Adjuvant Trastuzumab Induces Ventricular Remodeling Despite Aerobic Exercise Training

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Abstract

Purpose: To examine the effect of aerobic training in mitigating trastuzumab-mediated left ventricular (LV) remodeling in women with human epidermal growth factor receptor 2 (HER2)-positive breast cancer.

Experimental Design: Seventeen women (53 ± 7 years) with HER2-positive breast cancer did aerobic training during the first 4 months of adjuvant trastuzumab. Peak oxygen consumption and magnetic resonance imaging assessment of LV volumes, mass, and rest and peak (dobutamine stress) ejection fraction were assessed before and after 4 months of trastuzumab.

Results: Participants attended 59% ± 32% of prescribed exercise sessions at 78% ± 6% of peak heart rate. Peak exercise heart rate, systolic and diastolic blood pressure, power output, and oxygen consumption were not different after training (all *P*-values > 0.05). Exercise adherence predicted change in peak oxygen consumption ($r = 0.77$; $P = 0.000$). Resting end-diastolic (pre: 120 ± 23 mL versus post: 133 ± 16 mL) and end-systolic volumes (pre: 44 ± 12 mL versus post: 55 ± 11 mL) and mass (pre: 108 ± 21 g versus post: 114 ± 18 g) increased, whereas ejection fraction (pre: 64% ± 4% versus post: 59% ± 4%) decreased from baseline to post-intervention (all *P*-values < 0.05). Peak ejection fraction was lower after 4 months (pre: 79 ± 4 versus post: 76 ± 6%; $P = 0.087$).

Conclusion: Initiation of adjuvant trastuzumab therapy is associated with LV cavity dilation and reduced ejection fraction despite aerobic exercise training. The long-term consequences of trastuzumab-induced LV remodeling and the means to prevent LV dysfunction require further study.

Approximately 20% of newly diagnosed invasive breast cancers have amplification of the human epidermal growth factor receptor type 2 (HER2; refs. 1, 2). Randomized trials have shown that the addition of trastuzumab (Herceptin), a humanized monoclonal antibody targeting the extracellular domain of HER2, to standard chemotherapy is associated with substantial improvements in disease-free survival and overall survival in women with HER2-positive early breast cancer (3–5). Trastuzumab, however, causes heart failure and asymptomatic decline in left ventricular (LV) systolic function in 0.4% to 4.1% and 3% to 18% of women, respectively (4–6).

The mechanisms of trastuzumab-associated LV dysfunction are incompletely understood. Because ErbB2 signaling plays a pivotal role in maintaining normal LV morphology and function (7, 8), ventricular remodeling, the process in which the LV cavity enlarges and ejection fraction deteriorates, could result from inhibition of this pathway. Indeed, preclinical studies showed that ErbB2 conditional mutant mice displayed LV remodeling features common to dilated cardiomyopathy (7, 8). No study has assessed the effects of adjuvant trastuzumab on LV remodeling in humans; although many report ejection fraction, none have measured and reported LV structural and functional changes. Because LV remodeling precedes clinical heart failure (9, 10), interventions that reverse this process may prevent trastuzumab-mediated systolic dysfunction or heart failure. Our group previously showed that aerobic training can reverse LV remodeling in clinically stable heart failure patients (11). We investigated the effect of aerobic training on LV remodeling among women undergoing trastuzumab treatment for HER2-positive early breast cancer. We hypothesized that aerobic training would prevent trastuzumab-mediated LV remodeling.

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Translational Relevance

A short course of trastuzumab is associated with left ventricular cavity dilation and decreased systolic function despite aerobic training. Future studies are required to determine the full time course of ventricular remodeling during trastuzumab therapy as well as the role that antiremodeling therapies may play in preventing it from occurring.

Materials and Methods

Setting and participants. Consecutive patients at the Cross Cancer Institute, Edmonton, Canada with HER2-amplified or HER2-overexpressed resected invasive breast cancer were screened for this study. Eligible women were ≥18 y of age and had pre-trastuzumab ejection fraction ≥50% by radionuclide angiography. Women were ineligible if they were medically unsuitable for chemotherapy or trastuzumab, had an abnormal exercise stress test, or had preexisting cardiac disease. Ethics approval was obtained from the University of Alberta Biomedical Panel and the Alberta Cancer Board, and written informed consent was obtained before study participation.

Design and procedures. With the use of a single group design, eligible participants were identified at multidisciplinary new-patient clinic visits, and interested participants did the following tests immediately before beginning trastuzumab and after 4 mo of trastuzumab therapy.

Cardiopulmonary exercise test. The cardiopulmonary exercise test was done on an electrically braked cycle ergometer. The initial power output was set at 15 W and increased by 15 W every 2 min. During the test, heart rate, blood pressure, rate of perceived exertion, and expired gas analysis were measured in accordance with the recommendations of Jones et al. (12). The highest oxygen consumed over a 1-min period was used as the peak oxygen consumption score. Healthy, age-predicted peak exercise heart rate and oxygen consumption values were determined with the use of standard equations (13, 14).

Assessment of LV volumes, mass, and systolic function. Magnetic resonance imaging assessment of LV volumes, mass, and ejection fraction was done with a 1.5 Tesla Magnetom Sonata scanner (Siemens Medical Solutions). Steady-state free precession cine techniques were used to acquire parallel, 8-mm-thick short-axis slices (plus a 2-mm gap) throughout the LV to quantify end-diastolic and end-systolic volumes at the endocardial and epicardial surfaces with the use of standard post-processing software (Syngo MR; Siemens). Heart rate and blood pressure were monitored during this test. LV mass was determined by the product of myocardial density and myocardial volume (15), and ejection fraction was calculated as: end-diastolic volume - end-systolic volume/end-diastolic volume. After resting measures were acquired, dobutamine was infused at 10, 20, and 40 μg/kg/min for 5 min per stage until 85% of peak heart rate was achieved. If target heart rate was not reached, then atropine (0.5 to 1 mg) was given.

Aerobic training intervention. Supervised aerobic training was done 3 d per week during the initial 4 mo of trastuzumab therapy. Specifically, after a 5-min warm-up period, participants exercised on a cycle ergometer for 30 to 60 min at a heart rate equal to 60% to 90% of peak oxygen consumption. This was followed by a 5-min cool-down period. All exercise training sessions were supervised by an exercise physiologist.

Adjuvant trastuzumab and chemotherapy regimens. Trastuzumab was given i.v. at 3 weekly intervals with an initial dose of 8 mg/kg followed by 6 mg/kg. The choice of adjuvant chemotherapy regimen was at the discretion of the treating physician. The treatment plans were (*a*) 100 mg/m^2 fluorouracil, 100 mg/m^2 epirubicin, and 500 mg/m^2 i.v. cyclophosphamide every 3 wk for six cycles, or 60 mg/m^2 doxorubicin and 600 mg/m^2 i.v. cyclophosphamide every 3 wk for four cycles followed by trastuzumab (n = 3); (*b*) anthracycline regimen (as above) for four cycles followed by 100 mg/m^2 i.v. docetaxel every 3 wk for four cycles, with initiation of trastuzumab with the first administration of docetaxel (n = 6); or (*c*) 75 mg/m^2 i.v. docetaxel with carboplatin area under the curve 6 i.v. every 3 wk for six cycles, with trastuzumab starting with the first administration of chemotherapy (n = 8).

Statistical considerations. The change in outcome measures from baseline to 4 mo was determined with the use of paired t tests. Logistic regression was done to examine the effect that prior anthracycline therapy had on LV remodeling (change in resting LV volumes, mass, ejection fraction) and peak oxygen consumption. Multiple regression analysis was done to determine the effect of the trastuzumab dose on LV remodeling. The effect of exercise adherence (number of sessions attended/total number of required sessions) on study end points was also assessed through regression analysis. A P-value of <0.05 was considered significant for all statistical tests.

Results

Participants were recruited from August 2006 to April 2008 (Fig. 1). We screened 191 patients; 47 were deemed eligible, and 21 were recruited to the study. After baseline testing, two participants did not receive trastuzumab and were excluded: one was found to have HER2-negative disease on central retesting, and one had a resting ejection fraction <50%. Two participants withdrew from the study (one only completed the baseline cardiopulmonary exercise test, and the other withdrew before completing the aerobic training program due to treatment-induced fatigue). Accordingly, our study sample consisted of 17 participants.

The participant characteristics are shown in Table 1. The participants' mean age and weight were 53 ± 7 y and 78 ± 21 kg, respectively. The American Joint Committee on Cancer version 6.0 stage distribution of participants was as follows: I (n = 5), IIA (n = 6), IIB (n = 4), and IIIA (n = 2). Nine participants had undergone mastectomy. Only two women received left-sided adjuvant radiation: one received chest wall radiotherapy only, and one received chest wall, supraclavicular, and internal mammary fields.

Change in cardiopulmonary function. At baseline, our participants had a normal peak exercise heart rate; however, their peak oxygen consumption (indexed to body mass) was 21% lower than age-matched healthy sedentary women (14). During the aerobic training program, participants attended 59% ± 32% (range, 0% to 100%) of scheduled exercise sessions at 78% ± 6% of baseline peak heart rate.

Aerobic training during trastuzumab therapy was not associated with a change in peak exercise heart rate, systolic blood pressure, diastolic blood pressure, respiratory exchange ratio, power output, or peak oxygen consumption (Table 2). However, exercise adherence predicted change in peak oxygen consumption (r = 0.77; P < 0.001). Similarly, changes in hemoglobin (r = 0.73; P < 0.01) and total 4-month dose of trastuzumab (r = -0.51; P = 0.039) were associated with changes in peak oxygen consumption.

Change in LV volumes, mass, and ejection fraction. There was no statistically significant change in resting heart rate, systolic and diastolic blood pressure, or hemoglobin. Resting LV end-diastolic and end-systolic volumes and mass (pre: 108 ± 21 g versus post: 114 ± 18 g) increased (all P-values < 0.05), whereas ejection fraction significantly decreased during the 4-month

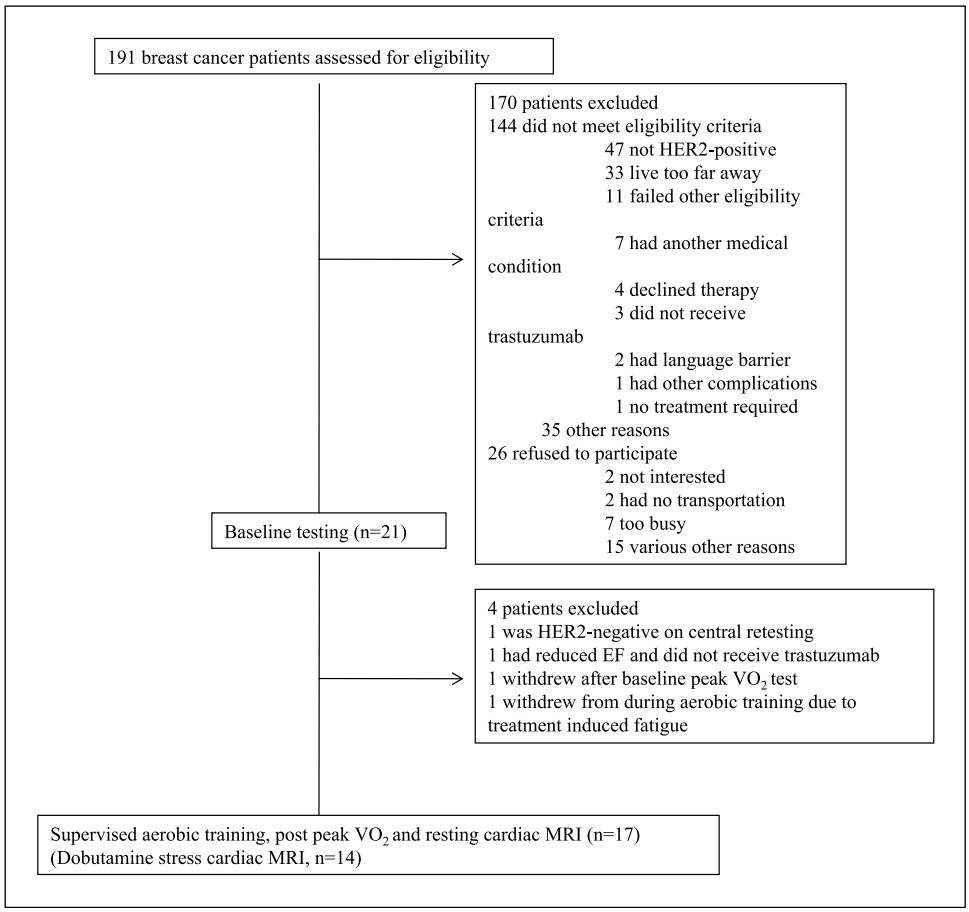

Fig. 1. Flow of participants through the study.

intervention (Fig. 2A). Heart rate during peak dobutamine stress remained unchanged (pre: 145 ± 10 beats per minute versus post: 146 ± 10 beats per minute). Peak end-diastolic and end-systolic volumes were significantly higher, whereas peak ejection fraction was lower after 4 months compared with pre-intervention values (Fig. 2B). LV remodeling measures were not related to prior anthracycline use, total 4-month dose of trastuzumab, or exercise adherence (all *P*-values > 0.05).

Asymptomatic LV dysfunction. Trastuzumab was discontinued in three participants (18%) before the 4-month assessment due to an asymptomatic decline in ejection fraction. Two of these participants were started on an angiotensin-converting enzyme inhibitor. No participant was diagnosed with or had overt heart failure symptoms during the study period.

Discussion

The major new finding of this study is that a short course of trastuzumab is associated with LV cavity dilation and decreased systolic function despite aerobic training. To our knowledge, this is the first study to assess LV remodeling in women with HER2-positive breast cancer during adjuvant trastuzumab and the first to investigate the efficacy of aerobic training to mitigate this effect.

Two recent studies have reported that aerobic training does not improve peak oxygen consumption (16, 17) in women with breast cancer receiving standard adjuvant chemotherapy. We extend these findings by showing that aerobic training does not alter peak oxygen consumption in women with HER2-positive breast cancer during adjuvant trastuzumab. Because the improvement in peak oxygen consumption was directly related to the number of supervised exercise sessions, with favorable changes only occurring when participants attended ≥55% of prescribed exercise sessions, we suspect that our participants attended an insufficient number of sessions for the group, overall, to achieve beneficial training adaptations. Alternatively, failure to increase peak oxygen consumption may also be due to reduced oxygen delivery to the active muscles. Specifically, the reduced hemoglobin, peak exercise heart rate, and peak stress ejection fraction found at the end of the study would result in decreased oxygen delivery and peak oxygen consumption. Indeed, those participants with the greatest increase in hemoglobin also had highest change in peak oxygen consumption. Taken together, our findings suggest that supervised aerobic training can prevent the expected decline in peak oxygen consumption that occurs during the first 4 months of adjuvant trastuzumab provided that participants adhere to the exercise regimen.

Crone et al. (7) and Ozcelik et al. (8) reported that conditional mutant mice with ventricular restricted deletion of ErbB2 exhibited ventricular remodeling, as manifest by a significantly larger LV cavity size (7, 8), decreased wall thickness (7) and systolic function (7, 8), as well as impaired myocardial contractility during peak dobutamine stress (7). We have replicated these findings in humans, by showing that 4 months of adjuvant

Table 1. Participant characteristics

Age (y)	53 ± 7
Height (cm)	164 ± 9
Weight (kg)	78 ± 21
Primary tumor size	
T_1, ≤ 2 cm	8
T_2, 2-5 cm	9
Nodal status	
N_0	8
N_1	3
N_2	5
N_3	1
Type of surgery	
Breast-conserving surgery	8
Mastectomy	9
Heart rate (bpm)	77 ±11
Systolic blood pressure (mmHg)	121 ± 12
Hemoglobin (g/L)	124 ± 13
Smoking status	
Current	3
Ex-smoker	4
Never	10
Diabetic	1
Medications	
Antihypertensive	3
Cholesterol lowering	1
Peak VO_2 (mL/kg/min)	20 ± 4
% Age-predicted	79 ± 18
Peak exercise heart rate (bpm)	168 ± 13
% Age-predicted	98 ± 8

NOTE: Data are mean ± SD; *n* = 17.p.
Abbreviations: bpm, beats per minute; VO_2, oxygen consumption.

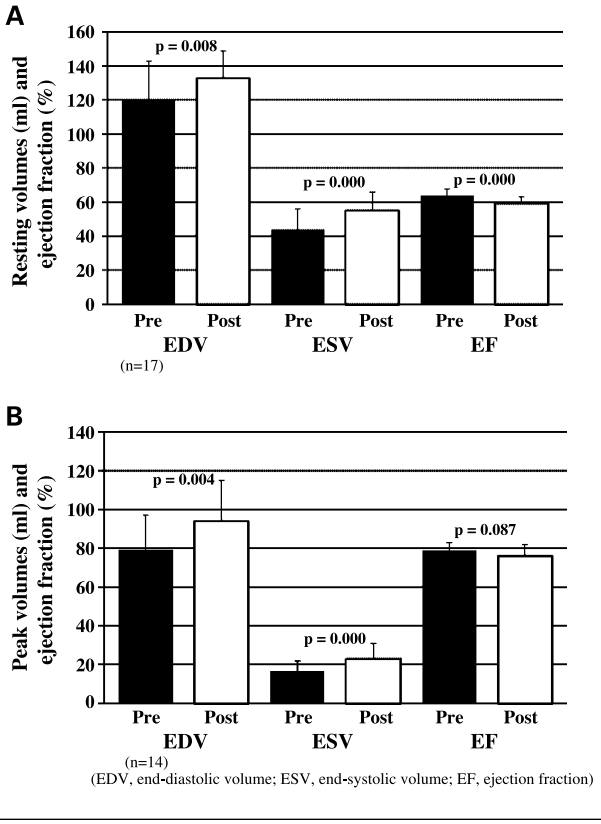

Fig. 2. *A* and *B*, effects of aerobic training during trastuzumab therapy on resting and peak LV volumes and ejection fraction.

trastuzumab results in LV remodeling, even in the setting of concurrent aerobic training. This observation is in marked contrast to our earlier finding that aerobic training can reverse LV remodeling in clinically stable heart failure patients (11). The reason for this discordant finding is uncertain; it may be due to our aerobic training intensity being insufficient as a stimulus to prevent LV remodeling. Whereas Wisloff et al. (18) reported that high-intensity (95% of peak heart rate) aerobic interval exercise was the most effective training regimen to reverse LV remodeling in clinically stable heart failure patients, it is unclear whether women undergoing adjuvant chemotherapy and trastuzumab are able to exercise at a sufficiently high aerobic intensity to attenuate trastuzumab-mediated LV remodeling. Alternatively, it is possible that our participants may need to exercise for a longer duration to prevent LV remodeling; however, this is unlikely because an increase in cavity size and a decline in pump function occurred during 4 months of treatment and were not related to the number of aerobic training sessions attended. Importantly, the remodeling pattern we observed is not due to aerobic training because this form of exercise does not result in a decrease in LV systolic function (at rest or during peak pharmacologic stress; ref. 19).

Table 2. Effects of aerobic training during trastuzumab therapy on cardiorespiratory function during peak cycle exercise

	Pre	Post	*P*
HR (bpm)	168 ± 13	164 ± 16	0.2
SBP (mmHg)	183 ± 23	175 ± 23	0.1
DBP (mmHg)	86 ± 8	81 ± 7	0.08
RER	1.18 ± 0.1	1.20 ± 0.1	0.4
RPE (10 scale)	9 ± 2	9 ± 2	0.7
VO_2 (L/min)	1.51 ± 0.4	1.58 ± 0.3	0.5
VO_2 (mL/kg/min)	19.8 ± 4.2	21.7 ± 6.6	0.2
PO (W)	104 ± 23	104 ± 21	1

Abbreviations: HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; RER, respiratory exchange ratio; RPE, rate of perceived exertion; PO, power output.

The incidence of LV systolic dysfunction associated with adjuvant trastuzumab given to a relatively unselected population in standard practice has not been well studied. Our finding that trastuzumab was discontinued in 18% of participants due to asymptomatic decline in ejection fraction is similar to that reported previously (20). The medium-term and long-term consequences of trastuzumab-mediated LV remodeling are unknown. However, given that LV remodeling precedes clinical heart failure (9) and that heart failure is generally progressive (10), the observed early decline in LV systolic function with trastuzumab may increase the risk of overt heart failure, particularly when coupled with increased hemodynamic load or other cardiac stress (21).

The limitations of our study include the single-group nonrandomized design and lack of a nonexercise control group. Another limitation is that LV remodeling was only assessed during the first 4 months of trastuzumab therapy. Thus, future

studies are required to examine the full time course of LV remodeling as well as the role that antiremodeling therapies, that is, angiotensin-converting enzyme inhibitors (22), angiotensin receptor blockers (23), β blockers (24), and aldosterone antagonists (25), may play in preventing it from occurring. A final limitation is our small sample size. Importantly, cardiac magnetic resonance imaging is the gold standard measure for assessing LV volumes and mass, allowing for clinically meaningful ventricular remodeling changes to be detected with a smaller study sample (26, 27). Indeed, we found significant changes in resting LV volumes, mass, and ejection fraction despite our small sample, which confirms prior preclinical work (7, 8).

In summary, our study shows that initiation of trastuzumab is associated with LV cavity dilation and reduced ejection fraction despite aerobic training. The long-term consequences of trastuzumab-induced LV remodeling and the means to prevent systolic dysfunction require further study.

Disclosure of Potential Conflicts of Interest

Dr. Mackey has received honoraria from the Roche Speakers' Bureau.

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