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The Utility of Cardiac Biomarkers, Tissue Velocity and Strain Imaging, and Cardiac Magnetic Resonance Imaging in Predicting Early Left Ventricular Dysfunction in Patients With Human Epidermal Growth Factor Receptor II–Positive Breast Cancer Treated With Adjuvant Trastuzumab Therapy

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Objectives The aim of this study was to evaluate whether cardiac biomarkers, tissue velocity (TVI) and strain imaging, and cardiac magnetic resonance imaging can predict early left ventricular (LV) dysfunction in human epidermal growth factor receptor II–positive breast cancer patients treated with trastuzumab in the adjuvant setting.

Background Early indexes of LV systolic dysfunction with noninvasive cardiac imaging would be useful for addressing the cardiac safety profile of trastuzumab, potentially avoiding the detrimental effects of heart failure.

Methods We used cardiac biomarkers, TVI and strain imaging, and cardiac magnetic resonance imaging to detect pre-clinical changes in LV systolic function, before conventional changes in left ventricular ejection fraction (LVEF) in human epidermal growth factor receptor II–positive breast cancer patients treated with trastuzumab in the adjuvant setting.

Results Of 42 patients (mean age 47 ± 9 years) prospectively followed between 2007 and 2009, 10 (25%) developed trastuzumab-mediated cardiomyopathy (CM). Troponin T, C-reactive protein, and brain natriuretic peptide did not change over time. Within 3 months of adjuvant therapy with trastuzumab, there was a significant difference in the lateral S′ between the normal cohort and the CM group (9.1 ± 1.6 cm/s and 6.4 ± 0.6 cm/s, respectively, $p < 0.05$). Similarly, the peak global longitudinal and radial strain decreased as early as 3 months in the trastuzumab-mediated cardiotoxicity group. As compared with both global longitudinal and radial strain, only S′ was able to identify all 10 patients who developed trastuzumab-mediated CM. The LVEF subsequently decreased at 6 months of follow-up in all 10 patients, necessitating discontinuation of the drug. All 10 patients demonstrated delayed enhancement of the lateral wall of the LV within the mid-myocardial portion, consistent with trastuzumab-induced CM.

Conclusions Both TVI and strain imaging were able to detect pre-clinical changes in LV systolic function, before conventional changes in LVEF, in patients receiving trastuzumab in the adjuvant setting. (J Am Coll Cardiol 2011;57:2263–70) © 2011 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

a′ = late diastolic annular velocity of the lateral wall
AC = adriamycin and cyclophosphamide
BNP = brain natriuretic peptide
CHF = congestive heart failure
CM = cardiomyopathy
CRP = C-reactive protein
CV = coefficient of variation
e′ = early diastolic annular velocity of the lateral left ventricular wall
FEC = fluorouracil, epirubicin, and cyclophosphamide
LGE = late gadolinium enhancement
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction
MRI = magnetic resonance imaging
NPV = negative predictive value
PPV = positive predictive value
S′ = systolic annular velocity of the lateral left ventricular wall
TnT = troponin T
TTE = transthoracic echocardiography
TVI = tissue velocity imaging

Breast cancer is the second leading cause of death due to cancer in women in Canada (1). The treatment for breast cancer is individualized to each patient and involves a combination of surgery, chemotherapy, and radiation therapy. Typically, 2 to 3 chemotherapeutic agents are given with each treatment cycle, with the most common regimen including a combination of 5-fluorouracil, anthracyclines (epirubicin or doxorubicin), and cyclophosphamide (FEC) (2).

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An increased understanding of the biology of breast cancer has lead to the identification of novel therapeutic targets. Among these targets, human epidermal growth factor receptor II (HER-2), a member of the epidermal growth factor receptor family, is detected as overexpressed in 25% to 30% of all breast cancers (3). Amplification of HER-2 confers aggressive behavioral traits on breast cancer cells, including enhanced growth and proliferation, increased invasiveness, and metastatic capability (3).

Trastuzumab is a humanized monoclonal antibody that targets the extracellular portion of the HER-2 membrane protein, which is approved for the treatment of patients with HER-2 positive breast cancer, both in the adjuvant and metastatic settings (4–9). Despite its rapid adoption in the management of breast cancer, trastuzumab is known to potentiate the cardiotoxic effects of anthracyclines. The use of trastuzumab is associated with a 5% to 10% risk of asymptomatic cardiac dysfunction and a 1% risk of symptomatic congestive heart failure (CHF) in clinical trials (7–9). Recent studies have shown a higher risk of nearly 1 in 4 breast cancer patients developing trastuzumab-mediated cardiac dysfunction, reversible in a majority of cases (10,11). Early subclinical detection of trastuzumab-induced cardiotoxicity would be clinically useful in this patient population.

Cardiac biomarkers are protein molecules that are widely used in the early detection of heart failure. Serum levels of troponin T (TnT), C-reactive protein (CRP), and brain natriuretic peptide (BNP) have been shown to be sensitive markers of left ventricular (LV) dysfunction and powerful markers of morbidity and mortality in the heart failure setting (12–14). All 3 cardiac biomarkers have been evaluated after anthracycline treatment (15,16). However, their ability to predict early cardiac dysfunction remains unknown in the clinical setting of trastuzumab-mediated cardiotoxicity.

One of the current methods of monitoring LV function in patients receiving adjuvant trastuzumab therapy is determination of left ventricular ejection fraction (LVEF) with serial transthoracic echocardiography (TTE). However, assessment of LVEF is dependent on hemodynamic conditions and fails to detect early subtle alterations in LV systolic function that occurs in the later stages of chronic disease. Tissue velocity imaging (TVI) and strain imaging are sensitive, noninvasive echocardiographic techniques that allow for the early detection of LV systolic dysfunction, before a decrease in conventional LVEF (17). Tissue velocity imaging has been validated in murine models of chemotherapy-induced cardiac dysfunction (18,19) and recently evaluated in the clinical setting of doxorubicin and trastuzumab-induced cardiac dysfunction (20,21). However, early detection of cardiac injury with cardiac biomarkers and TVI in the clinical setting of adjuvant trastuzumab therapy has yet to be investigated.

In addition to TTE, cardiac magnetic resonance imaging (MRI) might be used for the noninvasive assessment of LV volumes and LVEF in the breast cancer setting (22,23). Improvements in both spatial and temporal resolution have made cardiac MRI the gold standard for the noninvasive assessment of LV systolic function (24). Although delayed enhancement imaging with cardiac MRI might identify patients with trastuzumab-mediated cardiotoxicity (22,23), its use for the early prediction of LV dysfunction remains unexplored.

Thus, we sought to evaluate whether cardiac biomarkers, TVI and strain imaging, and cardiac MRI can predict early LV dysfunction in HER-2 positive breast cancer patients treated with trastuzumab in the adjuvant setting.

Methods

From January 2007 to January 2009 inclusive, 42 consecutive female patients were prospectively identified to have received trastuzumab in the adjuvant setting of HER-2 overexpressing breast cancer. After the anthracycline-based chemotherapy regimen, the patients received a loading dose of 8 mg/kg of trastuzumab followed by a maintenance dose of 6 mg/kg every 3 weeks for 1 year. Trastuzumab-mediated cardiomyopathy (CM) was defined as a decline in LVEF of at least 10% below 55%, with accompanying signs or symptoms of CHF, necessitating discontinuation of the drug (6–8) The study protocol was approved by the local institutional review board.

In total, the patient population was evaluated at 6 separate time points: 1) before the initiation of anthracycline-based

chemotherapy; 2) before the initiation of trastuzumab therapy (3 weeks after the final cycle of chemotherapy); 3) 3 months; 4) 6 months; 5) 9 months; and 6) 12 months after the initiation of trastuzumab. At each visit, blood was drawn to measure TnT, CRP, and BNP, and a standard TTE was performed. The patients underwent a cardiac MRI at baseline and 12 months after the initiation of trastuzumab treatment.

Troponin T, CRP, and BNP were evaluated at 6 separate time points. Quantitative determinations of TnT levels were performed with a third-generation Roche Elecsys assay (Roche Diagnostics, Inc., Indianapolis, Indiana). The CRP levels were measured with the Immage 800 (Beckman Coulter, Brea, California) antigen-antibody precipitant rate reaction. The N-terminal pro-BNP levels were measured with an electrochemiluminescence sandwich immunoassay (Elecsys ProBNP, Roche Diagnostics) with the Roche 2010 system.

Serial TTE with TVI was performed on a GE Vivid 7 platform (General Electric, Milwaukee, Wisconsin). For 2-dimensional TTE, parasternal and apical views were obtained with a standard echocardiograph (GE Vivid 7, General Electric) with a multifrequency transducer. The LV cavity dimensions and LVEF were determined from 2-dimensional images according to established criteria, including the modified biplane Simpson's method (25).

Tissue Doppler-derived indexes were recorded at the base of the lateral mitral annuli to determine longitudinal endocardial velocities. These indexes included systolic (S′), early diastolic (e′), and late diastolic (a′) velocities. Doppler-independent strain was also assessed with offline semi-automated speckle tracking techniques in the parasternal and apical views to determine both global longitudinal and radial strain (EchoPac, Version 7.01, General Electric) (17).

Serial cardiac MRI was performed with a 1.5-T scanner (Avanto, Siemens, Erlangen, Germany) at baseline and 12 months of follow-up. Transverse images were acquired with an inversion recovery prepared dark blood HASTE sequence (repetition time [TR] 600 ms, echo time [TE] 26 ms, 6 mm slice thickness, 1.8 mm interslice gap, matrix 256 × 104). Cine bright-blood images in the 4- and 2-chamber long-axis planes were performed with a breath-hold balanced steady-state free precession sequence (true fast imaging with steady-state precession, TR 42 ms, TE 1.2 ms, fractional anisotropy 70°, 6 mm slice thickness, matrix 192 × 174). Cine breath-hold balanced steady-state free precession short-axis images then encompassed the entire LV from the base to the apex (stack of 10 sequential short-axis slices; TR 64 ms, TE 1 ms, fractional anisotropy 80°, 8 mm slice thickness, 1.6 mm interslice gap, matrix 192 × 132) to obtain an LVEF. To evaluate for myocardial edema, dark blood T2-weighted turbo spin echo short-axis images were obtained (TR 1,800 to 2,100 ms, TE 74 ms, 8 mm slice thickness, 4 mm interslice gap, matrix 256 × 175). Late gadolinium enhancement (LGE) images were obtained after 10 min of 0.2 mmol/kg injection of gadolinium (Gd-DTPA, Magnevist, Schering, Germany) with a T1-weighted inversion recovery-prepared multislice true fast imaging with steady-state precession sequence with magnitude and phase-sensitive reconstruction. Images were acquired sequentially in the short axis, followed by horizontal and vertical long-axis images (TR 700 ms, TE 1.0 ms, fractional anisotropy 40°, 8 mm slice thickness, 1.6 mm interslice gap, matrix 192 × 144). To quantify the myocardial mass of the LGE, the endocardial and epicardial borders of the short-axis view of the LV were manually traced. The computer-assisted detection algorithm defined LGE as any region with a signal intensity ≥2 SD above a reference remote myocardial region. The LGE mass was expressed as a percentage of the LV mass. Quantitative analysis was performed with dedicated computer software (CMR^{44}, Release 3.0.0, Circle Cardiovascular Imaging, Calgary, Alberta, Canada).

The data are summarized as mean ± SD or n (%). Paired Student *t* tests were used to compare continuous variables. Chi-square and Fisher exact tests were applied to compare categorical variables. Comparison of variables between the normal population and trastuzumab-induced CM at the same time point were done with the Mann-Whitney *U* test. Comparison of variables within each group versus baseline was performed with repeated measures analysis of variance and Dunnett's test. A significant decrease in LVEF was defined as an ejection fraction drop >10%, as compared with the baseline echocardiogram. A significant decrease in TVI or strain was defined as a decrease exceeding the receiver-operator characteristic curve defined cutoff value of the relevant parameter assessed at the first available echocardiogram. Due to the small sample size of the CM group, the difference between baseline and 3-month measurements for S′, longitudinal strain, and radial strain were used as input variables. This allowed for development of binormal receiver-operator characteristic curves and the calculation of cutoff values based on optimal choices for sensitivity and specificity from the curves. Receiver-operator characteristic curve analysis was applied to determine cutoff values, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for S′, longitudinal strain, and radial strain measurements. Sensitivity, specificity, PPV, and NPV were calculated with Bayes' Theorem, assuming a 25% prevalence of CM patients in the study population (26). Intra-observer variability and inter-observer variability for TVI and strain were measured by the intraclass correlation coefficient and by the coefficient of variation (CV) with the root-mean-square method. A p value <0.05 was considered statistically significant. The Statistical Analysis System (version 8.01, SAS Institute, Cary, North Carolina) was used to perform the analysis.

Results

The study population included 42 patients (mean age 47 ± 9 years) with an average body mass index of 25 ± 7 kg/m^2. Of the entire population, 10 (24%) women developed

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trastuzumab-induced CM, defined as a decline in LVEF of at least 10% below 55%, with accompanying signs or symptoms of CHF, necessitating discontinuation of the drug. The prevalence of underlying cardiovascular risk factors was low in this patient population, as shown in Table 1. There was no difference in the location and size of breast cancer, axillary lymph node involvement, or radiation use between the 2 groups (Table 1). The majority of patients (88%) received 6 cycles of FEC 100, whereas the remaining 12% received 4 cycles of adriamycin and cyclophosphamide (AC) therapy. The median delivered dose intensity, as percentage of the protocol-assigned dose, was 100% for both FEC and AC, respectively. The maximum cumulative dose for epirubicin (600 mg/m^2) and adriamycin (240 mg/m^2) was not exceeded in any patient and did not differ between the normal cohort and those patients who developed trastuzumab-mediated CM. All patients received adjuvant therapy with trastuzumab within 3 ± 1 months of completing the chemotherapy regimen.

At baseline, cardiac biomarkers—including TnT, CRP, and BNP—were within normal limits for the entire population (Table 2). At 12 months of follow-up, there was no significant change in biomarker levels between the normal cohort and those patients who developed trastuzumab-mediated CM.

The mean LVEF for the total population was 63 ± 4% at baseline with conventional echocardiography (Table 3). Within 6 months of treatment with trastuzumab, there was a significant difference between the normal cohort and those patients who developed LV systolic dysfunction, with LVEF values of 64 ± 4% and 42 ± 9%, respectively ($p < 0.05$). In women with CM, there was a progressive decline in LVEF to 39 ± 5% at 9 months, despite discontinuation of trastuzumab and initiation of heart failure therapy with angiotensin-converting enzyme inhibitors and beta blockers. The LVEF began to recover in the majority of patients at 12 months with a mean LVEF of 49 ± 4% (Table 3).

Tissue velocity imaging and strain values were similar between both groups at baseline (Table 3). Within 3 months of adjuvant therapy with trastuzumab, there was a significant difference in the lateral S′ between the normal cohort and those patients who developed LV systolic dysfunction (9.1 ± 1.6 cm/s and 6.4 ± 0.6 cm/s, respectively, $p < 0.05$). With a cutoff value of 0.60 cm/s (difference between baseline and 3-month values for S′), all 10 patients who developed trastuzumab-mediated CM were above this threshold (Table 4). The sensitivity, specificity, PPV, and NPV were 93%, 99%, 96%, and 98%, respectively (Table 4). There were no false positives in the normal cohort (n = 32). The LVEF subsequently decreased ≥10% in the CM group at 6 months and continued to decline up to 9 months of follow-up. There was no difference in e′ and a′ between the normal cohort versus CM at each time point.

Similarly, the peak global longitudinal and radial strain decreased as early as 3 months in the CM group (Table 3). The peak global longitudinal strain decreased from −19.8 ± 1.8% at baseline to −16.4 ± 1.1% at 3 months and continued to decline up to 9 months. With a cutoff value of 2.00% (difference between baseline and 3-month values for peak longitudinal strain), 7 of 10 CM patients were above this threshold (Table 4). The sensitivity, speci-

Table 1 Baseline Characteristics of Total Population

Characteristics	Normal (n = 32)	CM (n = 10)	Total Population (n = 42)	p Value
Age (yrs)	46 ± 8	47 ± 10	47 ± 9	0.48
BMI (kg/m^2)	26 ± 5	25 ± 6	25 ± 7	0.90
CV risk factors				
Hypertension	4 (13)	1 (10)	5 (12)	1.00
Diabetes	4 (13)	2 (20)	6 (14)	0.62
Hyperlipidemia	12 (38)	3 (30)	15 (36)	1.00
Smoking history	2 (6)	2 (20)	7 (17)	0.24
Family history of CAD	4 (13)	3 (30)	12 (29)	0.33
Location of Ca				
Right	19 (59)	6 (60)	25 (60)	1.00
Left	11 (34)	4 (40)	15 (39.5)	1.00
Bilateral	2 (2.6)	0 (0)	2 (2.0)	1.00
Size of Ca (cm)	3.0 ± 2.0	3.2 ± 1.4	3.1 ± 1.7	0.83
Radiation	31 (97)	10 (100)	41 (98)	1.00
Lymph node +	19 (58)	5 (50)	24 (57)	0.72
Chemotherapy				
FEC	29 (91)	8 (80)	37 (88)	0.58
AC	3 (7)	2 (20)	5 (12)	0.58

n = 42. Values are mean ± SD or n (%). p values were calculated by Student *t* test for difference in means between normal and cardiomyopathy (CM) groups and the Fisher exact test for differences in proportions.

AC = adriamycin, cyclophosphamide; BMI = body mass index; Ca = cancer; CAD = coronary artery disease; CV = cardiovascular; FEC = fluorouracil, epirubicin, cyclophosphamide.

Table 2 Summary of Serial Cardiac Biomarkers of Patients With and Without Trastuzumab-Mediated CM in Entire Population

Cardiac Biomarkers	Normal (n = 32)	CM (n = 10)	p Value
Troponin T (μg/l)			
Baseline	<0.01	<0.01	1.00
3 months	<0.01	<0.01	1.00
6 months	<0.01	<0.01	1.00
9 months	<0.01	<0.01	1.00
12 months	<0.01	<0.01	1.00
CRP (mg/l)			
Baseline	5.5 ± 1.2	5.8 ± 1.7	0.76
3 months	5.4 ± 1.8	5.6 ± 1.9	0.81
6 months	6.1 ± 1.1	6.0 ± 1.4	0.88
9 months	5.8 ± 1.4	6.3 ± 2.1	0.72
12 months	6.0 ± 1.6	6.2 ± 1.7	0.84
NT-proBNP (pmol/l)			
Baseline	27.5 ± 2.4	28.4 ± 2.5	0.81
3 months	28.3 ± 2.2	29.1 ± 1.9	0.80
6 months	28.2 ± 2.1	28.7 ± 1.3	0.89
9 months	29.1 ± 3.1	30.1 ± 3.1	0.88
12 months	30.5 ± 1.9	31.4 ± 2.8	0.84

n = 42. Values are mean ± SD unless otherwise indicated.

CRP = C-reactive protein (normal reference: <8 mg/l); NT-proBNP = N-terminal pro-brain natriuretic peptide (normal reference: <35 pmol/l); TnT = cardiac troponin T (normal reference: <0.01 μg/l); other abbreviations as in Table 1.

ficity, PPV, and NPV were 79%, 82%, 60%, and 92%, respectively (Table 4). There were only 3 false positives in the normal cohort (n = 32). Similarly, the peak global radial strain decreased from 41.4 ± 10.5% at baseline to 34.5 ± 15.2% at 3 months in the CM group and continued to decline up to 9 months (Table 3). With a cutoff value of 0.80% (difference between baseline and 3-month values for peak radial strain), 9 of 10 CM patients were above this threshold (Table 4). The sensitivity, specificity, PPV, and NPV were 86%, 81%, 60%, and 95%, respectively (Table 4). There were only 3 false positives in the normal cohort (n = 32). The LVEF subsequently decreased ≥10% in the CM group at 6 months and continued to decline up to 9 months of follow-up.

The intraobserver intraclass coefficients for S′ with TVI, peak global longitudinal strain, and peak global radial strain were 0.96 (CV 2.4%), 0.94 (CV 3.5%), and 0.91 (CV 3.2%), respectively. The interobserver intraclass coefficients for S′ with TVI, peak global longitudinal strain, and peak global radial strain were 0.92 (CV 4.2%), 0.90 (CV 5.2%), and 0.82 (CV 5.4%), respectively.

The LV volumes and LVEF were within normal limits at baseline in both groups with cardiac MRI (Table 5). There was no change in LVEF in the normal group over the 12-month follow-up (Table 5). As compared with the normal group, LV end-diastolic volume, and LV end-systolic volume, as assessed by cardiac MRI, increased in the CM group at 12 months of follow-up with a decrease in the LVEF from 66 ± 5% to 47 ± 4%. There was evidence of subepicardial linear delayed enhancement in the lateral wall of the LV in all 10 patients who developed trastuzumab-induced cardiac dysfunction (Fig. 1). The average size of LGE was 18 ± 4% of LV mass in these patients. In the remaining 32 patients who did not develop trastuzumab-

Table 3 Echocardiographic Parameters of Patients With and Without Trastuzumab-Mediated CM in Entire Population

Echocardiographic Variables	Normal (n = 32)	CM (n = 10)	p Value
LV dimensions			
LVEF			
Baseline	62 ± 5	64 ± 3	0.31
3 months	60 ± 8	58 ± 4	0.69
6 months	64 ± 4	42 ± 9*†	<0.001
9 months	65 ± 4	39 ± 5*†	<0.001
12 months	61 ± 9	49 ± 4*†	<0.001
TDI parameters			
Mean S′ (cm/s)			
Baseline	8.9 ± 1.4	9.2 ± 1.6	0.47
3 months	9.1 ± 1.6	6.4 ± 0.6*†	<0.001
6 months	8.9 ± 0.8	4.3 ± 0.5*†	<0.001
9 months	9.0 ± 0.7	3.9 ± 0.7*†	<0.001
12 months	8.7 ± 1.1	5.8 ± 0.8*†	<0.001
Mean e′ (cm/s)			
Baseline	8.2 ± 1.1	8.1 ± 1.4	0.63
3 months	8.1 ± 1.0	8.0 ± 0.8	0.72
6 months	8.3 ± 0.8	8.1 ± 0.6	0.28
9 months	8.4 ± 0.9	8.3 ± 0.4	0.41
12 months	8.5 ± 1.2	8.2 ± 1.4	0.19
Mean a′ (cm/s)			
Baseline	7.9 ± 1.1	7.8 ± 1.3	0.58
3 months	7.8 ± 1.0	7.6 ± 1.1	0.32
6 months	7.7 ± 0.8	7.5 ± 0.9	0.38
9 months	7.9 ± 0.9	7.7 ± 1.1	0.44
12 months	8.0 ± 1.2	7.9 ± 1.1	0.56
2D speckle tracking			
Peak global longitudinal strain			
Baseline	−20.2 ± 2.4	−19.8 ± 1.8	0.72
3 months	−19.9 ± 2.3	−16.4 ± 1.1*†	<0.001
6 months	−19.4 ± 2.8	−15.4 ± 1.8*†	<0.001
9 months	−20.1 ± 1.7	−12.4 ± 2.1*†	<0.001
12 months	−19.8 ± 1.9	−15.9 ± 2.7*†	<0.001
Peak global radial strain			
Baseline	40.1 ± 11.1	41.4 ± 10.5	0.57
3 months	42.4 ± 13.2	34.5 ± 15.2*†	<0.001
6 months	41.3 ± 15.4	30.5 ± 16.5*†	<0.001
9 months	40.4 ± 15.2	29.4 ± 12.3*†	<0.001
12 months	44.5 ± 17.2	33.4 ± 16.4*†	<0.001

n = 42. Values are mean ± SD. *p < 0.05 was considered significant, comparing normal population versus cardiomyopathy (CM) at same time point with the Mann-Whitney *U* test. †p < 0.05 was considered significant versus baseline within each group with a repeated measures analysis of variance and Dunnett's test.

2D = 2-dimensional; a′ = late diastolic annular velocity of the lateral wall; e′ = early diastolic annular velocity of the lateral left ventricular wall; LV = left ventricle; LVEF = left ventricular ejection fraction; S′ = systolic annular velocity of the lateral left ventricular wall; TDI = tissue Doppler imaging.

Table 4 ROC Curve Analysis for TVI and Strain Imaging

Echocardiographic Variables	Cutoff Value	Sensitivity (95% CI)	Specificity	PPV	NPV
S′ (cm/s)	0.60	0.93 (0.59–0.99)	0.99	0.96	0.98
Longitudinal strain	2.00	0.79 (0.51–0.96)	0.82	0.60	0.92
Radial strain	0.80	0.86 (0.57–0.98)	0.81	0.60	0.95

The cutoff values with the difference of baseline and 3-month measurements for the systolic annular velocity of the lateral left ventricular wall (S′), longitudinal strain, and radial strain. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are shown for each respective echocardiographic parameter.

CI = confidence interval; ROC = receiver-operator characteristic; TVI = tissue velocity imaging.

Table 5 Cardiac MRI Parameters of Patients With and Without Trastuzumab-Mediated CM in Entire Population

CMR Variables, LV Dimensions	Normal (n = 32)	CM (n = 10)	p Value
LVEDV (ml)			
Baseline	155 ± 22	161 ± 19	0.78
12 months	161 ± 21	190 ± 23*†	<0.05
LVESV (ml)			
Baseline	55 ± 10	58 ± 12	0.71
12 months	58 ± 14	98 ± 18*†	<0.05
LVEF			
Baseline	65 ± 3	66 ± 5	0.89
12 months	63 ± 5	47 ± 4*†	<0.05

n = 42. Values are mean ± SD. *p < 0.05 was considered significant comparing normal population versus CM at same time point with the Mann-Whitney *U* test. †p < 0.05 was considered significant versus baseline within each group with a repeated measures analysis of variance and Dunnett's test.

CMR = cardiac magnetic resonance imaging; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; other abbreviations as in Tables 1 and 3.

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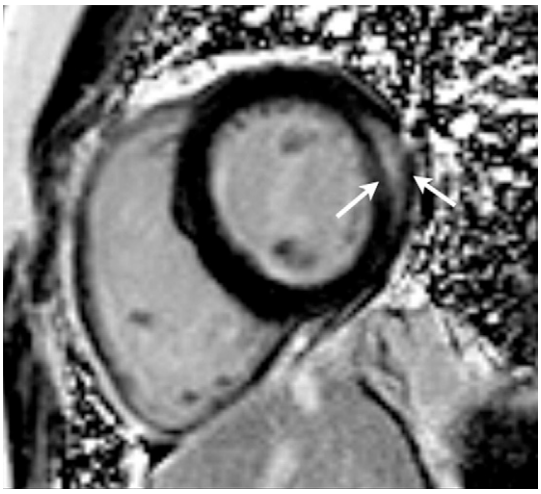

Figure 1 **Delayed Enhancement Cardiac Magnetic Resonance Imaging in Trastuzumab-Mediated Cardiotoxicity**

Short-axis phase sensitive reconstructed inversion recovery–true fast imaging with steady-state precession image through the mid-ventricle at the level of the papillary muscles, demonstrating midmyocardial delayed enhancement **(arrows)** in the lateral wall of a patient who developed trastuzumab-mediated cardiotoxicity.

mediated CM, there was no evidence of delayed enhancement of the LV on cardiac MRI.

Discussion

Despite the clear therapeutic benefits of trastuzumab in reducing breast cancer disease and recurrence in the adjuvant setting, increased cardiotoxicity is a major concern, especially when used in combination with anthracyclines. The current study provides valuable insight into the use of noninvasive imaging in the early detection of trastuzumab-induced CM in the clinical setting of breast cancer. Although cardiac biomarkers did not predict the development of cardiac dysfunction, both TVI and strain imaging were able to detect pre-clinical changes in LV systolic function, before conventional changes in LVEF. Cardiac MRI demonstrated changes in LV volumes and LVEF with characteristic delayed enhancement findings observed in trastuzumab-mediated CM.

Identifying women at risk of developing trastuzumab-induced cardiac dysfunction continues to be an ongoing challenge. In recent years, plasma biomarkers have been extensively evaluated for early prediction of increased morbidity and mortality in the clinical setting of heart failure (12–14). Specifically, increased levels of TnT, CRP, and BNP have been detected in a number of studies evaluating LV systolic dysfunction due to chronic anthracycline treatment (15,16). Although subclinical activation of cardiac biomarkers might occur in anthracycline-mediated CM (15,16), our study did not demonstrate any significant changes over 1 year of follow-up. The small number of patients (n = 10) who developed trastuzumab-induced cardiac dysfunction in the current study might account for the lack of power for detecting a significant change in biomarker levels.

As compared with cardiac biomarkers, echocardiography with TVI and strain rate might be able to detect pre-clinical changes in LV systolic function. Tissue velocity imaging—a modification of conventional blood-flow Doppler that images tissue-derived, high-amplitude, and low-velocity Doppler signals—is able to detect subtle, early changes in LV systolic dysfunction before a decrease in conventional LVEF parameters (17). Although recent animal studies have demonstrated the utility of TVI for the early detection of anthracycline mediated cardiac dysfunction (18), we recently validated its potential application for the early detection of trastuzumab-induced cardiotoxicity (19). We demonstrated that TVI results were abnormal in mice receiving either doxorubicin or trastuzumab + doxorubicin as early as 24 h after treatment and were predictive of ensuing LV systolic dysfunction and increased mortality (19). Although TVI changed acutely on day 1, LVEF values did not decrease until day 3 of the study (19). Whether TVI and strain rate can detect subtle alterations in trastuzumab-induced CM in the clinical setting, however, required further study.

Recently, 2 clinical studies have evaluated the utility of myocardial deformation in the pre-clinical detection of trastuzumab-mediated cardiac dysfunction. Hare et al. (20) evaluated a total of 35 breast cancer patients who received trastuzumab in the adjuvant (n = 27) and metastatic setting (n = 8). Although TVI (S′) was not specifically evaluated, 18 patients demonstrated a reduction in global longitudinal strain rate at 3 months after trastuzumab treatment (20). Three of 18 patients had concurrent drop in LVEF assessment, and 2 additional patients demonstrated a future decrease in LVEF within 20 months of follow-up (20). Although there was no change in serial assessment of radial or longitudinal strain in their study, there was a trend in decreasing values that might have been detected with either longer follow-up or a larger cohort of patients developing trastuzumab-induced CM (20). Similarly, Ho et al. (21) evaluated 19 breast cancer patients who received doxorubicin followed by adjuvant trastuzumab therapy. In this small study, there was no difference in TVI or strain parameters comparing trastuzumab-treated patients with control subjects (21). Although the study by Hare et al. (20) suggested that strain rate might be able to predict LV systolic dysfunction in breast cancer patients receiving trastuzumab in the adjuvant setting, the small number of patients in the study by Ho et al. (21) was not powered to detect meaningful changes in parameters of myocardial deformation.

In our study, TVI and strain parameters did allow for the early detection of subclinical cardiac dysfunction before conventional echocardiographic parameters in breast cancer patients receiving trastuzumab in the adjuvant setting. Although there was no difference in conventional LVEF at

3 months after initiation of adjuvant trastuzumab therapy, TVI (S′) and strain decreased in all 10 patients who developed cardiotoxicity. As compared with both global longitudinal and radial strain, only S′ was able to identify all 10 patients who developed trastuzumab-mediated CM, with no false positives in the normal cohort at 3 months. The LVEF subsequently decreased at 6 months of follow-up in all 10 patients, necessitating discontinuation of the drug. Although reduced diastolic parameters including e′ have been shown to be early predictors of developing hypertrophic CM (27), we did not find a similar pattern in trastuzumab-mediated CM, likely due to absence of significant LV hypertrophy in our patient population. As compared with the previous clinical studies, our patient population of 42 breast cancer patients receiving adjuvant therapy with trastuzumab is the largest to date for assessing meaningful changes in TVI and strain for the early prediction of LV systolic dysfunction. Additionally, we evaluated S′ with TVI and global longitudinal and radial strain with 2-dimensional speckle tracking, allowing for a comprehensive approach for assessing myocardial deformation in this select patient population.

As compared with echocardiography, cardiac MRI is the gold standard for the accurate determination of LV volumes and LVEF. Although cardiac MRI has been validated for serial monitoring of LVEF in breast cancer patients receiving adjuvant therapy with trastuzumab (22,23), its high cost and low availability precludes its utility on a routine clinical basis. Nonetheless, this is the first comprehensive study to evaluate cardiac biomarkers, echocardiography, and cardiac MRI in the early detection of trastuzumab-mediated cardiotoxicity. We demonstrated that, in patients who developed a CM, the LV cavity volumes were increased with a subsequent decrease in LVEF at 12 months of follow-up. Finally, all 10 patients demonstrated delayed enhancement of the lateral wall of the LV within the mid-myocardium portion, a common feature in breast cancer patients with trastuzumab-induced CM (22,23).

Study limitations. Although 10 of 42 patients demonstrated early changes in TVI and strain parameters on TTE, the number of patients who developed trastuzumab-mediated cardiac dysfunction was small. A larger population with longer follow-up would be necessary to substantiate these findings. Additionally, whether delayed enhancement cardiac MRI and/or T2 sequences for myocardial edema would be useful as an early predictor of ensuing LV systolic dysfunction requires further study in this patient population.

Conclusions

Early detection of trastuzumab-mediated cardiotoxicity with noninvasive imaging, in particular TVI and strain, might allow one to adjust treatment and/or the prophylactic administration of cardioprotective agents, before the development of irreversible cardiac dysfunction.

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Key Words: biomarkers ■ breast cancer ■ cardiac MRI ■ cardiomyopathy ■ doxorubicin ■ strain ■ tissue velocity imaging ■ trastuzumab.