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ORIGINAL REPORT

Role of Three-Dimensional Echocardiography in Breast Cancer: Comparison With Two-Dimensional Echocardiography, Multiple-Gated Acquisition Scans, and Cardiac Magnetic Resonance Imaging

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ABSTRACT

Purpose
In patients with breast cancer, the administration of doxorubicin and trastuzumab is associated with an increased risk of cardiotoxicity. Although multiple-gated acquisition (MUGA) scans and two-dimensional transthoracic echocardiography (TTE) are conventional methods for baseline and serial assessment of left ventricular ejection fraction (LVEF) in these patients, little is known about the use of real-time three-dimensional TTE (RT3D TTE) in this clinical setting. The aim of this study was to assess the accuracy of MUGA, 2D TTE, and RT3D TTE for determining LVEF in comparison to cardiac magnetic resonance imaging (CMR).

Methods
Between 2007 and 2009 inclusive, 50 female patients with human epidermal growth factor receptor 2–positive breast cancer received adjuvant trastuzumab after doxorubicin. Serial MUGA, 2D TTE, RT3D TTE, and CMR were performed at baseline, 6, and 12 months after the initiation of trastuzumab.

Results
A comparison of left ventricular end diastolic volume (LVEDV) demonstrated a modest correlation between 2D TTE and CMR ($r = 0.64$ at baseline; $r = 0.69$ at 12 months, respectively). A comparison of LVEDV between RT3D TTE and CMR demonstrated a stronger correlation ($r = 0.87$ at baseline; $r = 0.95$ at 12 months, respectively). Although 2D TTE demonstrated a weak correlation with CMR for LVEF assessment ($r = 0.31$ at baseline, $r = 0.42$ at 12 months, respectively), both RT3D TTE and MUGA showed a strong correlation when compared with CMR ($r = 0.91$ at baseline; $r = 0.90$ at 12 months, respectively).

Conclusion
As compared with conventional MUGA, RT3D TTE is a feasible, accurate, and reproducible alternate imaging modality for the serial monitoring of LVEF in patients with breast cancer.

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INTRODUCTION

Breast cancer and cardiovascular disease are major public health concerns in North America. These two diseases are intricately involved as treatment of one disease may lead to detrimental effects in the other. Although the current combination of surgical resection, radiotherapy, and chemotherapy may lead to remission in patients with breast cancer, the administration of chemotherapeutic-based agents, in particular doxorubicin, is associated with an increased risk of cardiotoxicity.[1-4] The introduction of novel monoclonal antibodies in breast cancer therapy, which target growth factor receptors, further compounds this issue of drug-induced cardiac dysfunction.

Trastuzumab (Herceptin; Genentech, South San Francisco, CA), a humanized monoclonal antibody against the extracellular domain of the human epidermal growth factor receptor 2 (HER2) protein,[5] is used in both the adjuvant and metastatic settings of breast cancer.[6-12] Despite its clear therapeutic benefits, cardiotoxicity is a major concern, especially when trastuzumab is used in combination with anthracyclines. Although clinical trials have demonstrated that the risk of developing asymptomatic

left ventricular (LV) systolic dysfunction after receiving trastuzumab is up to 10%,[13-17] recent studies have shown an even higher risk of nearly one in four women developing this drug-induced cardiomyopathy, albeit reversible in a majority of cases.[18-20]

Serial monitoring of LV ejection fraction (LVEF) using noninvasive cardiac imaging is the most important clinical diagnostic tool in early recognition of cardiac dysfunction.[21-24] Multiple-gated acquisition scans (MUGA) and two-dimensional transthoracic echocardiography (2D TTE) are conventional methods for baseline and serial assessment of LV systolic function in patients with breast cancer undergoing chemotherapy.[22-24] Although MUGA measurements are highly reproducible with a low intraobserver and interobserver variability, there is the issue of radiation and inaccurate LVEF measurements in patients with underlying arrythmias.[22-24]

TTE is commonly used either as an alternative imaging modality for serial assessment of LVEF in patients with breast cancer or as confirmation of a poor LVEF detected by MUGA. Despite the portability, lack of radiation, ease of use, and increased availability of TTE for monitoring LVEF, two-dimensional echo has poorer intra- and interobserver variability in this clinical setting.[25] Although cardiac magnetic resonance imaging (CMR) is considered the gold standard for the noninvasive assessment of LVEF in myocardial disorders, including chemotherapy- and trastuzumab-induced cardiac dysfunction,[26,27] its high cost and low availability at most centers preclude its use for serial monitoring of cardiotoxicity in patients with breast cancer.

The recent introduction of real-time three-dimensional TTE (RT3D TTE) has shown to be a feasible and reliable method of assessing LVEF in patients with a range of cardiovascular diseases.[28-38] Using CMR as the gold standard, RT3D TTE is more accurate at assessing LV volumes and LVEF, in comparison to 2D TTE.[28-40] Little is known, however, about the use of RT3D TTE for serial monitoring of LVEF in the breast cancer setting.

The aim of this study was to assess the consistency of MUGA, 2D TTE, and, in particular, RT3D TTE for determining LVEF in comparison to CMR in a breast cancer population receiving doxorubicin and trastuzumab in the adjuvant setting.

METHODS

From January 2007 to August 2009 inclusive, 50 consecutive female patients were prospectively identified to have received trastuzumab in the adjuvant setting of HER2-overexpressing breast cancer at a tertiary care oncology center. Eligible patients with breast cancer had either node-positive disease of any tumor size or node-negative disease, if on pathologic examination the tumor size was greater than 1 cm. After therapy with either fluorouracil, epirubicin, and cyclophosphamide (FEC) 100 or adriamycin and cyclophosphamide (AC), all 50 patients received adjuvant trastuzumab at a loading dose of 8 mg/kg of body weight, one time intravenously, followed by maintenance doses of 6 mg/kg every 3 weeks for 1 year. Patients with underlying atrial fibrillation, interventricular conduction delay, or contraindication to undergo a CMR imaging were excluded from this study.

Before initiation of trastuzumab and serially at 6 and 12 months, all 50 patients received MUGA, 2D TTE, RT3D TTE, and CMR examinations. All patients were in sinus rhythm and all imaging exams were performed within 1 week of each other. The study protocol was approved by the local institutional review board.

Serial MUGA scans were evaluated in all 50 patients using standard established guidelines to determine LVEF.[41] Specifically, erythrocyte labeling was done using in vivo or modified in vitro method with technetium 99m-labeled RBCs with an activity of approximately 11 to 13 MBq/kg. Images were acquired with a Siemens e-cam gamma camera (Siemens, Erlangen, Germany) equipped with a parallel hole, high-resolution general purpose collimator, with energy window of 20% symmetrically placed over a photopeak of 140 keV. Data were acquired in EKG-synchronized frame mode using 24 frames per cardiac cycle, with 64 × 64 matrix of 16-bit pixels for approximate pixel size of 2 to 4 mm. Acquisition times were adjusted to achieve a minimum of 200,000 counts per frame. Patients were resting and supine and the best septal view was individually adjusted from 45-degree left anterior oblique position with 10° to 15° caudal tilt. Scintigrams were smoothed off-line using standard algorithms and the LV region of interest, as well as background activity, were selected automatically by the computer program (E. Soft; Siemens Medical Solutions) with manual correction by the interpreting physicians as deemed necessary. LV time-activity curves were constructed and LVEF was calculated as LVEF = (background-corrected end-diastolic counts – background corrected end-systolic counts)/(background-corrected end-diastolic counts).

Serial TTE was performed using 2D and 3D techniques on a GE Vivid 7 platform (GE, Milwaukee, IL). For 2D TTE, parasternal and apical views were obtained using a standard echocardiograph (GE Vivid 7; GE) with a multifrequency transducer. LV cavity dimensions and LVEF were determined from two-dimensional images according to established criteria, including the modified biplane Simpson's method.[42] Measurements of LV end diastolic volume (LVEDV), LV end systolic volume (LVESV), and LVEF were obtained using off-line analysis.[42]

RT3D TTE was performed using a dedicated broadband, wide angle, matrix array transducer to acquire the entire LV cavity within the pyramidal scan volume. Acquisition of full volume data sets was triggered to the R wave of every cardiac cycle to allow for an acquisition time of four heart beats during breath hold. The subvolumes were automatically stitched to a sequence of full 3D volumes covering the entire LV, and stored digitally for offline analysis. The apical views were aligned to the standard four chamber, two chamber, and three chamber views using TomTec software (TomTec Imaging Systems, Unterschleissheim, Germany) to calculate LVEDV, LVESV, and LVEF.[43]

Serial CMR was performed using a 1.5 T scanner (Avanto; Siemens). In conjunction with an ECG, a breath hold and a segmented TrueFISP sequence was performed in order to achieve 16 to 20 images, covering the entire cardiac cycle. The images that were obtained were two long-axis views and six short-axis views, to cover the central two thirds of the ventricles, omitting the base and apex. The image field of view was 265 × 340 mm^2, the acquisition matrix was 160 × 256, the repetition time was 3.14 ms, with an echo time of 1.57 ms, bandwidth/pixel of 930 Hz, k-space line per segment of 24, and a breath-hold duration of 10 seconds for 2 slices. A 6-mm slice thickness

Table 1. Baseline Clinical Characteristics of Study Population (n = 50)

Clinical Characteristic	No.	%
Mean age, years	52	
SD	8	
Mean BMI, kg/m^2	24	
SD	4	
CV risk factors		
Hypertension	5	10
Diabetes	4	8
Hyperlipidemia	6	12
Smoking history	3	6
Family history of CAD	4	8

Abbreviations: SD, standard deviation; BMI, body mass index; CV, cardiovascular; CAD, coronary artery disease.

Table 2. Bland-Altman Graph Agreements Between 2D TTE, RT3D TTE, and MUGA Measurements of LVESV, LVEDV, and LVEF With Cardiac Magnetic Resonance As the Gold Standard at Baseline, 6 Months, and 12 Months Follow-Up

	LVESV (ml)		LVEDV (ml)		LVEF (%)		
Parameter	2D TTE	RT3D TTE	2D TTE	RT3DTTE	2D TTE	RT3D TTE	MUGA
Baseline							
Mean difference	−1.5	−0.47	−9.2	−1.5	5.24	−1.1	−0.52
SD	13.2	6.6	23.7	13.8	4.9	2.3	2.6
6-month follow-up							
Mean difference	−23.6	−6.8	−38.6	−14.5	−0.56	−1.1	−0.86
SD	28.8	11.6	32.7	15.4	7.7	1.9	2.0
12-month follow-up							
Mean difference	−15.7	−4.9	−36.3	−12.7	−3.7	−1.5	−0.3
SD	22.5	7.6	31.7	11.0	6.1	2.3	2.2

Abbreviations: LVESV, left ventricular end systolic volume; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; 2D TTE, two-dimensional transthoracic echocardiography; RT3D TTE, real time three-dimensional transthoracic echocardiography; MUGA, multiple-gated acquisition scans; SD, standard deviation.

with a 4-mm inter-slice gap was used to avoid major influences of partial volume effects.

The CMR images were analyzed using CMR[42] (release 2.2.0; Circle Cardiovascular Imaging, Calgary, Alberta, Canada). Cardiac dimensions and LV systolic function were evaluated from two-dimensional images according to the Society for Cardiovascular Magnetic Resonance guidelines.[45] Endocardial and epicardial contours of the ventricular walls were manually traced on all images containing the LV in each end-diastolic and end-systolic slice. The sum of the marked areas was used to calculate the end-diastolic volume (EDV) and the end-systolic volume (ESV). Stroke volume was calculated using the stroke volume = EDV − ESV formula. The EDV phase was defined visually as the point when the image was at its largest volume, and the ESV was defined visually as the point when the image was at its smallest volume. Papillary muscles and trabeculae were excluded when doing the volume measurements.

The reproducibility of the LV volumes and LVEF by 2D TTE and RT3D TTE was evaluated by calculating the intra- and interobserver variability of both techniques. Intraobserver variability of 2D TTE and RT3D TTE measurements were assessed by the primary interpreter (D.J.) in 20 randomly selected patients. A second interpreter (T.F.) assessed interobserver variability in 20 other randomly selected patients. Both interpreters were blinded to the results of the other imaging techniques.

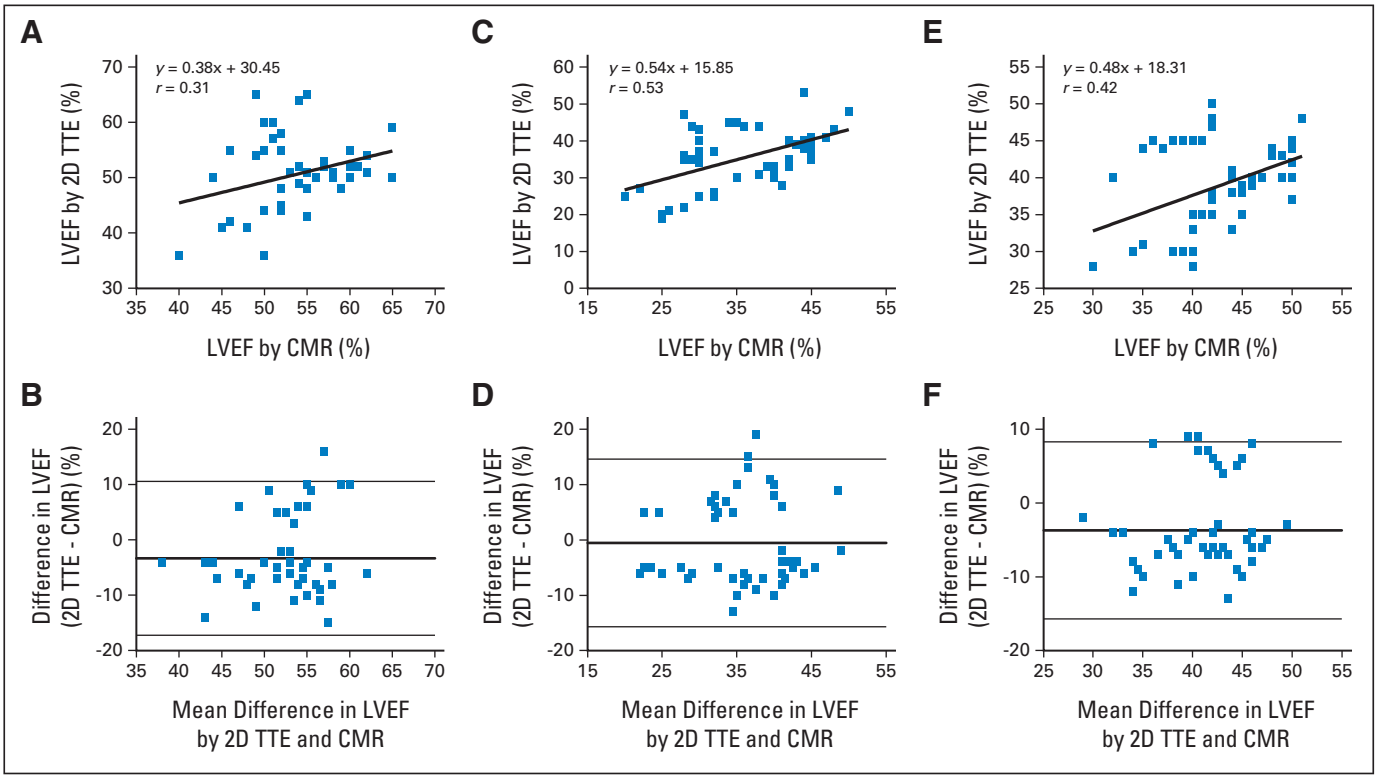

Fig 1. Linear regression and Bland-Altman plots comparing left ventricular ejection fraction (LVEF) of two-dimensional transthoracic echocardiography (2D TTE) versus cardiac magnetic resonance imaging (CMR) at (A,B) baseline, (C,D) 6 months, and (E,F) 12 months.

The data are summarized as mean with or without standard deviation (SD) or number and percentage. Linear regression analysis and Bland-Altman plots were used to compare LV volumes and LVEF between the various imaging modalities. The Bland-Altman method is a plot of the differences of the data on a chart with mean difference ± 1.96 × SD of the differences.[46] The 95% agreement limits are ± 1.96 × SD of the differences. A repeated measures analysis of variance was performed at baseline, 6-month, and 12-month time periods with the various imaging modalities used as within-subject factors. Tukey's multiple comparison test and Dunnett's test were used to check for any significant differences between the imaging modalities. Agreement between intra- and interobserver variability of the LV volumes and LVEF between the imaging modalities was computed from the absolute differences between repeated measurements using the Mann-Whitney *U* test. All tests were two sided, and a *P* value less than .05 was considered statistically significant. The Statistical Analysis packages (SAS version 9.01; SAS Institute, Cary, NC; Statistica software version 6.1; Statsoft, Tulsa, OK) were used to perform the analysis.

RESULTS

The study population included 50 patients (mean age [SD] 52 ± 8 years) with an average body mass index of 24 ± 4 kg/m^2. As presented in Table 1, there was a low prevalence of cardiovascular risk factors including hypertension, diabetes, hyperlipidemia, smoking history, and family history of coronary artery disease. All patients were in sinus rhythm with no underlying conduction abnormalities.

Serial assessment of LVESV on 2D TTE demonstrated a modest correlation ($r = 0.55$ at baseline; $r = 0.40$ at 6 months; $r = 0.59$ at 12 months, respectively) as compared with CMR. The LVESV on RT3D TTE, however, demonstrated a stronger correlation with CMR ($r = 0.89$ at baseline; $r = 0.87$ at 6 months; and $r = 0.93$ at 12 months, respectively) with a slope considerably closer to 1.0. A comparison of LVESV using Bland-Altman analyses between 2D TTE, RT3D TTE, and CMR at baseline, 6, and 12 months are presented in Table 2. As compared with 2D TTE, RT3D TTE demonstrated tighter limits of agreement with a lower bias and SD in the noninvasive assessment of LVESV in comparison to CMR.

Serial assessment of LVEDV on 2D TTE demonstrated a modest correlation ($r = 0.64$ at baseline; $r = 0.50$ at 6 months; $r = 0.69$ at 12 months, respectively) as compared with CMR. The LVEDV on RT3D TTE, however, demonstrated a stronger correlation with CMR ($r = 0.87$ at baseline; $r = 0.82$ at 6 months; $r = 0.95$ at 12 months, respectively) with a slope considerably closer to 1.0. A comparison of LVEDV using Bland-Altman analyses between 2D TTE, RT3D TTE, and CMR at baseline, 6, and 12 months are presented in Table 2. Again, as compared with 2D TTE, RT3D TTE demonstrated tighter limits of agreement with a lower bias and SD in the noninvasive assessment of LVEDV in comparison to CMR.

LVEF measurements for 2D TTE, RT3D TTE, and MUGA in comparison to CMR reference values are shown in Figures 1, 2, and 3 and Table 2. The LVEF by 2D TTE yielded a weak correlation with CMR as shown in Figure 1 ($r = 0.31$ at baseline; $r = 0.53$ at 6 months; $r = 0.42$ at 12 months, respectively). In contrast, LVEF by RT3D TTE showed a strong correlation with CMR as shown in Figure 2 ($r = 0.91$ at baseline; $r = 0.97$ at 6 months; and $r = 0.90$ at 12 months, respectively). Similar to RT3D TTE, MUGA measurements for LVEF demonstrated a strong correlation to CMR reference measurements as

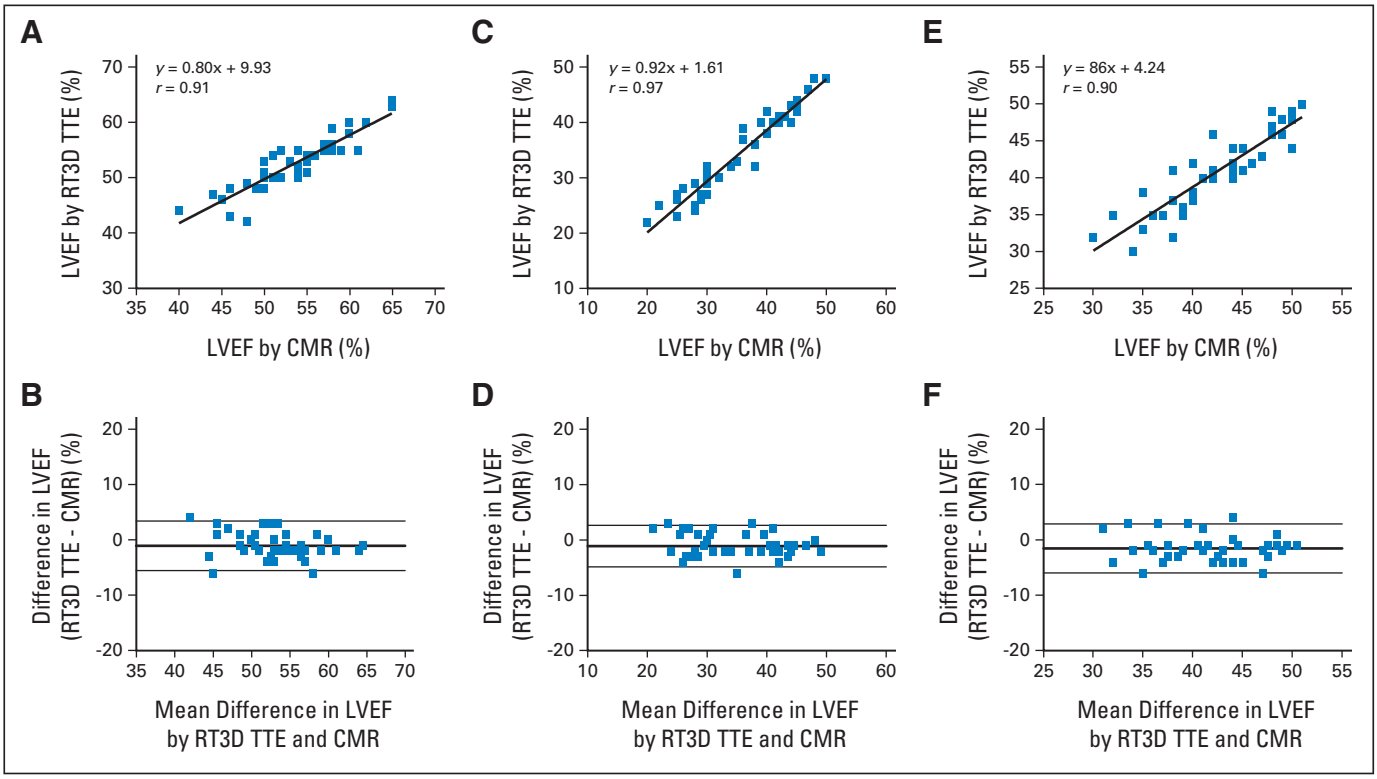

Fig 2. Linear regression and Bland-Altman plots comparing left ventricular ejection fraction (LVEF) of real-time three-dimensional transthoracic echocardiography (RT3D TTE) versus cardiac magnetic resonance imaging (CMR) at (A,B) baseline, (C,D) 6 months, and (E,F) 12 months.

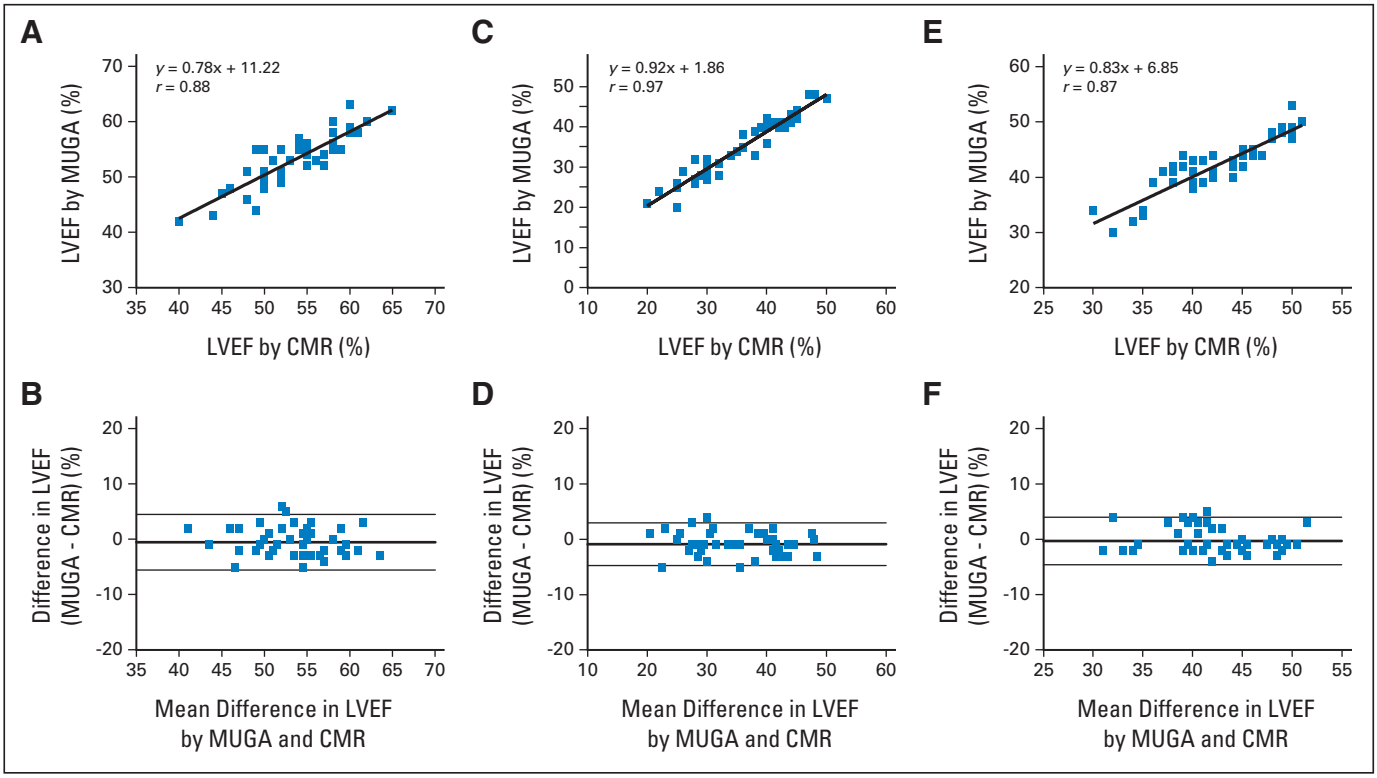

Fig 3. Linear regression and Bland-Altman plots comparing left ventricular ejection fraction (LVEF) of multiple-gated acquisition scans (MUGA) versus cardiac magnetic resonance imaging (CMR) at (A,B) baseline, (C,D) 6 months, and (E,F) 12 months.

shown in Figure 3 ($r = 0.88$ at baseline; $r = 0.97$ at 6 months; and $r = 0.87$ at 12 months, respectively). In addition to similar correlation values, both RT3D TTE and MUGA yielded similar Bland-Altman results as presented in Table 2. Comparing RT3D TTE with MUGA directly as shown in Fig 4, there was a strong correlation in LVEF determination ($r = 0.85$ at baseline; $r = 0.97$ at 6 months; and $r = 0.85$ at 12 months, respectively).

Table 3 demonstrates the results of the intraobserver and interobserver variability of LV volumes and LVEF derived from both techniques of echocardiography, revealing high reproducibility with RT3D TTE.

DISCUSSION

In this study, we demonstrated that for serial monitoring of LVEF in patients with breast cancer receiving adjuvant trastuzumab therapy after treatment with an anthracycline, RT3D TTE yields comparable measurements to those of conventional MUGA using CMR as the gold standard. RT3D TTE is a feasible and reproducible method for assessing accurate changes in LV volumes and LVEF as compared with 2D TTE in this patient population. Although our results indicate a slight underestimation of LVEF for RT3D TTE compared with MUGA, the correlation to CMR between both modalities is similar.

As with all potentially cardiotoxic treatments for breast cancer, MUGA and 2D TTE are the most widely used noninvasive cardiovascular imaging modality for serial assessment of cardiac dysfunction.[22-24] The cardiotoxic effects of anthracycline and trastuzumab therapy are manifested by a decrease in LVEF.[1-4,13-18] Discontinuation of trastuzumab is warranted if a significant decrease in LVEF is detected on MUGA.[8-10] Although MUGA is commonly used for cardiac monitoring in this patient population, it is limited by cost, complexity, and use of ionizing radiation (equivalent to one or two chest x-rays) over serial examinations.[22-24]

TTE is a feasible alternative for the noninvasive assessment of LVEF in this patient population. A number of previous studies have compared the accuracy of LVEF by 2D TTE and MUGA in the setting of anthracycline-induced cardiotoxicity. In 2001, Nousiainen et al[21] compared 2D TTE and MUGA in patients with lymphoma receiving doxorubicin treatment. Of 30 patients, radionuclide angiography demonstrated 10 patients (36%) with a reduced LVEF lower than 50%. Using 2D TTE in the same population however, only five patients (19%) demonstrated a reduced LVEF lower than 50%.[21] In addition, a study of 21 children with leukemia and solid tumors underwent serial 2D TTE and MUGA monitoring concurrently while being treated with anthracyclines.[47] Two-dimensional TTE was significantly less sensitive for the detection of a decline in LVEF in comparison to MUGA. Whereas eight of 21 patients demonstrated a decrease in LVEF by more than 10% using MUGA, only three patients demonstrated LV systolic dysfunction using TTE.[47] Conventional 2D TTE is thus limited by its low sensitivity, specificity, and reproducibility in comparison to radionucliotide imaging tests in patients receiving anthracyclines.[21-24,47] These shortfalls in 2D TTE are due to constraints with foreshortening errors, reliance on geometric assumptions, dependency on acoustic windows, and variable operator skill.[34,48]

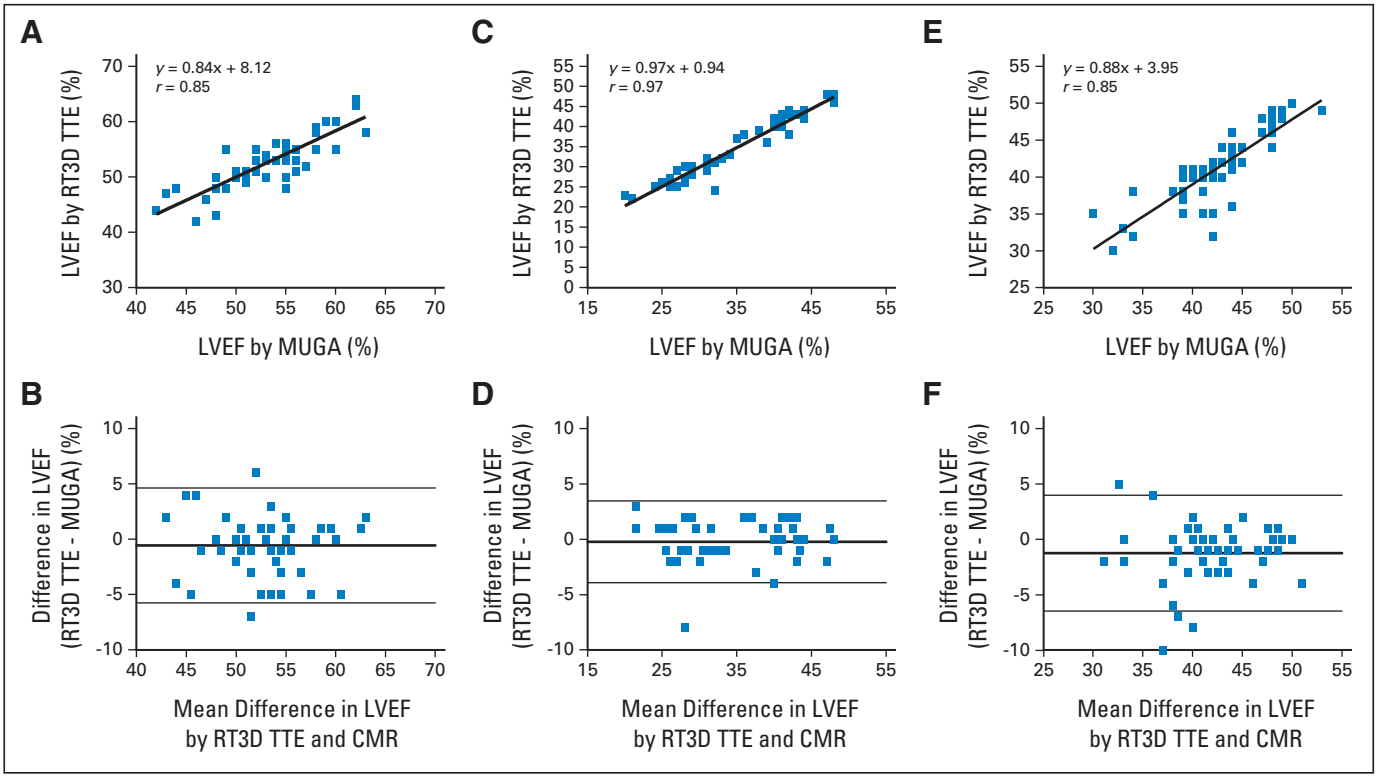

Fig 4. Linear regression and Bland-Altman plots comparing left ventricular ejection fraction (LVEF) of multiple-gated acquisition scans (MUGA) versus real-time three-dimensional transthoracic echocardiography (RT3D TTE) at (A,B) baseline, (C,D) 6 months, and (E,F) 12 months. CMR, cardiac magnetic resonance imaging.

Of all noninvasive imaging modalities, however, CMR is the most accurate and reproducible tool for the estimation of LV volumes and function.[26,49,50] Using a 3D data set, CMR has been validated to be more accurate and reproducible compared with echocardiography.[26,49,50] In addition, serial monitoring of patients with breast cancer to detect subtle changes in LV volumes and LVEF may be done with much higher certainty using CMR.[51] The high cost, low availability, and requirement for highly trained specialists at most centers however preclude its use for serial monitoring of cardiotoxicity in this clinical setting.

RT3D TTE accurately assesses LV morphology and function in normal populations and in various cardiovascular diseases.[28-39] In healthy patients, RT3D TTE has demonstrated excellent correlation to reference CMR values using a number of methods including volume-time curve,[38] manual and semi-automatic border detection,[34] and rapid full-volume acquisition.[33,36] In patients with congenital heart

Table 3. Intraobserver and Interobserver Variability in LV Volumes and LVEF

	Intraobserver				Interobserver			
	Absolute		%		Absolute		%	
Parameter	Mean	SD	Mean	SD	Mean	SD	Mean	SD
LVEDV (ml)								
2D TTE	12.2	6.4	11.8	5.3	14.2	4.5	9.8	4.2
RT3D TTE	8.3	4.4	6.8	3.7	9.6	3.1	6.4	3.4
LVESV (ml)								
2D TTE	13.1	6.2	10.4	5.5	12.2	5.5	9.4	5.1
RT3D TTE	7.1	3.4	5.2	2.8	9.1	2.9	7.3	3.1
LVEF (%)								
2D TTE	15.1	4.2	11.4	5.2	13.2	5.1	10.4	4.9
RT3D TTE	8.1	3.4	6.2	2.6	9.3	3.6	7.1	3.1

NOTE. Absolute values are population mean ± SD of absolute differences between repeated measurements; % values are population mean ± SD of absolute differences of repeated measurements normalized by the average of the two repeated measurements.

Abbreviations: LV, left ventricular; SD, standard deviation; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; 2D TTE, two-dimensional transthoracic echocardiography; RT3D TTE, real-time three-dimensional transthoracic echocardiography.

diseases of various geometric abnormalities including dilated left ventricles, LV volumes and function were comparable using RT3D TTE and CMR with high agreement between both modalities.[37] In the setting of hypertrophic cardiomyopathy, Bicudo et al[30] demonstrated that RT3D TTE is reliable in comparison to magnetic resonance imaging with strong observer agreements for calculating LV mass, volumes, and LVEF. Furthermore, the role of RT3D TTE has established utility in the setting of congestive heart failure and compares well with CMR.[34,36,40]

This study highlights the potential application of RT3D TTE for monitoring LVEF in the breast cancer setting. To our knowledge, our study demonstrated for the first time that RT3D TTE is an accurate and practical method of screening for potential cardiotoxicity among patients with breast cancer receiving adjuvant trastuzumab treatment. Similar to MUGA, which has a small variability in LVEF, RT3D TTE provided accurate LV volumes and LVEF with high agreement to the gold standard of CMR. Ultimately, the choice of imaging technique for the clinician will be based on local availability. Although MUGA and 2D TTE will likely continue to be the modality of choice for serial assessment of LVEF in this adult patient population, RT3D TTE may be a feasible alternative.

Similar to other studies using RT3D TTE, this methodology is affected by the quality of the acoustic windows obtained by echocardiography. Although we were able to perform RT3D TTE in all patients in this study population, there will be patients in whom adequate echocardiographic windows will be difficult to attain due to underlying body habitus. In addition, although post processing of LV volumes and LVEF are time consuming, similar constraints hold true in the analysis of MUGA images. Future improvements in automated detection of endocardial borders in RT3D TTE may facilitate application of this noninvasive method in the breast cancer setting.

As compared with conventional MUGA, RT3D TTE is a feasible, accurate, and reproducible alternate imaging modality for the serial monitoring of LVEF in patients with breast cancer receiving chemotherapy and adjuvant trastuzumab therapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Jonathan Walker, Davinder S. Jassal
Administrative support: Davinder S. Jassal
Provision of study materials or patients: Davinder S. Jassal
Collection and assembly of data: Jonathan Walker, Navdeep Bhullar, Nazanin Fallah-Rad, Matthew Lytwyn, Mehrdad Golian, Tielan Fang, Davinder S. Jassal
Data analysis and interpretation: Jonathan Walker, Navdeep Bhullar, Nazanin Fallah-Rad, Matthew Lytwyn, Mehrdad Golian, Tielan Fang, Arthur R. Summers, Ivan Barac, Iain D. Kirkpatrick, Davinder S. Jassal
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