CMR which obviates additional sequence acquisition and allows faster processing time, we evaluated both peak systolic strain and early diastolic strain rate using FT-CMR. We observed significant reductions in systolic strain GLS and GCS at 6 and 12 months, which corresponded to a subtle decline in LVEF, despite *increases* in LVEDV. In contrast, we did not observe corresponding changes in early diastolic strain rate measurements. Moreover, we did not observe a consistent relationship between diastolic strain rate parameters and LVEF or LV volumes (LVEDV, LVESV) at 6 months or at 18 months. However, we did find a significant relationship between changes in early diastolic strain rate parameters and LVEF and LV volumes from 6 to 12 months. Despite these significant correlations, it is important to note that the most reliable strain parameters GLSR-E and GCSR-E were not significantly different from baseline measurements. Moreover, these additional analyses should be interpreted with caution due to multiplicity of testing, given the small sample size of our cohort. Taken together, our results suggest that early diastolic strain rate measurements by FT-CMR are likely not sensitive to detect early trastuzumab-related myocardial injury, while peak systolic strain GLS and GCS are more useful indicators of the earliest sign of cardiac injury during treatment. Interestingly, the aforementioned study by Jordan et al. demonstrated that deterioration in systolic strain was related to a reduction in LVEDV, suggesting that a reduced preload may be the major determinant of decreased systolic function [12]. Our results differ from theirs in that we observed an *increased* LVEDV at 6 and 12 months, implying that the decreased peak systolic strain was not due to a reduction in preload. Our results also differ from the study by Negishi et al. whereby they detected a significant decrease in echocardiographically measured diastolic longitudinal strain rate, and highlighted its potential prognostic value for predicting LV dysfunction [35]. These disparities could be attributed to different imaging modality used and low incidence of cardiotoxicity in our study compared to their cohort. However, our study results are consistent with another recent study by Reuvekamp et al. which demonstrated that diastolic parameters on radionuclide ventriculography are not useful as earlier predictors of cardiotoxicity in a retrospective study of 77 trastuzumab-treated patients [25]. While a recent systematic analysis compared systolic strain across modalities [39], such studies are lacking for diastolic strain rate. Until such studies are available, it is important to recognize that echocardiogram and FT-CMR-derived diastolic strain rates may not be interchangeable. Hence, diastolic strain rates measured by other modalities may still be useful in detecting early myocardial injury, while diastolic strain rates by FT-CMR appear less useful than peak systolic strain in this setting.

Our study has several strengths. This cohort included patients with few exclusion criteria and CMR were performed using different vendors in two centres, which enhanced the generalizability of our results. All CMR analyses were completed in a blinded fashion and serial CMRs were analyzed in random order. Our study reported temporal changes in diastolic strain rate measured by FT-CMR over 18 months, providing one of the longest longitudinal CMR follow-up for trastuzumab-treated patients. While previous studies have evaluated diastolic function using echocardiography [25, 33, 40], much less data is available using CMR. Nonetheless, the utility of FT-CMR-derived diastolic function using myocardial tagging has been demonstrated in other populations aside from cardiotoxicity. For instance, in the MESA (Multi-Ethnic Study of Atherosclerosis) study, tagged FT-CMR-derived diastolic function parameter strain relaxation index predicted HF and atrial fibrillation over 8-year period [41]. Consequently, to the best of our knowledge, this study is the first to examine whether diastolic strain rates by FT-CMR as a marker of diastolic dysfunction could be a useful tool for detecting subclinical LV dysfunction. Since the diastolic strain parameters are readily available with the systolic strain parameters, our study addresses a clinically relevant question about their comparative utility for subclinical myocardial injury monitoring during trastuzumab treatment.

Despite these strengths, our study has several limitations. Our small cohort has limited power to detect small changes in early diastolic strain rates. Similarly, our study may have been underpowered to detect correlations between early diastolic strain rate parameters and other FT-CMR-derived parameters and cardiac biomarkers, given that there were patients who did not participate in follow up CMRs at 6, 12, and 18 months. Only one patient developed clinical cardiotoxicity requiring temporary withholding of trastuzumab therapy. However, the goal of our study was to identify early and subtle changes in myocardial function; hence, this cohort of patients without overt cardiotoxicity and clinical HF are precisely the patients in whom early and reliable detection of subclinical changes is most relevant. Although we observed a reduction in LVEF at 6 and 12 months, the change in LVEF was small and preserved within normal range, unlikely to raise clinical suspicion for myocardial injury. As such, characterizing subtle changes in strain during trastuzumab treatment in patients who do not have overt cardiotoxicity may provide important prognostic information over LVEF to identify women at risk of developing long-term adverse cardiovascular events. We did not delineate strain and strain rate changes between 1 and 5 months or long term beyond our study period (> 18 months). The temporal resolution of CMR is lower than echocardiography, and this may impact on the accuracy of strain rate measurements by CMR. Our study findings may be limited by the accuracy of FT-CMR-derived diastolic strain rate measurements, as technical factors such as temporal and spatial resolution of SSFP cine images may have affected quality and accuracy of FT techniques. Furthermore, FT-CMR derived strain measurements require additional validation studies prior to its routine use in clinical practice. Although we derived GRSR-E using FT-CMR, there have been limited studies validating its accuracy using FT-CMR against myocardial tagging. Nevertheless, the temporal resolution of our CMR examinations was reflective of routine clinical practice. Diastole is a complex phenomenon and while there are various other measures of diastolic function, they are beyond the scope of this study. Nevertheless, given the emerging data supporting the clinical utility of LV systolic strain in monitoring early cardiotoxicity (albeit requiring confirmation), our study addresses the important question of whether diastolic strain rates may provide additional information in reflecting early myocardial injury. While we did not detect diastolic strain rate changes during trastuzumab therapy, future studies are required to replicate our findings in larger cohorts and to re-evaluate this question in patients experiencing overt cardiotoxicity to determine prognostic implications.

Conclusion

In this prospective longitudinal study of breast cancer patients treated with trastuzumab, we observed no significant temporal change in diastolic strain rate measurements up to 18 months, which is in contrast to changes observed in peak systolic strain at 6 and 12 months. Similarly, while systolic strain correlated with LVEF reduction, there were no consistent correlations between early diastolic strain rates and LVEF. These results suggest that FT-CMR-derived systolic strain and LVEF have greater potential for identifying the earliest signs of myocardial injury during trastuzumab therapy, while FT-CMR-derived diastolic strain rate is unlikely to provide any substantial incremental value. Additional studies are required to confirm these findings in a larger cohort of breast cancer patients with long term follow up.

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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.

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