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Myocardial strain imaging by cardiac magnetic resonance for detection of subclinical myocardial dysfunction in breast cancer patients receiving trastuzumab and chemotherapy☆

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ABSTRACT

Background: Our objectives were to evaluate the temporal changes in CMR-based strain imaging, and examine their relationship with left ventricular ejection fraction (LVEF), in patients treated with trastuzumab.
Patients and methods: In this prospective longitudinal observational study, 41 women with HER2+ breast cancer treated with chemotherapy underwent serial CMR (baseline, 6, 12, and 18 months) after initiation of trastuzumab (treatment duration 12 months). LVEF and LV strain (global longitudinal[GLS] and circumferential[GCS]) measurements were independently measured by 2 blinded readers.
Results: Of the 41 patients, 56% received anthracycline-based chemotherapy. Compared to baseline (60.4%, 95%CI 59.2–61.7%), there was a small but significant reduction in LVEF at 6 months (58.4%, 95%CI 56.7–60.0%, $p = 0.034$) and 12 months (57.9%, 95%CI 56.4–59.7%, $p = 0.012$), but not at 18 months (60.2%, 95%CI 58.2–62.2%, $p = 0.93$). Similarly, compared to baseline, GLS and GCS decreased significantly at 6 months ($p = 0.024$ and < 0.001, respectively) and 12 months ($p = 0.002$ and < 0.001, respectively) with an increase in LV end-diastolic volume, but not at 18 months. There were significant correlations between the temporal (6 month-baseline) changes in LVEF, and all global strain measurements (Pearson's $r = -0.60$ and $r = -0.75$ for GLS and GCS, respectively, all $p < 0.001$).
Conclusion: There was a significant reduction in LV strain during trastuzumab treatment, which correlated with a concurrent subtle decline in LVEF and was associated with an increase in LV end-diastolic volume. LV strain assessment by CMR may be a promising method to monitor for subclinical myocardial dysfunction in breast cancer patients receiving chemotherapy. Future studies are needed to determine its prognostic and therapeutic implications.

Abbreviations: LV, left ventricle; GLS, global longitudinal strain; CMR, cardiac magnetic resonance; LVEF, left ventricular ejection fraction; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; NYHA, New York Heart Association; Nt-proBNP, N-terminal prohormone of brain natriuretic peptide; hs-TnI, high-sensitivity troponin I; EDV, end-diastolic volume; ESV, end-systolic volume; FT-CMR, feature-tracking magnetic resonance; GRS, global radial strain; GLS-R, global longitudinal strain rate; GRS-R, global radial strain rate; HARP, harmonic phase analysis; SPAMM, spatial modulation of magnetisation; SSFP, steady-state free-precession.

☆ These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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1. Background

Patients with breast cancer are at risk of developing cardiac complications due to the cardiotoxic properties of breast cancer treatment regimens, and up to 1 in 4 patients treated with trastuzumab will develop cardiac dysfunction [1,2]. Accurate, reproducible methods to detect chemotherapy associated cardiac dysfunction are therefore required.

Simpson's biplane method by echocardiography remains the most commonly used method to evaluate left ventricular (LV) function [3]. More recently, global longitudinal strain (GLS) has demonstrated a high sensitivity for the early detection of subclinical LV dysfunction [3]. These techniques are however limited by the adequacy of acoustic windows and image quality. Cardiac magnetic resonance (CMR) imaging is the gold standard for evaluation of LV volumes and function. CMR derived techniques such as strain imaging to assess subclinical LV dysfunction are promising, but their role in assessing cardiac function during and after cancer treatment has yet to be determined.

The aim of this study was to evaluate whether strain derived from CMR using widely available, semi-automated algorithms can detect changes in myocardial function during and after treatment for breast cancer, and the relationships between changes in LV strain measurements, left ventricular ejection fraction (LVEF) and biomarkers.

2. Methods

From December 2009 to December 2013, women diagnosed with breast cancer and overexpression of HER2 on pathology, who had not received trastuzumab therapy previously and were to be treated with chemotherapy and trastuzumab, were enrolled. Study design and all inclusion and exclusion criteria were previously published [4]. All patients underwent serial radionuclide ventriculography for monitoring of LVEF, as part of standard of care. Inclusion criteria were: women aged 18 years or older, Eastern Cooperative Oncology Group (ECOG) performance status 0–2, histologically confirmed diagnosis of invasive breast carcinoma with HER2 overexpression, planned treatment with standard chemotherapy and trastuzumab, baseline LVEF >50% by radionuclide ventriculography. Exclusion criteria were: previous treatment with trastuzumab or any other anti-HER2 agent (e.g. lapatinib, pertuzumab), pre-existing symptomatic HF (NYHA Class III or IV), recent acute coronary syndrome, permanent atrial fibrillation and inability to undergo MRI. Patient demographic characteristics, vital signs, tumor characteristics and staging, planned chemotherapy and radiotherapy regimen, type of surgery and cardiovascular risk factors were collected at baseline. Blood sample was collected for measurements of serum Nt-proBNP (Roche Diagnostics GmbH, Manheim, Germany) and high-sensitivity troponin I (hs-TnI).

Serial CMR was performed at 4 time points (baseline, 6, 12, 18 months). All patients received trastuzumab after the baseline CMR was performed and up to 12 months. 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. 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 320–330 × 320-330 mm, matrix size 256 × 196, temporal resolution of <40 ms (depending on the heart rate) and flip angle 50 degrees. CMRs were de-identified and recoded in a random fashion, and analyzed with CVi42 software (Circle Cardiovascular, Calgary, Alberta, Canada). A single blinded experienced reader measured LVEF and a second blinded experienced reader independently performed all LV strain data analysis. Endocardial and epicardial borders of the LV were contoured on successive short-axis cine images at end-diastole and end-systole. Left ventricular end-diastolic volumes (LVEDV) and left ventricular end-systolic volumes (LVESV) were measured using the short-axis stack. LVEF was calculated using the blood volume method, including papillary muscles and trabeculations. Strain imaging was obtained by feature-tracking magnetic resonance (FT-CMR) method according to standard methods [4]. Both endocardial and epicardial borders were manually drawn and the contoured values were used to calculate GLS, global longitudinal strain rate (GLS-R), global circumferential strain (GCS) and global circumferential strain rate (GCS-R). Multiple long-axis cine images were tracked to derive GLS, while short-axis cine images were used to derive GCS. Strain values were obtained for each segment and global values defined as the mean of all segmental values. Negative strain values describe shortening of the myocardium related to its original length. Positive changes (i.e. less negative) in GLS and GCS imply *decreased* longitudinal and circumferential shortening.

2.1. Statistical analysis

Continuous data are expressed in mean ± standard deviation. Mixed linear models were used to evaluate changes in LVEF, LVEDV, and the strain parameters over time, with Sidak correction for multiple pairwise comparisons with the baseline measurements. To determine whether temporal changes differed between the groups treated with anthracycline and not treated with anthracycline, we tested for interaction between anthracycline and time in the model. The associations between changes in LVEF and strain from baseline to 6 months were assessed by Pearson's correlation coefficients. The relationships between changes in Nt-proBNP and hs-TnI, and strain parameters were assessed by the non-parametric Spearman's (or Kendall's tau-b) correlation test. Data were analyzed using SPSS version 22 (IBM). Statistical significance was defined as a two-sided p value <0.05.

3. Results

Forty-one patients were enrolled. CMR data were available for 41 patients at baseline, 35 at 6 months, 35 at 12 months and 33 patients at 18 months; patients did not undergo all CMRs as per protocol, due to either the use of breast tissue expanders, change in treatment or personal reasons. Baseline characteristics of the 41 participants are shown in Table 1. One (2.4%) patient experienced cardiotoxicity for which trastuzumab was subsequently withheld for one cycle.

The temporal changes in LVEF by CMR are shown in Fig. 1A. At baseline, mean LVEF was normal (mean 60.4 ± 4.2%). There was a significant decrease in LVEF at 6 and 12 months. At 18 months, LVEF was not significantly different from the baseline value ($p = 0.93$). Compared to baseline, LVEDV increased significantly at 3 months ($p = 0.024$) and 6 months ($p = 0.046$), but did not differ at 18 months ($p = 0.91$).

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). However, at 18 months, these parameters were not significantly different from baseline (Fig. 1B and C).

Table 1
Baseline characteristics.

	Total ($n = 41$)
Demographics	
Age, years	52 ± 11
BMI, kg/m^2	27 ± 6
Cardiovascular risk factors	
Coronary heart disease	1 (2%)
Hypertension	10 (24%)
Diabetes	4 (10%)
Dyslipidemia	3 (8%)
Current smoking	10 (24%)
Beta-blockers	3 (9%)
ACE Inhibitors	3 (9%)
Breast Cancer	
Early	27 (66%)
Locally invasive	13 (32%)
Metastatic	0 (0%)
Breast cancer side	
Left	27 (66%)
Right	14 (34%)
Type of surgery	
Lumpectomy	21 (51%)
Mastectomy	19 (46%)
Both	1 (2%)
Left-side radiotherapy	12 (32%)
Anthracycline-based chemotherapy	23 (56%)
Vital signs	
Systolic blood pressure, mmHg	125 ± 15
Diastolic blood pressure, mmHg	75 ± 9
Heart rate, bpm	79 ± 13
Cardiac biomarkers at baseline	
Nt-Brain natriuretic peptide, ng/mL[a]	57(33–128)
High-sensitivity Troponin-I, ng/mL[a]	<0.006(<0.006–0.012)
Cardiac magnetic resonance parameters at baseline	
Left ventricular end-diastolic volume, (ml)	130 ± 25
Left ventricular end-systolic volume, (ml)	51 ± 12
Left ventricular ejection fraction, (%)	60.5 ± 4.3
Left ventricular mass index (LVMI g/m2)	44.8 ± 7.6

Data shown as mean ± SD.
[a] Median (interquartile range).

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