Adjunctive inspiratory muscle training during a rehabilitation program in patients with breast cancer: an exploratory double-blind, randomized, controlled pilot study.

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Running head: Inspiratory muscle training in breast cancer

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Conflicts of interest

We declare no conflicts of interest.

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Adjunctive inspiratory muscle training during a rehabilitation program in patients with breast cancer: an exploratory double-blind, randomized, controlled pilot study.

ABSTRACT

Objective: To investigate whether inspiratory muscle training (IMT) offered adjunctively to an exercise training program reduces symptoms of dyspnea in breast cancer survivors.

Design: double-blind, parallel-group, randomized controlled trial

Setting: Outpatient rehabilitation program in a university hospital

Participants: Ninety-eight female breast cancer patients who completed adjuvant treatment and subsequently entered cancer rehabilitation were screened for participation. Inclusion criteria were reduced inspiratory muscle strength and/or symptoms of dyspnea. Twenty patients were randomly assigned to an intervention group (n=10) or a control group (n=10).

Intervention: Both groups received a 3-month exercise training program in combination with either IMT (intervention) or sham-IMT (control).

Main outcome measure(s): Changes in dyspnea intensity perception (10-point Borg scale) at comparable time points (isotime) during constant-workrate cycling was the primary outcome. Secondary outcomes included changes in respiratory muscle function, exercise capacity, and changes in symptoms of dyspnea during daily life (transitional dyspnea index - TDI).

Results: The intervention group achieved a larger reduction in exertional dyspnea at isotime in comparison with the control group (-1.8 points; 95%CI, -3.7 to 0.13; p=0.066). The intervention group also exhibited larger improvements in dyspnea during daily life (TDI score, +2.9 points; 95%CI, 0.5 to 5.3; p=0.022), and improved both respiratory muscle endurance (+472s; 95%CI, 217 to 728; p=0.001) as well as cycling endurance (+428s, 95%CI, 223 to 633; p=0.001) more than the control group.

Conclusion: Due to the limited sample size all obtained findings need to be interpreted with caution. The study offers initial insights into the potential of adjunctive IMT in selected breast cancer survivors. Larger multicenter studies should be performed to further explore the potential role and general acceptance of this intervention as a rehabilitation tool in selected patients after breast cancer treatment.

Keywords: Breast neoplasm; Breathing exercises; Dyspnea; Exercise; Muscle strength; Physical therapy; Randomized Controlled Trial; Rehabilitation

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List of abbreviations

BDI	Baseline Dyspnea Index
CI	Confidence interval
IMT	Inspiratory muscle training
Pemax	Maximal expiratory pressure
Pimax	Maximal inspiratory pressure
MID	Minimal important difference
TDI	Transitional Dyspnea Index

Breast cancer is the most prevalent type of cancer in women worldwide.[1] As a result of early diagnosis and advanced treatments, the number of breast cancer survivors increases. [2] However, up to 90% of breast cancer survivors experience long-term impairments following treatment. [3] These may include decreased strength, aerobic capacity, as well as fatigue. [3–5]

Additionally, dyspnea, marked by a sensation of breathing discomfort (especially on physical exertion) is a frequently reported symptom in (breast) cancer survivors. [6–9] Potential causes of exertional dyspnea could be impairments in pulmonary function and respiratory muscle function. [6] Kluthcovsky et al. studied cancer-related fatigue in breast cancer survivors and observed an association between fatigue and dyspnea. [5] These authors noticed that patients often used the terms 'fatigue' or 'exhaustion' when referring to dyspnea. As a result, symptoms of dyspnea remain often undiagnosed and frequently untreated. [5] Furthermore, respiratory muscle function is often not assessed, leaving the association between respiratory muscle function and dyspnea underexplored. Both limb and respiratory muscle strength is often decreased in these patients. [6,7,9] Moreover chest wall compliance is frequently reduced after cancer treatments, which increases the load on the respiratory muscles, especially during exercise. [6,10] Impairments in pulmonary function are also common and will further increase respiratory muscle work during exercise. [11]

Exercise training programs are effective in improving physical fitness and reducing fatigue after breast cancer treatment. [4,12,13] These programs typically consist of a combination of aerobic and resistance exercises. [12,13] Implementing specific inspiratory muscle training (IMT) adjunctively to exercise training programs has previously resulted in larger improvements in respiratory muscle function and dyspnea in patients with chronic respiratory disease. [14,15]

There is currently however no evidence for the effects of adjunctive inspiratory muscle training added to an exercise training program in breast cancer survivors. Therefore, this study aimed to evaluate the effectiveness of adjunctive IMT in symptomatic breast cancer survivors with impaired respiratory muscle function. We hypothesized that adjunctive IMT would result in larger improvements in symptoms of dyspnea compared to an exercise training program offered without adjunctive IMT.

Methods

Trial design

The design of the study is a double-blind, parallel-group, randomized controlled trial. Patients who agreed to participate were randomized into an intervention group or a control group at a 1:1 ratio. Both groups participated in an exercise training program, but only the intervention group received additional respiratory muscle training. The control group received a sham treatment. This study was approved by the local ethics committee (reference no. MP003175).

Participants

Participants were recruited in the local university hospitals, Department of Physical Medicine and Rehabilitation between May 2018 and January 2019. Stable breast cancer patients who completed adjuvant treatment and were as a result allowed to participate in the offered rehabilitation program, were eligible to participate in the study. Additionally, patients had to exhibit reduced maximal inspiratory pressure ([PImax] below predicted normal value), indicative of impaired respiratory muscle function or symptoms of dyspnea in daily life (score of ≤9/12 on Baseline Dyspnea Index [BDI]) to remain eligible. [16] Exclusion criteria were the presence of underlying chronic cardiac or respiratory disease that might have contributed to symptoms of dyspnea. Subjects had to provide written informed consent before participation in accordance with the Declaration of Helsinki.

Group allocation was conducted using sealed opaque envelopes in random block sizes of 4 and 6 (order unknown to investigators) according to an established method. [17] Participants and outcome assessors were blinded to group allocation. Therapists offering the exercise training program or the adjunctive intervention were not blinded to group allocation.

Intervention

Following baseline measurements, a 3-month intervention program was started. Both groups followed the identical exercise training program. Additionally, the intervention group performed two IMT sessions per day, consisting of 30 breaths against a resistance of 50% of their PImax, 4-5 minutes per session, for 7days/week, for 12 weeks, using an electronic

tapered flow resistive loading device (POWERbreathe®KHP2) [a]. This device enables constant monitoring of training data and ensures higher performed total work during training sessions compared to other methods. [18] Patients were instructed to fill their diaries by copying stored data from the device. Total work and training load during the training program were subsequently extracted from the diaries. Supervised training sessions, including measurements of PImax, were planned to be performed on-site every two weeks after the exercise training sessions of the rehabilitation program. Furthermore, training loads were increased at these visits to maintain the external load at ~50% of PImax at respective measurements throughout the study period. Ratings of perceived inspiratory effort on a modified Borg scale (10-point Borg scale of 4-5 out of 10) were used to support decisions on increasing training load. The control group completed the same amount of IMT sessions but trained at ~10% of their initial PImax. This training load remained unchanged to avoid training stimuli. To increase adherence, both treatments were presented as active interventions. The training was presented as 'strength training' in the intervention group, and as 'endurance training' in the control group. Participants in the control group were able to follow the active treatment after the completion of the study. All assessments except for the maximal cardiopulmonary exercise test and the lung diffusion capacity were repeated after the intervention period.

Assessments

Table S1 (supplementary material) presents an overview of all outcome measurements. An overview of the study design is depicted in Table S2 (supplementary material).

Pulmonary function

Full pulmonary function testing including spirometry, lung volumes and diffusion capacity was performed at the department of pneumology according to current ERS guidelines. [19–21] Reference values from the Global Lung Function Initiative were used to interpret the outcomes. [22,23]

Respiratory Muscle Function

Respiratory muscle function was evaluated by measuring the maximal inspiratory pressure and expiratory pressure (PImax and PEmax respectively) using a microRPM Pressure Meter [b] and respiratory muscle endurance (POWERbreatheKH2) [a] in accordance with international guidelines. [24] During assessments of maximal mouth pressures, patients had to perform maximal quasi-static inspiratory and expiratory efforts starting from either residual volume or total lung capacity for the measurements of PImax and PEmax, respectively. The maximum one-second plateau pressure of the three best maneuvers that differed by less than 10% was retained and compared with reference values. [19] The endurance breathing test was conducted with an established protocol. [24] After standardized instructions, patients were instructed to breathe against a constant submaximal external resistance until task failure. [24] Patients were encouraged to perform as many forceful and deep inhalations and complete exhalations in the device as possible. Breathing duration, number of breaths and total external work performed during the protocol were registered.

Symptoms of Dyspnea

A modified Borg scale (0-10) was used during the endurance breathing test, constant-workrate cycling test (primary outcome) and 6-min walk test to assess the intensity of dyspnea throughout the tests. The Multidimensional Dyspnea Profile scale was used to assess dyspnea by evaluating overall breathing discomfort at the end of the constant-workrate cycling test. [25] To measure the change in the severity of dyspnea during daily life we employed the BDI and the corresponding Transitional Dyspnea Index (TDI). The BDI/TDI consist of three different categories namely functional impairment, the magnitude of task and magnitude of effort. [26] All categories were rated in five grades from 0 (severe) to 4 (unimpaired). [26] Scores were added up to obtain a general score, ranging from 0 to 12 representing the severity of dyspnea at baseline. Therefore, the lower the score, the worse the severity of dyspnea. [26] The TDI was subsequently used to quantify the change in dyspnea from baseline. Changes in dyspnea were rated by seven grades, ranging from -3 (major deterioration) to +3 (major improvement) for each category. [26] The change scores on all categories were added up to give a general image of the change in dyspnea during daily life, ranging between -9 and +9. The modified Medical Research Council dyspnea scale (mMRC) rates dyspnea intensity on a score between 0 (unimpaired) and 4 (severe) in terms of breathing possibility during daily activities. [27] This dyspnea scale and the BDI/TDI explore dyspnea intensity differently, hence they complement each other perfectly. [28]

Exercise Capacity

Assessment of maximal exercise capacity was performed during the initial screening procedure through a cardiopulmonary exercise test, which was performed on an electronically-braked cycle ergometer (Ergoline 800s) [c] with detailed metabolic and cardiopulmonary measurements (Vs229d) [c]. Endurance exercise capacity was assessed using constant-workrate cycling against a workload (Watts) of 80% of the peak work rate achieved during the cardiopulmonary exercise test. Before the constant-workrate cycling test, forced vital capacity and maximal voluntary ventilation were assessed by spirometry. Throughout the test, heart rate, oxygen saturation, minute ventilation, as well as other breathing and exercise parameters were recorded. Secondary parameters were extracted as 30-s averages which were subsequently used to determine values at a standardized timepoint (isotime) and peak exercise. In addition, minute by minute intensity of dyspnea and leg discomfort was evaluated using a modified Borg scale (0-10). [29] Blood pressure and inspiratory capacity were measured every two minutes. In addition, functional exercise capacity was evaluated using a 6-min walk test. [30] Before and after the test, patients were asked to rate leg discomfort and symptoms of dyspnea on a modified Borg scale (0-10). [29] Additionally, the walking distance was measured as well as oxygen saturation and heart rate throughout the test.

Peripheral Muscle Strength

Handgrip strength was measured using handheld dynamometry. Patients had to keep the elbow of the tested side in 90 degrees of flexion and a neutral position of pro-and supination while performing the test. Both sides were tested three times and the maximal value was retained. [31,32]

Statistical Analyses

A sample size of 10 patients in the intervention group and 10 patients in the control group was required to detect a between-group difference of 1.3 units (SD: 1) for the change in

dyspnea intensity rating on a modified Borg dyspnea scale (0-10) between pre-and post-intervention assessments at isotime during the constant-workrate cycling test with a statistical power (ß) of 80% and a risk for a type I error (α) <5%. All data were analyzed following the intention-to-treat principle. Statistical procedures were performed using SPSS version 27.0 [d]. Post-intervention between-group differences were compared adjusting for baseline differences in an analysis of covariance and adjusted mean differences between groups are reported alongside their 95% confidence interval (CI). [33] In addition, paired samples t-tests or Wilcoxon's tests were applied to examine within-group differences before and after treatment. To further investigate within-group changes from pre- to post-intervention at different time points during the constant-workrate cycling test, two-way repeated-measures analyses of variance were conducted. Alongside these results, partial eta squared values are reported as a measure of effect size. Furthermore, exploratory correlates of training outcomes with changes in respiratory muscle function and symptoms of dyspnea were investigated using linear bivariate correlation tests.

Results

Study population

Figure 1 displays the flow of participants throughout the different phases of the study. Twenty stable breast cancer patients were enrolled. One patient in the control group was not willing to complete the exercise training program nor the sham intervention and was subsequently dropped out of the study. Additionally, another patient from the control group did not follow the sham intervention but did perform pre-and post-measurements and was subsequently conserved in the analyses. Finally, the exercise and breathing pattern data of a patient in the intervention group was missing during the post-intervention constant-workrate cycling test due to calibration issues.

Baseline characteristics

Table 1 presents an overview of the baseline characteristics. All participants were females aged between 36 and 69 and except for PImax (mean difference, -17cmH_2O; 95%CI, -30 to -4; p=0.015), no relevant baseline differences were observed between groups. This was also true for the different adjuvant treatments that patients received. These data are presented in Figure 2.

Respiratory muscle training

Table S3 (supplementary material) presents an overview of the mean training data for each group. Adherence with prescribed training sessions was 63 ± 18% and 41 ± 28% in the intervention and control group, respectively (total sessions performed, 105 ± 49 vs 68 ± 37). Total work performed throughout the training intervention was higher in the intervention group compared to the control group (21670J ± 12266 vs 2813J ± 1781; 95%CI, -27615 to -10099; p= 0.002). In the intervention group, training resistance started at 47 ± 9% of their baseline PImax in the first week of training and ended at 59 ± 16% in the last week of training. Weekly mean inspiratory resistance (%Pimax baseline) is shown in Figure 3

Main outcomes

After the intervention period, dyspnea scores at isotime were significantly lower only in the intervention group, while between-group differences did not reach statistical significance (p=0.066) in analogy with between-group differences in MDP scores of dyspnea unpleasantness recorded at peak exercise (p=0.091; Table 2). The intervention group exhibited a significantly larger increase in constant-workrate endurance cycling time compared to the control group (Table 2 and Figure 4). Reductions in sensations of leg fatigue and minute ventilation during exercise were comparable between groups (Table 2 and Figure 3). Changes in breathing pattern were also comparably small in both groups (Table 2 and Figure S1). The scores on the transitional dyspnea index (TDI) questionnaire increased significantly in the intervention group compared to the control group (p=0.022, Table 2). As displayed in Table 2, Pimax increased from -74cmH_2O ± 11 to -93cmH_2O ± 19 in the intervention group and from -91cmH_2O ± 16 to -98cmH_2O ± 13 in the control group (unadjusted mean difference, 12cmH_2O; 95% CI, -5 to 30; p=0.164; d=0.668). Furthermore, there was a significant and very large (d= 1.962) increase in respiratory muscle endurance time in favor of the intervention group (Table 2). Improvements in functional exercise

capacity as assessed by the 6-min walk distance and changes in handgrip strength were comparable between groups (Table 2).

External work performed during the respiratory muscle training intervention correlated significantly with changes in exercise time during the constant-workrate cycling test (r=0.785, p<0.001), changes in respiratory muscle endurance time (r=0.544, p=0.020), and TDI scores (r=0.697, p=0.001). Furthermore, changes in training load significantly correlated with changes in Pimax (r=-0.558, p=0.020).

Discussion

This study investigated the effects of adjunctive IMT on respiratory muscle function, symptoms of dyspnea and exercise capacity in selected breast cancer survivors. We observed relevant additional improvements in respiratory muscle function, endurance cycling time as well as symptoms of dyspnea during daily activities following adjunctive IMT. Moreover, this study implemented a sham treatment, effectively blinding the control group and accounting for placebo treatment effects in the process.

Respiratory muscle endurance improved considerably more (adjusted mean difference, +472s; 95% CI, 217 to 728) following adjunctive IMT in contrast to the sham control intervention. This constitutes a very large effect size (d=1.96). Average improvements in Pimax in the intervention group of 19cmH20, exceeded previously established minimal important differences (MID) of changes in inspiratory muscle strength in heart failure (MID, 11.4cmH_20) [34] and COPD (MID, 17.2cmH_20) [35]. This did however not result in a significant difference between groups, despite an unadjusted difference of 12cmH_2O (95% CI, -5 to 30; p=0.164) and a moderate to large effect size (d=0.668). Improvements in Pimax in our control group were larger compared to studies in COPD lacking a sham control intervention (7.4cmH_20 ± 4.9 vs 1.3cmH_20 ± 0.9) [36]. This together with the relatively small sample size might have contributed to this observation.

We hypothesized that adjunctive IMT would reduce symptoms of exertional dyspnea and increase exercise capacity. There was evidence for a reduction of self-reported dyspnea symptoms during daily life as shown by the significant improvement on the TDI questionnaire in the intervention group compared to the control group. Clinical relevance of this finding is illustrated by comparing the adjusted difference (2.9 points) with the

previously established MID of 1 point. [38] Although there was no significant between-group difference in change scores for the perceived intensity of dyspnea at comparable time points during the constant-workrate cycling test, a statistically significant reduction within the intervention group was observed
(Figure 3). The adjusted difference in dyspnea reduction of -1.8 points on the modified Borg scale (0-10) scores at isotime seems clinically relevant as compared to the MID of 1 point established in previous work. [37]

Improvements in endurance exercise capacity during a constant-workrate cycling test showed a substantial between-group difference (adjusted difference, 428s; 95%CI, 223 to 633; p=0.001). This additional improvement largely exceeds the MID of 46-105 seconds previously established in patients with chronic lung disease. [15]

While both groups showed relevant improvements no between-group difference was observed in the 6-min walk distance (adjusted mean difference, -5m; 95% CI, -45 to 35). The lack of between-group differences on this outcome provides further evidence that constant-workrate tests might be more suitable when investigating the effects of adjunctive interventions. [15,39] Regarding handgrip strength, no changes were observed, indicating the specificity of IMT to impact respiratory but not peripheral muscles.

Study limitations

In this study, training adherence was lower (62.7% and 40.7% for intervention and control groups respectively) compared to previous studies using comparable IMT protocols. [15,40] Due to limited staffing and larger physical distance between the rehab center and the hospital, we offered less regular supervised sessions than initially planned (every two weeks). Nevertheless, the average total number of training sessions performed (105±49 in the intervention group vs 68±37 in the control group) was considerable and comparable to previous studies. [15,40] However, for future research we recommend implementing regular supervised sessions to optimize treatment adherence and take full advantage of IMT programs.

Conclusion

Due to the limited sample size all obtained findings need to be interpreted with caution. The study offers initial insights into the potential of adjunctive IMT in selected breast cancer survivors. Larger multicenter studies should be performed to further explore the potential role and general acceptance of this intervention as a rehabilitation tool in selected patients after breast cancer treatment.

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Suppliers

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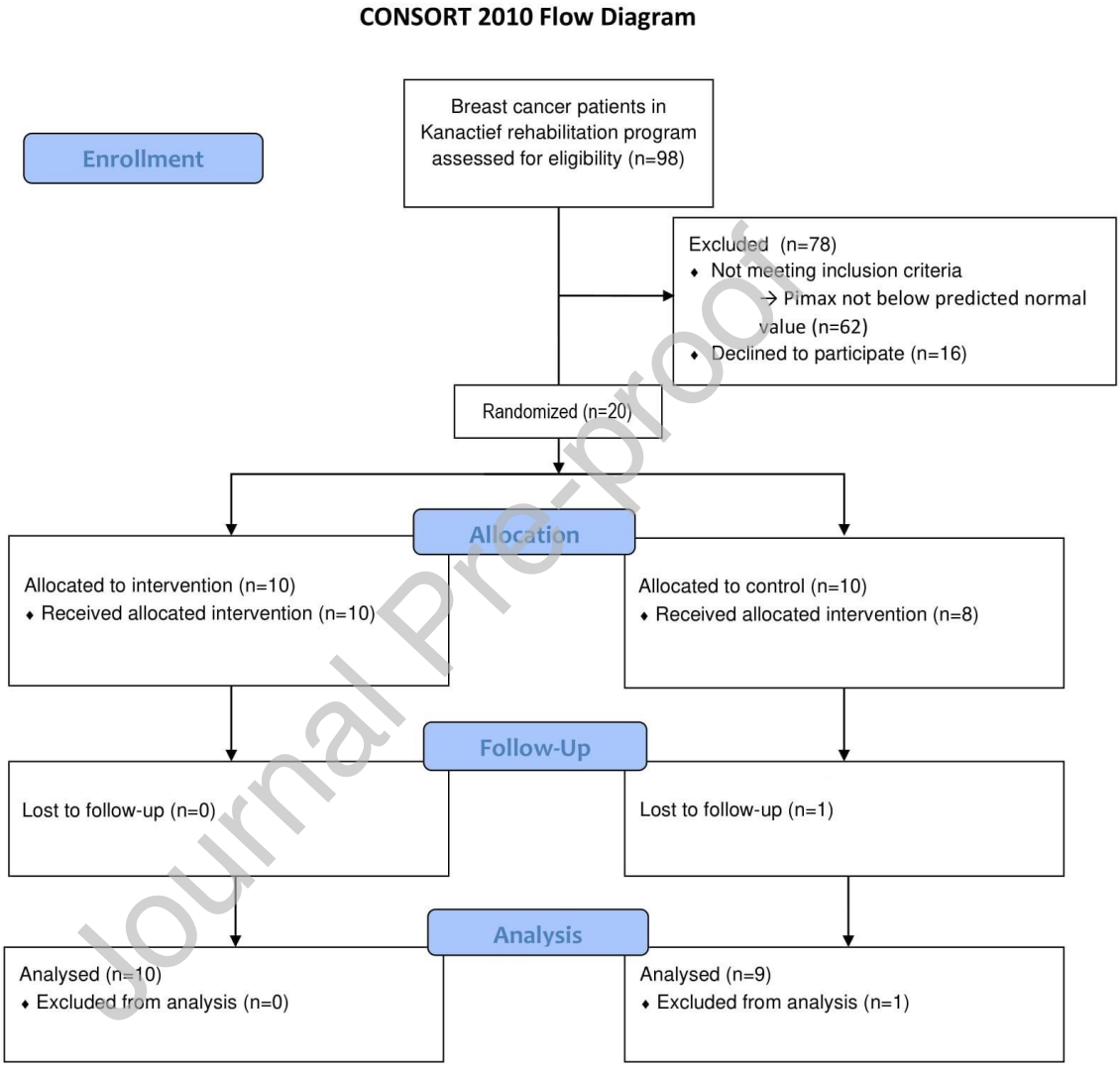
b. BD, Carefusion, 3750 Torrey View Court, San Diego, CA 92130, US

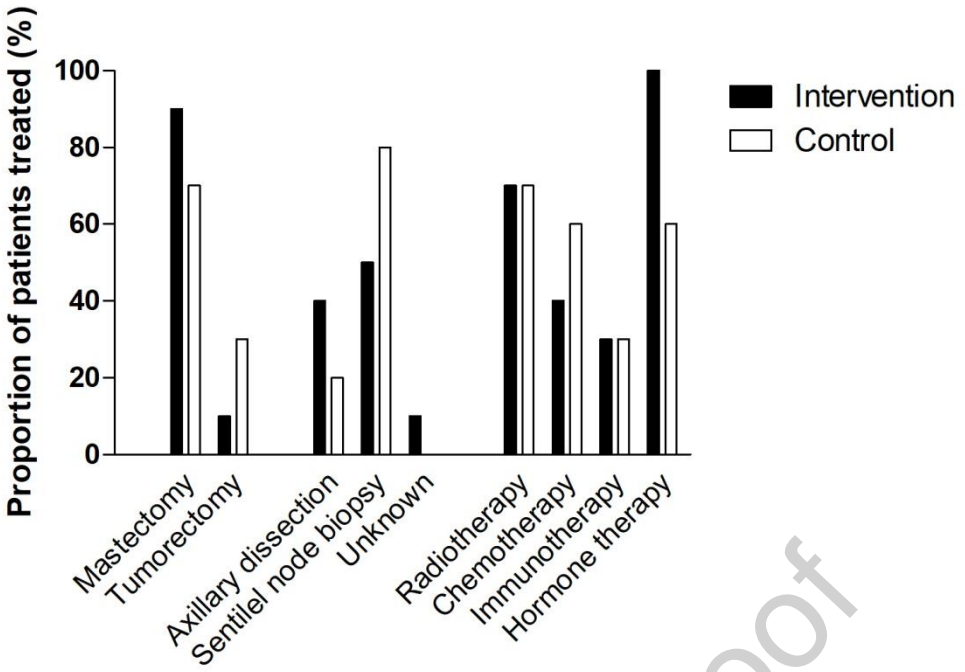
c. SensorMedics Corporation, 22705Savi Ranch Pkwy, Yorba Linda, California, US

d. IBM Corp, 1 Orchard Rd, Armonk, NY 10504, US

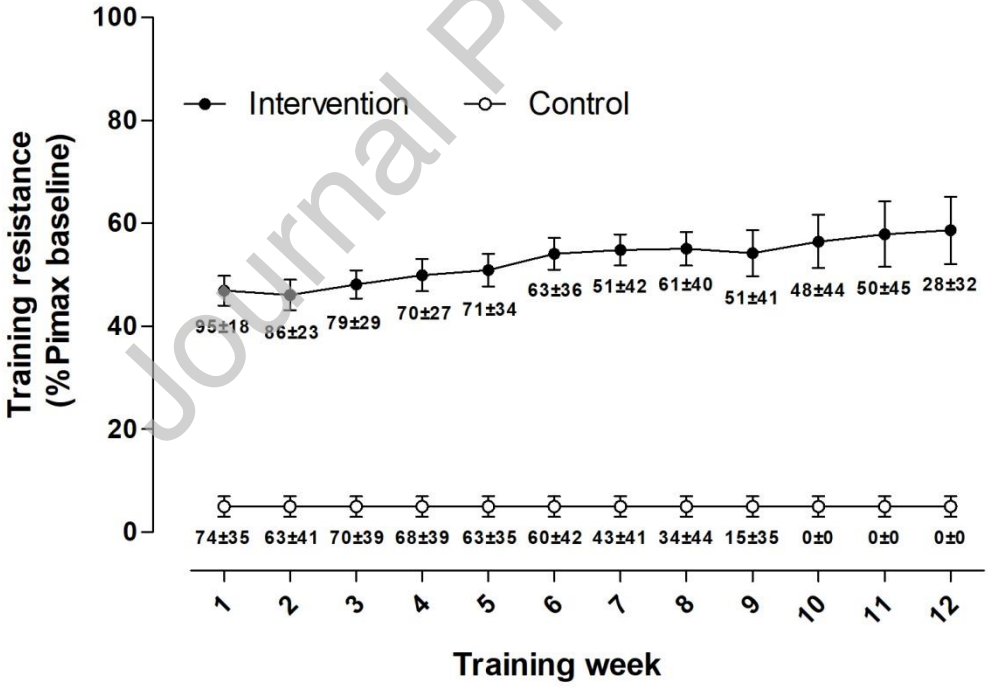
Figure captions



1) Figure 1 Consort flow diagram displaying the progress of participants through the phases of the study.

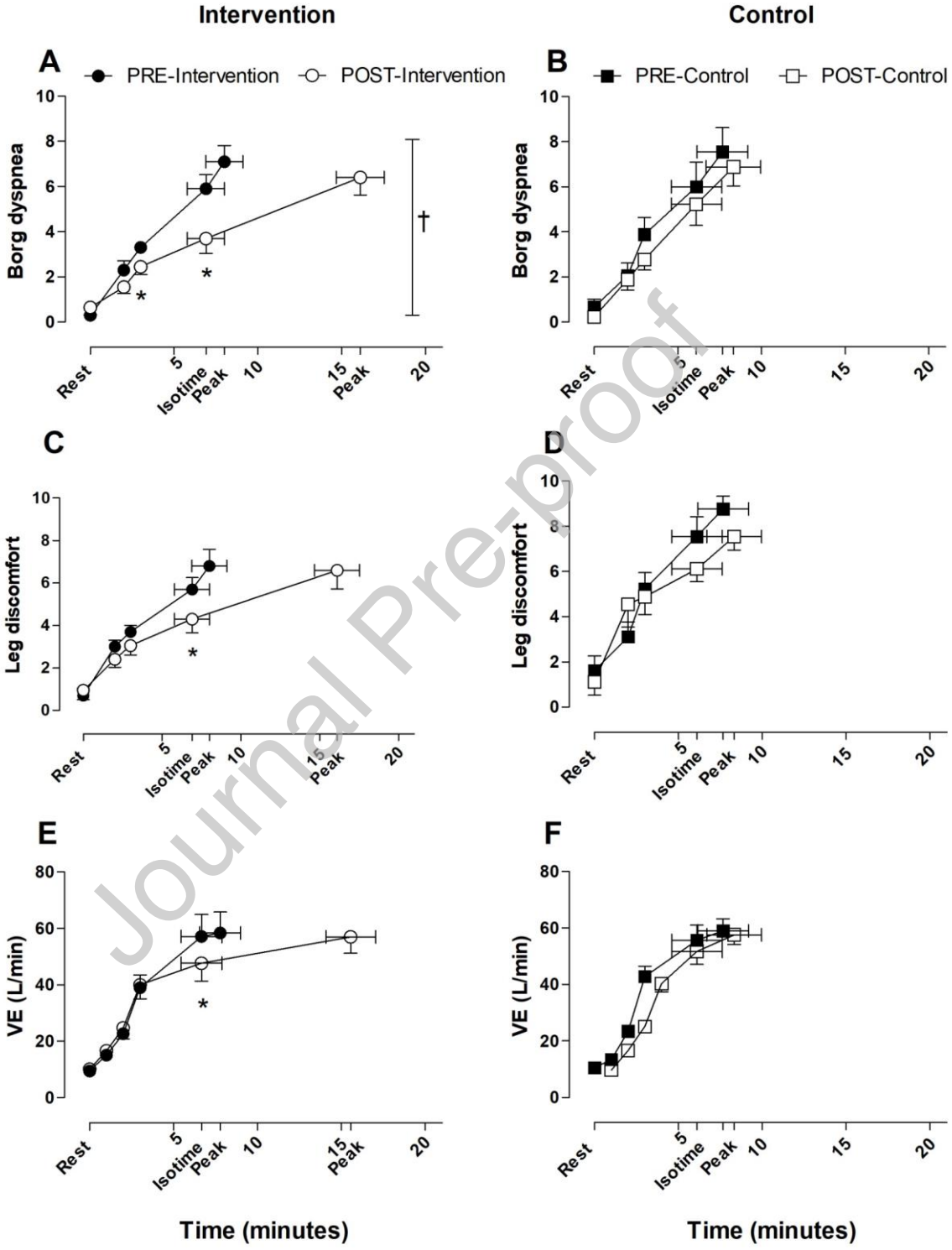


2) Figure 2 Adjuvant treatments received by study participants.



3) Figure 3 Mean inspiratory resistance during weekly inspiratory muscle training sessions throughout the intervention period. Training resistance is expressed as %baseline maximal inspiratory pressure measured from residual volume. Per cent

adherence to prescribed training sessions is displayed under weekly averages of training resistance. Values are means ± SE.



4) Figure 4 Dyspnea intensity, sensation of leg discomfort, and ventilation (VE) assessed during constant-workrate cycling tests. Pre-and-post active intervention measures of

(A) dyspnea intensity, (C) leg discomfort, and (E) VE. Pre-and-post control intervention measures of (B) dyspnea intensity, (C) leg discomfort, and (E) VE. Values are means ± SE. †Two-way repeated measures ANOVA: P = 0.01 for pre-to post-assessment effect. *Paired-samples t-test: P < 0.05, post- vs. preintervention.

Table 1. Baseline characteristics

	Intervention (n=10)	Control (n=10)
Age, years	*51±5*	*55±9*
Height, cm	*165±6*	*168±5*
Weight, kg	*71±14*	*75±15*
MEDICAL TREATMENTS		
TYPE OF BREAST SURGERY		
Mastectomy (% received)	*90*	*70*
Tumorectomy (% received)	*10*	*30*
TYPE OF AXILLARY SURGERY		
Axillary lymph node dissection (% received)	*40*	*20*
Sentinel node biopsy (% received)	*50*	*80*
Unknown (% received)	*10*	*0*
TYPE OF ADJUVANT TREATMENT		
Radiotherapy (% received)	*70*	*70*
Chemotherapy (% received)	*40*	*60*

Immunotherapy (% received)	*30*	*30*
Hormone therapy (% received)	*100*	*60*
PULMONARY FUNCTION		
FVC, L (%pred)	*3.7±0.5 (105±12)*	*3.5±0.6 (101±14)*
FEV1, L (%pred)	*2.9±0.4 (103±12)*	*2.8±0.7 (100±18)*
FEV1/FVC, %	*78.8±6.7*	*78.7±6.6*
RV, L (%pred)	*1.9±0.2 (107±12)*	*2.3±0.3 (121±20)*
FRC, L (%pred)	*3.1±0.4 (112±15)*	*3.2±0.5 (114±15)*
TLC, L (%pred)	*5.7±0.6 (111±10)*	*5.9±0.7 (112±13)*
Tlco, mmol/min/Kpa (%pred)	*6.3±0.9 (82±11)*	*6.4±0.8 (86±11)*
RESPIRATORY MUSCLE FUNCTION		
PImax, cmH_2O (%pred)	*-74±11 (69±10)*	*-91±15 (91±15)*
PEmax, cmH_2O (%pred)	*139±27 (77±15)*	*145±26 (85±14)*
Endurance breathing time, s	*209±79*	*266±126*
External resistance, %Pimax	*62±10*	*61±7*
SYMPTOMS OF DYSPNEA		
BDI, 0-12	*8.4±2.4*	*8.6±1.9*
MDP, 0-10	*6.7±1.8*	*6.4±2.9*
mMRC, 0-4	*0.8±0.4*	*1.0±0.7*
EXERCISE CAPACITY		
MAXIMAL EXERCISE CAPACITY		
VO2max, L/min (%pred)	*2.0±0.4 (91±19)*	*2.0±0.4 (97±27)*

Load, W	*123±28*	*118±30*
MaxHR, 1/min (%pred)	*158±13 (93±6)*	*151±17 (94±11)*
CONSTANT WORKRATE CYCLING		
Duration, min	*7.0±3.3*	*6.2±4.5*
Load, W (% peak work rate)	*98±20 (80±4)*	*94±22 (80±2)*
FUNCTIONAL CAPACITY		
6MWD, m (%pred)	*557±92 (84±14)*	*553±105 (86±18)*
PERIPHERAL MUSCLE STRENGTH		
Handgrip strength, N (%pred)	*255±53 (94±19)*	*248±29 (102±21)*

Data are presented as mean (SD). %Pimax, percentage of the mean inspiratory load relative to the Pimax; %pred, percentage of the predicted normal value; 6MWD, 6 minutes walking distance; BDI, baseline dyspnea index; cmH_2O, centimeter of water; FEV1, forced expiratory volume in 1 second; FRC, functional residual capacity; FVC, forced vital capacity; MaxHR, maximal heart rate; MDP, multidimensional dyspnea profile; mMRC modified medical research council scale; RV, residual volume; TLC, total lung capacity; TLco, diffusing capacity of the lungs for carbon monoxide; VC, vital capacity; VO2max, maximal oxygen uptake.

Table 2. *Changes in primary and secondary outcome measurements.*

	Intervention		Control		
	Pre-training	Post-training	Pre-training	Post-training	adjusted difference (95%CI) at post-training
			Respiratory muscle strength		
Pimax, cmH_2O	-74 ± 11	-93 ± 19*	-91 ± 16	-98 ± 13	-1 (-19 to 18)
Pemax, cmH_2O	139 ± 25	144 ± 28	143 ± 26	141 ± 27	6 (-14 to 25)
			Respiratory muscle endurance test		
Endurance breathing time, s	209 ± 79	741 ± 282*	269 ± 133	321 ± 236	472 (217 to 728)À
Total work, J	103 ± 61	560 ± 403*	206 ± 131	326 ± 157*	336 (24 to 648)À
Average Power, W	2.0 ± 1.2	5.9 ± 2,5*	4.5 ± 2.2	6.9 ± 1.9*	1.4 (-1.2 to 4.0)
Average Volume, L	1.8 ± 0.7	2.6 ± 0.7*	2.1 ± 0.6	2.5 ± 0.4*	0.3 (-0.3 to 0.8)
			CWR cycle ergometer exercise test		
Work rate, W	99 ± 23	98 ± 23	94 ± 24	94 ± 24	
Reason stopping, % dyspnea	57 ± 17	53 ± 19	41 ± 26	48 ± 15	-10 (-32 to 12)
otime					
Exercise capacity, s	400 ± 218		367 ± 272		
Dyspnea isotime, Borg units	5.8 ± 2.1	3.3 ± 1.9*	6.0 ± 3.3	5.2 ± 2.8	-1.8 (-3.7 to 0.13)
Leg discomfort, Borg units	5.4 ± 1.7	4.0 ± 1.9*	7.6 ± 2.6	7.6 ± 1.8	-1.3 (-3.2 to 0.6)
HR, Beats/min	150 ± 21	139 ± 22*	127 ± 28	134 ± 26	-15 (-27 to -3)À
VE, l/min	57.2 ± 23.2	47.7 ± 19.0*	55.7 ± 16.0	51.7 ± 13.6	-5.1 (-12.7 to 2.5)
V_T, liters	1.86 ± 0.52	1.73 ± 0.52	1.69 ± 0.22	1.65 ± 0.24	-0.05 (-0.30 to 0.19)
RR, Breaths/min	31 ± 6	28 ± 6	34 ± 10	32 ± 10	-2 (-7 to 2)
Vo2, l/min	1.71 ± 0.46	1.48 ± 0.44*	1.56 ± 0.38	1.49 ± 0.30	-0.1 (-0.3 to 0.0)
VCo2, l/min	1.95 ± 0.62	1.55 ± 0.51*	1.68 ± 0.41	1.64 ± 0.34	-0.27 (-0.55 to 0.00)À
RQ	1.13 ± 0.16	1.03 ± 0.15	1.08 ± 0.08	1.11 ± 0.10	-0.11 (-0.21 to -0.00)À
IC, liters	2.43 ± 0.35	2.57 ± 0.47	2.47 ± 0.29	2.49 ± 0.36	0.12 (-0.18 to 0.42)
eak exercise					
Exercise time, s	467 ± 218	933 ± 267*	460 ± 272	500 ± 294	428 (223 to 633)À

Dyspnea, Borg units	6.9 ± 2.3	6.0 ± 2.2	7.6 ± 3.2	6.9 ± 2.6	-0.5 (-2.6 to 1.5)
Leg discomfort, Borg units	6.4 ± 2.4	6.2 ± 2.7	8.8 ± 1.6	7.6 ± 1.8	-1.1 (-3.8 to 1.7)
HR, Beats/min	155 ± 16	145 ± 29	134 ± 26	139 ± 24	-16 (-31 to 0)
VE, l/min	58.4 ± 22.2	57.0 ± 17.3	59.0 ± 12.6	57.6 ± 10.2	-0.2 (-10.6 to 10.1)
Vo2, l/min	1.76 ± 0.44	1.64 ± 0.32	1.64 ± 0.33	1.59 ± 0.26	-0.00 (-0.25 to 0.24)
		Symptoms of dyspnea			
TDI total score (-9 to +9)		7.0 ± 1.2		4.1 ± 3.0	2.9 (0.5 to 5.3)À
MDP (A1, 0 to 10)	6.7 ± 1.9	4.8 ± 3.5*	6.4 ± 3.1	6.6 ± 2.6	-2.0 (-4.3 to 0.4)
mMRC (0 to 4)	0.8 ± 0.4	0.2 ± 0.4*	1.0 ± 0.7	0.7 ± 0.7	-0.4 (-0.8 to 0.1)
		Functional exercise capacity			
6MWD, m	557 ± 87	584 ± 71*	545 ± 101	580 ± 85	-5 (-45 to 35)
Dyspnea post 6MWD	2.9 ± 1.4	2.4 ± 1.6	3.3 ± 2.4	2.2 ± 0.9	0.2 (-1.2 to 1.6)
Leg discomfort post 6MWD	2.7 ± 1.7	2.6 ± 1.6	4.8 ± 2.9	3.6 ± 2.2	1.1 (-1.1 to 3.5)
Handgrip strength, N	255 ± 53	255 ± 50	248 ± 29	256 ± 34	4 (-15 to 23)

Data are presented as mean ± SD. 10-point Borg, modified borg dyspnea scale (0-10); 6MWD, six minutes walking distance; CWR, constant-workrate; HR, heart rate; IC, inspiratory capacity; isotime, the time of the post-measurement equal to the end of ime of the pre-measurement; MDP, multidimensional dyspnea profile; mMRC, modified medical research council scale; peak exercise, averaged last 30 sec of loaded cycling; RQ, respiratory quotient; RR, respiratory rate; VCo2, carbon dioxide production; VE, ventilation; Vo2, oxygen consumption; VT, tidal volume. *P < 0.05, within-group differences pre- vs. postintervention by paired -test or Wilcoxon test; ÀP < 0.05, between-group differences intervention vs. control by ANCOVA.