# Serial Measurements of Left Ventricular Systolic and Diastolic Function by Cardiac Magnetic Resonance Imaging in Patients with Early Stage Breast Cancer on Trastuzumab

Lan Song, MD[a,b], Christine Brezden-Masley, MD, PhD[b,c], Venkat Ramanan, PhD[d], Nilesh Ghugre, PhD[d], Joseph J. Barfett, MD, MSc[b,e], Kelvin K.W. Chan, MD, MSc, PhD[b,f], Rashida Haq, MD[b,c], Teresa Petrella, MD, MSc[b,g], Vinita Dhir, BSc[d], Laura Jimenez-Juan, MD[b,h], Binita Riya Chacko, MD[i], Vamshi Kotha, MD[j], Kim A. Connelly, MBBS, PhD[a,b], and Andrew T. Yan, MD[a,b,*]

**Our aim was to evaluate the temporal changes in left ventricular (LV) diastolic filling in relation to other LV parameters using cardiac MRI (CMR) in patients with HER2 positive breast cancer receiving trastuzumab therapy. Fourty-one women with early stage HER2+ breast cancer underwent serial CMR (baseline, 6, 12, and 18 months) after initiation of trastuzumab therapy. A single, blinded observer measured LV parameters on de-identified CMRs in random order. Linear mixed models were used to investigate temporal changes. Compared to baseline, there were significant decreases in systolic function as measured by both left ventricular ejection fraction (LVEF) ($p < 0.001$ at 6 and 12 months) and peak ejection rate corrected for end-diastolic volume (PER/LVEDV) ($p = 0.008$ at 6 months, $p = 0.01$ at 12 months). However, these differences were no longer significant at 18 months. In contrast, significant reductions in diastolic function as measured by LV peak filling rate corrected for end-diastolic volume (PFR/LVEDV) were observed at 6 months ($p = 0.012$), 12 months ($p = 0.031$), and up to 18 months ($p = 0.034$). There were no significant temporal changes in the time to peak filling rate corrected for cardiac cycle (TPF/RR). The reduction in PFR/LVEDV at 18 months was no longer significant when corrected for heart rate. In conclusion, there were significant subclinical deleterious effects on both LV systolic and diastolic function among patients receiving trastuzumab. While there was recovery in LV systolic function after therapy cessation at 18 months, reduction in PFR/LVEDV appeared to persist. Thus, diastolic dysfunction may serve as a marker of trastuzumab-induced cardiotoxicity that needs to be confirmed in a larger study.**  **(Am J Cardiol 2019;123:1173−1179)**

Treatment of HER2 positive breast cancers using trastuzumab has demonstrated dramatic improvements in outcome in both the adjuvant and metastatic settings.[1,2] However, its use is associated with a risk of trastuzumab-induced cardiotoxicity (TIC), which may lead to symptomatic heart failure, but is subclinical in the vast majority of cases.[3] This is a type II chemotherapy related cardiac dysfunction, in contrast to anthracycline induced toxicity (Type I), as it is idiosyncratic and not dose-related.[4,5] It is thought to be reversible but continued use of the offending agent despite decline in heart function may result in severe and irreversible cardiac injury.[6] Thus, early detection of TIC is of paramount importance. There is emerging evidence that subclinical diastolic dysfunction may precede systolic dysfunction in TIC,[7] although the temporal changes between the two have yet to be confirmed using a reliable imaging modality. Cardiac magnetic resonance imaging (CMR) is the current gold standard for assessment of ventricular volumes and function, with very good temporal resolution.[8,9] Using CMR, LV systolic function can be measured using LVEF and peak ejection rate (PER), whereas LV diastolic function is assessed by peak filling rate (PFR) and time to peak filling (TPF).[10] The aim of our study was to utilize CMR as a novel imaging modality to evaluate the temporal relationship between LV diastolic function, systolic function and volumetric

[a]Terrence Donnelly Heart Centre, St Michael's Hospital, Toronto, Canada; [b]University of Toronto, Toronto, Canada; [c]Division of Hematology/Oncology, St Michael's Hospital, Toronto, Canada; [d]Schulich Heart Research Program, Sunnybrook Research Institute and Department of Medical Biophysics, University of Toronto, Toronto, Canada; [e]Department of Medical Imaging, St Michael's Hospital, Toronto, Canada; [f]Sunnybrook Odette Cancer Centre, Canadian Centre for Applied Research in Cancer Control, Toronto, Canada; [g]Sunnybrook Odette Cancer Centre, Toronto, Canada; [h]Department of Medical Imaging, Sunnybrook Health Sciences Centre, Toronto, Canada; [i]Department of Radiology, Christian Medical College, Vellore, India; and [j]Department of Radiology, University of Calgary, Calgary, Canada. Manuscript received September 20, 2018; revised manuscript received and accepted December 19, 2018.

Funding sources: This study was supported by an operating grant from the Canadian Institutes of Health Research and an industry partnered grant from Roche Canada.

*Corresponding Author: Tel: (416) 864-5465; Fax: (416) 864-5159.
*E-mail address:* yana@smh.ca (A.T. Yan).

0002-9149/
https://doi.org/10.1016/j.amjcard.2018.12.046

parameters, in breast cancer patients treated with adjuvant trastuzumab.

## Methods

This was a prospective observational longitudinal study conducted in two tertiary care centres in Toronto, Canada.[11] In total, 41 women who were newly diagnosed with HER2 positive early breast cancer in January 2010 to December 2013 were enrolled after obtaining written consent. Inclusion criteria were age older than 18 years, histologically confirmed HER2 positive invasive breast cancer, planned treatment with adjuvant trastuzumab, a normal baseline LVEF (≥50%) as measured by radionuclide ventriculography (RNV), and Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. Exclusion criteria were pre-existing symptomatic heart failure (NYHA Class III or IV), recent acute coronary syndrome or coronary revascularization within 6 months, permanent atrial fibrillation, previous exposure to trastuzumab or other anti-HER2 agents (e.g., lapatinib, pertuzumab), contraindications to CMR, and pregnancy or nursing. Baseline characteristics including demographics, tumor staging, planned surgical, chemotherapy, and radiation treatment regimen, cardiovascular risk factors, vital signs, and cardiac biomarkers (NT-proBNP and high-sensitivity troponin I) were collected prior to initiation of trastuzumab.

After surgical staging with lumpectomy, mastectomy or both, chemotherapy consisting of anthracycline or non-anthracycline regimens were used for each subject at the discretion of the treating oncologist. Participants were to receive 18 cycles (12 months) of trastuzumab therapy. During the study period, participants underwent serial RNV for monitoring of LVEF, as part of the standard of care. TIC was defined as a decrease in LVEF of ≥10% to below the lower limit of normal or ≥15% from baseline value. If participants exhibited TIC based on RNV, trastuzumab therapy was interrupted for at least 1 cycle (3 weeks), until repeat RNV showed improvements in LVEF, only then would trastuzumab be re-initiated.

All subjects underwent serial CMR at 6 months intervals: at baseline prior to treatment initiation, at 6 months, 12 months, and 18 months. The last CMR at 18 months was completed 6 months after trastuzumab cessation. A 1.5 T scanner (Intera, Philips Medical Systems, Best, the Netherlands or a GE Signa Excite Cv, Milwaukee, WI) was used for all CMR examinations with 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. Segmented, balanced steady-state free-precession sequence was used for cine acquisition with the following typical parameters: TR 4 ms, TE 2 ms, slice thickness 8 mm, field of view 320 to 330 × 320 to 330 mm, matrix size 256 × 196, temporal resolution of < 40 ms (depending on the heart rate) and flip angle 50°. Phase sensitive inversion recovery sequences were obtained following administration of intravenous gadolinium contrast. CVi42 software (Circle Cardiovascular, Calgary, Alberta, Canada) was used for image postprocessing.

A single, blinded, trained reader measured LV parameters on de-identified CMRs in a random order. LV endocardial borders were manually contoured on successive short-axis cine images during each phase of the cardiac cycle, including papillary muscles and trabeculations as part of the blood pool. This generated a LV volume to time curve (Figure 1). The LV end systolic volume (LVESV) and LV end diastolic volume (LVEDV) were the cardiac phases with the smallest and largest LV volumes, respectively. LVEDV and LVESV were indexed (LVEDVi and LVESVi) to body surface area, which was calculated by the Mosteller formula. LVEF was calculated as (LVEDV-LVESV) /LVEDV × 100%. LV volume to time curves were plotted using 3 point least square linear fit per CVi42 software. The PER and PFR were acquired from the first derivative of the LV volume to time curve, where PER is the most negative slope and PFR is the most positive slope. Time to peak filling (TPF) is the time from end-systole to PFR (Figure 1). PFR is restricted to filling rates during early diastole (before atrial contraction). PER and PFR were corrected by dividing LVEDV to yield PER/LVEDV and PFR/LVEDV, respectively, while TPF was normalized by dividing the duration of the cardiac cycle (RR) to TPF/RR. LV volume and functional measurements were repeated on a random sample of 20 CMRs in a blinded fashion to assess intra-observer reproducibility.

Mean values with standard deviations were used to express continuous variables. Linear mixed models were used to investigate temporal changes in LV measurements at baseline, 6 months, 12 months, and 18 months. Sidak adjustment was used for pairwise comparisons of the 3 time points (6, 12, and 18 months) with baseline measurements. The non-parametric Spearman's correlation coefficients were calculated to examine the relationships between changes in systolic and diastolic variables and heart rate over time. We also examined correlations between systolic and diastolic variables, LVEDVi and cardiac biomarkers (NT-proBNP and high sensitivity troponin I). Additionally, we tested for potential interaction between anthracycline

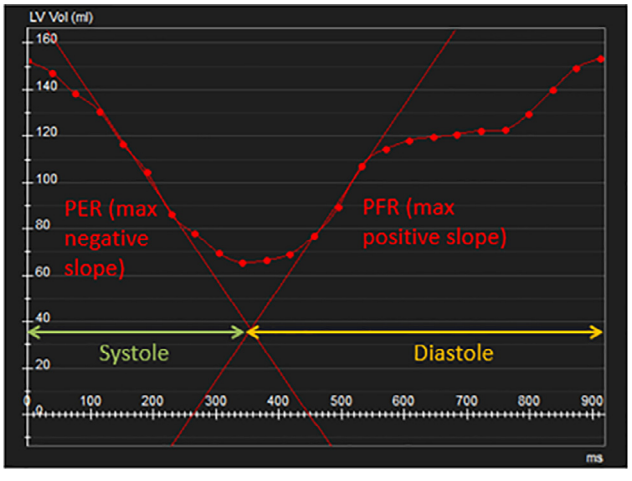


Figure 1. CMR image postprocessing using CVi42 software. Endocardial borders of the LV were contoured on successive short-axis cine images during the entire cardiac cycle. Volume to time curves was generated to yield LV volume and functional parameters.

use and time in the mixed linear models. Intra-observer reproducibility was assessed by the intraclass correlation coefficients for absolute agreement. A two-sided p value of <0.05 was defined as significant. Statistical analysis was performed using SPSS version 23 (IBM).

## Results

In total, 41 patients were enrolled in the study. All study subjects underwent CMR at baseline, while CMR data were available for 35 subjects at 6 months, 35 subjects at 12 months, and 33 subjects at 18 months. Table 1 shows the baseline characteristics of the study subjects. At baseline, there were no patients with heart failure. Only one subject experienced TIC (based on RNV measurement), for whom trastuzumab therapy was interrupted for one cycle. None of the study subjects experienced new clinical heart failure or died from heart failure during study follow-up.

Table 1
Baseline characteristics of study participants (n = 41)

| Variable | Total (n = 41) (%) |
|---|---|
| Age (years) | 52 ± 11 |
| Sex (female) | 41 (100%) |
| Body mass index, kg/m$^2$ | 26.8 ± 6.3 |
| Coronary artery disease * | 1 (2%) |
| Hypertension | 10 (24%) |
| Diabetes mellitus | 4 (10%) |
| Dyslipidemia † | 3 (7%) |
| Current smoker | 10 (24%) |
| Beta-blocker use | 3 (9%) |
| ACE inhibitor use | 3 (9%) |
| NYHA class III/VI symptoms | 0 (0%) |
| Breast cancer | |
| Stage | |
| Early | 27 (66%) |
| Locally invasive | 13 (32%) |
| Metastatic | 0 |
| Cancer side | |
| Left | 27 (66%) |
| Right | 14 (34%) |
| Type of surgical intervention | |
| Lumpectomy | 21 (51%) |
| Mastectomy | 19 (46%) |
| Both | 1 (2%) |
| Other treatments | |
| Left-sided radiotherapy | 12 (29%) |
| Anthracycline-based chemotherapy | 23 (56%) |
| Systolic blood pressure (mm Hg) | 125 ± 15 |
| Diastolic blood pressure (mm Hg) | 75 ± 9 |
| Heart rate (bpm) | 79 ± 13 |
| N-terminal pro b-type natriuretic peptide (ng/mL)‡ | 57 (33 to 128) |
| High-sensitivity troponin-I (ng/mL)‡ | < 0.006 (0.006 to 0.012) |
| Left ventricular end diastolic volume index (mL/m$^2$) | 72 ± 10.3 |
| Left ventricular end systolic volume index (mL/m$^2$) | 23 ± 6.0 |
| Left ventricular ejection fraction (%) | 68 ± 5.9 |
| Peak ejection rate/Left ventricular end diastolic volume | 3.31 ± 0.59 |
| Peak filling rate/Left ventricular end diastolic volume | 3.19 ± 0.71 |
| Time to peak filling/cardiac cycle | 0.180 ± 0.006 |

Data shown as mean ±SD, unless otherwise stated

* Coronary artery disease: stable angina, previous myocardial infarction, previous percutaneous coronary intervention, or coronary bypass surgery.

† Dyslipidemia: clinical diagnosis and/or treatment with lipid-modifying therapy.

‡ median (interquartile range)

In terms of LV volumes, there were significant increases in both LVEDVi and LVESVi at 6 months ($p < 0.001$ for both) and 12 months ($p = 0.007$ and $p < 0.001$, respectively) compared to baseline, while these differences were no longer significant at 18 months (Figure 2).

Mean LVEF was normal at baseline (68.0 ± 5.9%) and remained normal (defined as LVEF ≥57% by CMR) throughout the study. However, compared to baseline, there were significant decreases in both LVEF and PER/LVEDV at 6 months ($p < 0.001$ and $p = 0.008$, respectively) and at 12 months ($p < 0.001$ and $p = 0.01$, respectively). These differences were no longer significant at 18 months ($p = 0.64$ and $p = 0.52$, respectively) (Figures 3). LVEF and PER/LVEDV showed positive correlations at baseline ($r = 0.58$, $p < 0.001$), and over the first 6 months ($r = 0.64$, $p < 0.001$). (Table 2). Table 3 shows there were no significant correlations between LV systolic and diastolic parameters, and biomarkers NT-BNP and troponin-I at baseline.

There were significant decreases in PFR/LVEDV at 6 months ($p = 0.010$), 12 months ($p = 0.027$) and until the end of the study at 18 months ($p = 0.029$) (Figure 4). Meanwhile, no significant changes were observed in TPF/RR ($p = 0.096$, 0.79, and 0.19 at 6, 12, and 18 months, respectively) over the study period (Figure 4). Additionally, there was no correlation between TPF/RR and PFR/LVEDV at baseline (Table 2) or over 6 months (Table 4).

There was a significant positive correlation between PFR/LVEDV and heart rate ($r = 0.45$, $p = 0.003$) at baseline. After adjusting for heart rate, the temporal changes in PFR/LVEDV over 18 months became non-significant (overall $p = 0.14$).

At baseline, PFR/LVEDV correlated positively with both PER/LVEDV and LVEF, while TPF/RR correlated positively with PER/LVEDV but not with LVEF (Table 2). The relationships between changes from baseline to 6 months were similar (Table 4).

There was no significant interaction between anthracycline and time for PER/LVEDV ($p = 0.96$), PFR/LVEDV ($p = 0.089$) and TPF/RR ($p = 0.93$). Intraobserver reproducibility was assessed using intraclass correlation coefficients (95% confidence interval [CI]) which were 0.96 (0.89 to 0.98, $p < 0.001$) for PFR, 0.94 (0.87 to 0.98, $p < 0.001$) for PER and 0.74 (0.43 to 0.89, $p < 0.001$) for TPF.

## Discussion

In this prospective, longitudinal observational study of 41 patients treated with trastuzumab, we found significant decreases in systolic function, and corresponding increases in LV volumes at 6 months and 12 months. These differences were no longer significant at 18 months. In contrast, significant reductions in diastolic function were observed up to 18 months when measured by PFR/LVEDV, while there were no significant differences in TPF/RR. After adjusting for heart rate, the changes seen in PFR/LVEDV became

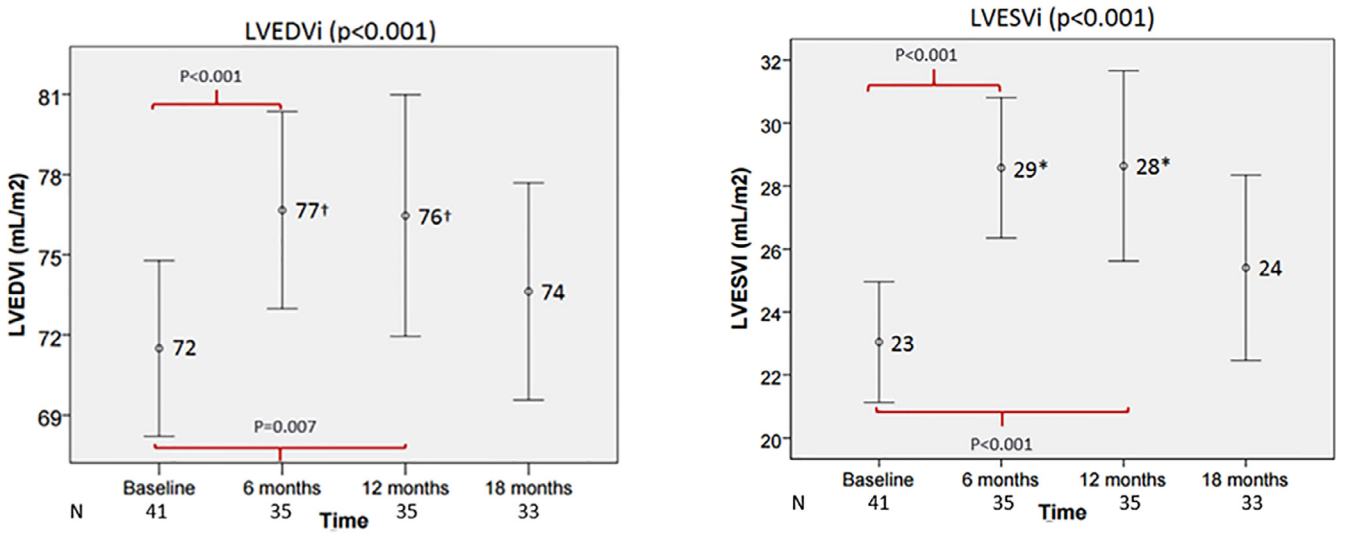


Figure 2. Temporal trends in LV systolic and diastolic volume indices before, during and after trastuzumab therapy. Numbers (N) below the x-axis indicate number of subjects included at each time point. p values in the graph titles refer to p value for overall comparisons (across 4 time points). Vertical bars indicate 95% confidence intervals (CI). *p < 0.001 and †p < 0.05 for Sidak-adjusted pairwise comparisons with baseline.

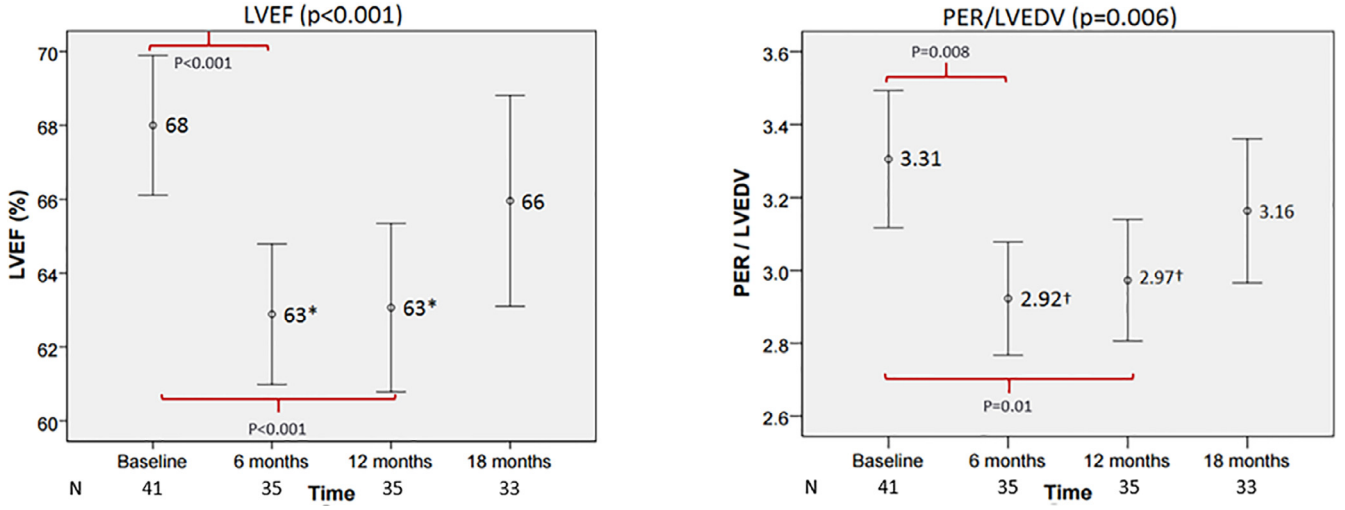


Figure 3. Temporal trends in LV systolic function as measured by LVEF and PER/LVEDV before, during and after trastuzumab therapy. Numbers (N) below the x-axis indicate number of subjects included at each time point. p values in the graph titles refer to p value for overall comparisons (across 4 time points). Vertical bars indicate 95% confidence intervals (CI). *p < 0.001 and †p < 0.05 for Sidak-adjusted pairwise comparisons with baseline.

non-significant. Our study provides novel insights into the subclinical changes in LV volume and function during and after trastuzumab therapy and supports the use of CMR as a safe and sensitive technique in this patient population in research and clinical practice.

The mechanism of LV dysfunction in TIC remains unclear; multiple methods have been used to visualize its damaging effects on LV diastolic function.[7,12,13] Imaging techniques that have been employed include resting and stress echocardiography, 99 mTc-annexin V scintigraphy, RNV, and strain imaging. Despite this, accurate measurement of diastolic function remains challenging. CMR is the current preferred imaging modality in evaluating cardiac structure and function, due to its unparalleled accuracy and reproducibility.[8–10] CMR may also be superior in assessing diastolic parameters such as PFR and TPF given its more accurate volume assessments. It can also provide additional information such as tissue and scar characterization, and other systolic and diastolic parameters from a single examination.[14]

The predictive value of diastolic dysfunction for TIC has been evaluated in several studies to date using other imaging modalities, with conflicting results. Cochet et al[15] conducted an observational study demonstrating that baseline diastolic dysfunction is an independent predictor of TIC. In contrast, Honda et al[13] evaluated diastolic function using echocardiography and found that E/e' at baseline or 3 months after therapy initiation was not significantly associated with subsequent LVEF decline. More recently, Reuvekamp et al[7] used RNV to evaluate LVEF and PFR and TPFR in TIC. Similar to our study, both systolic and

Table 2
Spearman's correlation coefficients (r) between various LV volume, systolic, and diastolic parameters at baseline

| N = 41 | | LVEDVi | PER/LVEDV | LVEF | PFR/LVEDV | TPF/RR | Heart rate |
|---|---|---|---|---|---|---|---|
| LVEDVi | r | | −0.35 | −0.37 | −0.28 | −0.24 | −0.44 |
| | P | | 0.027 | 0.018 | 0.077 | 0.14 | 0.004 |
| LVEF | r | −0.37 | 0.58 | | 0.35 | 0.22 | 0.27 |
| | p | 0.018 | < 0.001 | | 0.025 | 0.17 | 0.089 |
| PER/LVEDV | r | −0.35 | | 0.58 | 0.41 | 0.41 | 0.59 |
| | p | 0.027 | | < 0.001 | 0.008 | 0.007 | < 0.001 |
| PFR/LVEDV | r | −0.28 | 0.408 | 0.35 | | 0.076 | 0.45 |
| | p | 0.077 | 0.008 | 0.025 | | 0.64 | 0.003 |
| TPF | r | 0.11 | −0.053 | 0.04 | −0.41 | 0.56 | −0.21 |
| | p | 0.49 | 0.74 | 0.80 | 0.008 | < 0.001 | 0.19 |
| TPF/RR | r | −0.24 | 0.41 | 0.22 | 0.076 | | 0.60 |
| | p | 0.14 | 0.007 | 0.17 | 0.64 | | < 0.001 |

All measurements were obtained at baseline.

LVEDV = left ventricular end-diastolic volume; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVi = left ventricular end-systolic volume index; PER = peak ejection rate; PFR = peak filling rate; RR = cardiac cycle; TPF = time to peak filling rate.

Table 3
Spearman's correlation coefficients (r) between various LV systolic and diastolic parameters with N-terminal pro b-type natriuretic peptide (NT-BNP) and high-sensitivity troponin-I (hs-TnI) at baseline

| Correlations between LV systolic and diastolic parameters with NT-BNP and hs-TnI at baseline | | | |
|---|---|---|---|
| | | hs-TnI (N = 37) | NT-BNP (N = 39) |
| PER/LVEDV | r | −0.11 | 0.023 |
| | p | 0.54 | 0.89 |
| PFR/LVEDV | r | −0.17 | −0.20 |
| | p | 0.32 | 0.23 |
| TPF | r | −0.053 | 0.066 |
| | p | 0.76 | 0.69 |
| TPF/RR | r | 0.073 | −0.052 |
| | p | 0.67 | 0.75 |

All measurements were obtained at baseline.

LVEDV = left ventricular end-diastolic volume; PER = peak ejection rate; PFR = peak filling rate; RR = cardiac cycle; TPF = time to peak filling rate.

diastolic functional parameters were adversely affected during treatment, but diastolic dysfunction did not predictably precede systolic dysfunction in their study population. Of note, 31% of patients who developed systolic dysfunction had persistently reduced LVEF, in contrast 64% of patients who developed diastolic dysfunction had persistently abnormal diastolic parameters at study completion. These results corroborate the findings in our study, where changes in systolic function, diastolic function, and even LV volumes appear concurrently during trastuzumab treatment, but diastolic dysfunction might be less reversible and persisted for longer after treatment cessation.

Interestingly, while there was excellent correlation between LVEF and PER/LVEDV, no such relationship was observed between the diastolic functional parameters of PFR/LVEDV and TPF/RR. In fact, there were no significant changes in TPF/RR over the study period. The reason for this dissociation between PFR/LVEDV and TPF/RR is not clear. TPF had lower intraobserver reproducibility compared to other variables. TPF was calculated using 3 point linear fit, which can be noisy and less reproducible than other algorithms, and this may have contributed to the non-significant results. Furthermore, it is possible that these variables need to be corrected for other functions in addition to LVEDV or RR. Indeed, there is currently no consensus about which parameters (if any) against which PFR and TPF need to be normalized. We elected to correct PFR against LVEDV and TPF against RR to account for differences in volumes, patient size, and length of the cardiac cycle. In latter analysis, we had also corrected for heart rate, after which the changes seen in PFR/LVEDV became non-significant. However, the effect of heart rate on PFR and TPF is not well established; in fact, none of the previous studies using similar variables corrected for heart rate. Thus, the exact significance of this finding remains to be determined.

There are several limitations to our study. The study population was small, and the follow-up period was relatively short. Several patients did not complete all 4 CMRs, but the linear mixed model allowed all available CMR data to be analyzed. Our study population was at low risk for TIC based on their baseline characteristics,[16] which might account for the lower rate of TIC in our cohort compared to published data. Strengths of our study include the novel use of CMR longitudinally to evaluate LV diastolic filling parameters of PFR and TPF in trastuzumab-treated patients, which is the first study of its kind to our knowledge. This multicenter study with few exclusion criteria lends greater generalizability to routine clinical practice. A rigorous blinding strategy was employed to reduce bias. If future studies confirm the subclinical changes in diastolic filling and their prognostic value, it would further support the routine use of CMR in this clinical context.

In conclusion, subclinical trastuzumab induced deleterious changes in LV systolic function, diastolic function and volumes can be detected by CMR. While there was recovery in systolic function after therapy cessation at 18 months, changes in the diastolic parameter PFR/LVEDV appeared to persist. Although the incremental clinical utility of monitoring for LV diastolic changes in early TIC remains to be determined, our study should lend support for both research and clinical use of CMR in patients treated with trastuzumab.

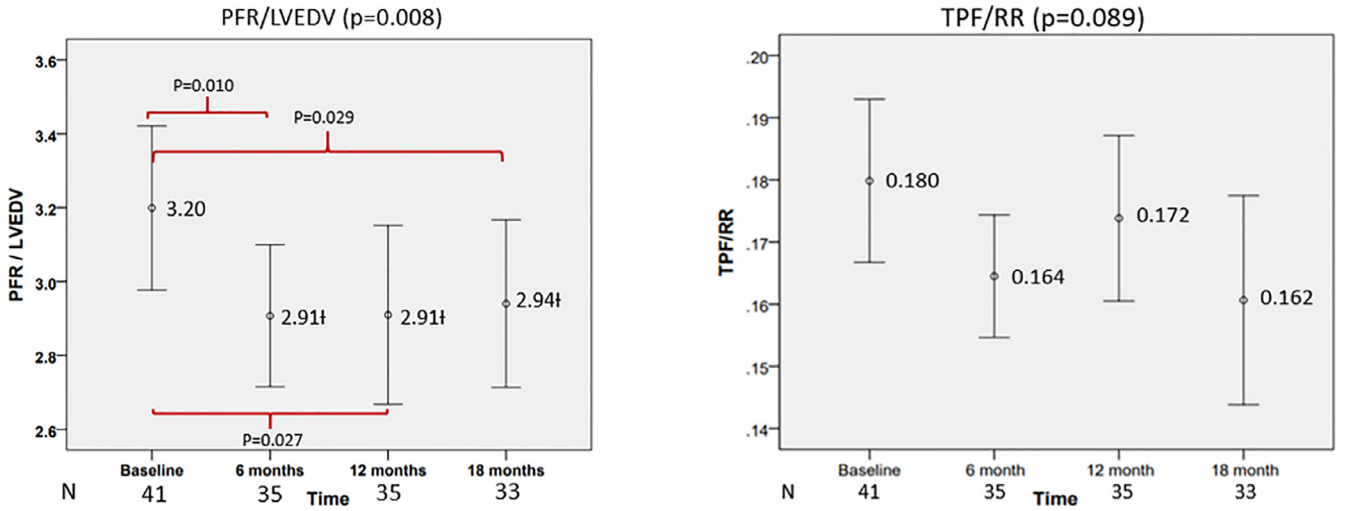


Figure 4. Temporal trends in LV diastolic function as measured by PFR/LVEDV and TPF/RR before, during and after trastuzumab therapy. Numbers (N) below the x-axis indicate number of subjects included at each time point. p values in the graph titles refer to p value for overall comparisons (across 4 time points). Vertical bars indicate 95% confidence intervals (CI). *p < 0.001 and †p < 0.05 for Sidak-adjusted pairwise comparisons with baseline.

Table 4
Spearman's correlation coefficients (r) between the changes from baseline to 6 months in various left ventricular systolic and diastolic parameters and N-terminal pro b-type natriuretic peptide (NT-BNP) and high-sensitivity troponin-I (hs-TnI)

| | | Correlations between changes from baseline to 6 months | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Correlation Coefficient = r (N = 35) | | LVEDVi change | PER/LVEDV change | LVEF change | PFR/LVEDV change | TPF/RR change | NT-BNP change* | hs-TnI change* |
| LVEDVi change | r | | −0.40 | −.0.039 | 0.26 | −0.18 | 0.20 | 0.042 |
| | P | | 0.019 | 0.83 | 0.14 | 0.30 | 0.31 | 0.83 |
| LVEF change | r | −0.039 | 0.64 | | 0.36 | 0.12 | 0.37 | −0.097 |
| | p | 0.83 | < 0.001 | | 0.035 | 0.49 | 0.049 | 0.62 |
| PER/LVEDV change | r | −0.40 | | 0.64 | 0.11 | 0.36 | 0.24 | −0.17 |
| | p | 0.019 | | < 0.001 | 0.54 | 0.036 | 0.21 | 0.39 |
| PFR/LVEDV change | r | 0.26 | 0.11 | 0.36 | | −0.19 | 0.056 | −0.027 |
| | p | 0.14 | 0.54 | 0.035 | | 0.27 | 0.77 | 0.89 |
| TPF/RR change | r | −0.18 | 0.36 | 0.12 | −0.19 | | −0.049 | −0.054 |
| | P | 0.30 | 0.036 | 0.49 | 0.27 | | 0.80 | 0.78 |

* N = 29LVEDV = left ventricular end-diastolic volume; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; PER = peak ejection rate; PFR = peak filling rate; RR = cardiac cycle; TPF = time to peak filling rate.

## Acknowledgment

We thank all the study coordinators and patients who participated in this study. This study was supported by an operating grant from the Canadian Institutes of Health Research and an industry partnered grant from Roche Canada. The study sponsors had no role in the study design, data collection or analysis, interpretation of the findings, writing the manuscript or the decision to submit the manuscript for publication. Dr Kim A Connelly is supported by a New Investigator award from the CIHR and an Early Researcher award from the Ministry of Ontario. Dr. Yan is supported by a Clinician-Scientist Award from the University of Toronto.

1. Pritchard K, Shepherd L, O'Malley F, Andrulis I, Tu D, Bramwell V, Levine M. HER2 and responsiveness of breast cancer to adjuvant chemotherapy. *N Engl J Med* 2006;354:2103–2111.
2. Yin W, Jiang Y, Shen Z, Shao Z, Lu J. Trastuzumab in the adjuvant treatment of HER2-positive early breast cancer patients: A meta-analysis of published randomized controlled trials. *PLoS One* 2011;6: e21030.
3. Bloom M, Hamo C, Cardinale D, Ky B, Nohria A, Baer L, Skopicki H, Lenihan D, Gheorghiade M, Lyon A, Butler J. Cancer therapy−related cardiac dysfunction and heart failure part 1: definitions, pathophysiology, risk factors, and imaging. *Circ Heart Fail* 2016;9:1–10.
4. Rochette L, et al. Anthracyclines/trastuzumab: New aspects of cardiotoxicity and molecular mechanisms. *Trends Pharmacol Sci* 2015; 36:326–348.
5. Ewer M, et al. Type II chemotherapy-related cardaic dysfunction: Time to recognize a new entity. *J Clin Oncol* 2005;23:2900–2902.
6. Bowles E, Wellman R, Feigelson H, Onitilo A, Freedman A, Delate T, Allen L, Nekhlyudov L, Goddard K, Davis R, Habel L, Yood M, McCarty C, Magid D, Wagner E. Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: A retrospective cohort study. *J Natl Cancer Inst* 2012;104:1293–1305.
7. Reuvekamp E, Bulten B, Nieuwenhuis A, Meekes M, de Haan A, Tol J, Maas A, Elias-Smale S, de Geus-Oei L. Does diastolic dysfunction precede systolic dysfunction in trastuzumab-induced cardiotoxicty? Assessment with multigated radionuclide angiography (MUGA). *J Nucl Cardiol* 2016;23:824–832.

8. Grothues F, Smith G, Moon J, Bellenger N, Collins P, Klein H, Pennell D. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol* 2002;90:29–34.
9. La Gerche A, Claessen G, Van de Bruaene A, Pattyn N, Van Cleemput J, Gewillig M, Bogaert J, Dymarkowski S, Claus P, Heidbuchel H. Cardiac MRI: a new gold standard for ventricular volume quantification during high-intensity exercise. *Circ Cardiovasc Imaging* 2013;6:329–338.
10. Paelinck B, Lamb H, Bax J, Van der Wall E, de Roos A. Assessment of diastolic function by cardiovascular magnetic resonance. *Am Heart J* 2002;144:198–205.
11. Barthur A, Brezden-Masley C, Connelly K, Dhir V, Chan K, Haq R, Kirpalani A, Barfett J, Jimenez-Juan L, Karur G, Deva D, Yan A. Longitudinal assessment of right ventricular structure and function by cardiovascular magnetic resonance in breast cancer patients treated with trastuzumab: A prospective observational study. *J Cardiovasc Magn Reson* 2017;19:44.
12. Cao L, Cai G, Chang C, Miao A, Yu X, Yang Z, Ma J, Zhang Q, Wu J, Guo X, Chen J. Diastolic dysfunction occurs early in HER2-positive breast cancer patients treated concurrently with radiation therapy and trastuzumab. *Oncologist* 2015;20:605–614.
13. Honda K, Takeshita K, Murotani K, Mitsuma A, Hayashi H, Tsunoda N, Kikumori T, Murohara T, Ando Y. Assessment of left ventricular diastolic function during trastuzumab treatment in patients with HER2-positive breast cancer. *Breast Cancer* 2017;24:312–318.
14. Caudron J, Fares J, Bauer F, Dacher J. Evaluation of left ventricular diastolic function with cardiac MR imaging. *Radiographics* 2011; 31:239–259.
15. Cochet A, Quilichini G, Dygai-Cochet I, Touzery C, Toubeau M, Berriolo-Riedinger A, Coudert B, Cottin Y, Fumoleau P, Brunotte F. Baseline diastolic dysfunction as a predictive factor of trastuzumab-mediated cardiotoxicity after adjuvant anthracycline therapy in breast cancer. *Breast Cancer Res Treat* 2011;130: 845–854.
16. Mantarro S, Rossi M, Bonifazi M, D'Amico R, Blandizzi C, La Vecchia C, Negri E, Moja L. Risk of severe cardiotoxicity following treatment with trastuzumab: A meta-analysis of randomized and cohort studies of 29,000 women with breast cancer. *Intern Emerg Med* 2016;11:123–140.