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Breast cancer surgery does not impact long-term pulmonary function and respiratory muscle strength

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ABSTRACT

Introduction: Long-term disabilities are frequently related to postoperative complications on breast cancer patients. **Objective:** To assess the effect of breast cancer surgery on pulmonary function and respiratory muscle strength over the course of 60 days after the surgery. **Methods:** Prospective study with 32 women. Pulmonary function was evaluated using spirometry and respiratory muscle strength was evaluated using manovacuometry. The evaluations were performed in preoperative period, between 12 to 48h after surgery, 30 and 60 days after the surgery. **Results:** Vital capacity (VC) and inspiratory capacity (IC) were diminished 48h after surgery (VC: 2.18±0.63; IC: 1.71±0.49; p<0.01 *vs* baseline), returned to the baseline parameters after 30 days (VC: 2.76±0.60; CI: 2.16±0.57; p<0.01 *vs* PO48h) and were maintained after 60 days of the surgery (VC: 2.64±0.60; CI: 2.11±0.62; p<0.01 *vs* PO48h). No difference was observed in tidal volume over the evaluations, except when comparing 60 days to the 48h after surgery values (0.84±0.37 vs 0.64±0.19, respectively; p=0.028). Respiratory muscle strength was reduced 48h after surgery (MIP: -33.89±12.9 cmH_2O; MEP: 39.72±21.0 cmH_2O; p<0.01 *vs* basal) and returned to baseline values after 30 (MIP: -50.1±21.2 cmH_2O; MEP: 59.86±24.7 cmH_2O; p<0.01 *vs* PO48h) and 60 days of the surgery (MIP: -50.78±19.2 cmH_2O; MEP: 61.67±23.4 cmH_2O; p<0.01 *vs* PO48h). **Conclusion:** Breast cancer surgery does not impact pulmonary function and respiratory muscle strength 30 days after the surgery.

Keywords: breast neoplasms; mastectomy; physical therapy specialty; spirometry.

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INTRODUCTION

Breast cancer is considered the most common cancer type and the main cause of death from cancer amongst women around the world[1-3]. In Brazil, the estimative for the established risk is around 62,9 cases per 100 000 women, with a death rate of 13 per 100 thousand[2]. Nowadays, therapeutic approaches have focused on women´s quality of life using minimal intervention that can guarantee the control of the disease and reduction in related mortality and morbidity[4]. However, partial or total resection of the breast with sentinel lymph node biopsy and/or axillary lymph node dissection is still the most frequent surgical treatment, in addition to chemotherapy, radiotherapy and/or targeted therapy[5].

Long-term disabilities are frequently related to postoperative complications, such as surgical wound and scarring (seromas, necrosis, abscesses, dehiscence, hematomas), axillary web syndrome[6-8], pain, restrictions in the range of motion (ROM), lymphedema, neuropathies and reduction in quality of life[4,9,10]. Additionally, it is thought that pulmonary complications such as atelectasis, pneumothorax and a reduction of diaphragm movement are frequent in extensive surgery under anesthetic, thoracic surgery and prolonged periods of bed rest[9,11]. However, it is unclear the impact of surgeries for breast cancer treatment on pulmonary function in women. The literature has only reported pulmonary changes related to radiotherapy and chemotherapy focusing on radiation pneumonitis and fibrosis[12-17].

Respiratory impairments likely decrease quality of life which may interfere in long-term treatment outcomes of breast cancer patients. Furthermore, increased ventilatory demand, reduced inspiratory capacity and inspiratory muscle weakness are potentially associated with exercise intolerance in breast cancer survivors which also impacts on long-term treatment outcomes[18].

Therefore, the aim of this prospective longitudinal study was to assess the effect of breast cancer surgery on pulmonary function and respiratory muscle strength over the course of 60 days after the surgery.

METHODS

Design

Thirty-five women with histological proven of breast carcinoma, aged above 18 years old, referred for breast-conserving surgery or mastectomy at a reference hospital located in the southern part of Brazil were assessed for eligibility in the present study. Women with other primary cancer types, prior breast or thoracic radiation, metastasized cancer diagnosed at the time of the eligibility assessment, surgical indication for nodulectomy without axillary leakage or sentinel lymph node biopsy, presence of ulceration in the breast, prior respiratory diseases or those who evolved surgical-anesthetic complication were excluded.

The present study was approved by the University and Hospital Human Research Ethics Committees, under protocol CAAE06099113.9.0000.0118, and was conducted respecting the fundamentals established in the Declaration of Helsinki. All participants signed a consent form once they had agreed to participate. Participants were evaluated prior to the surgery (within one week previous to the procedure), immediately after (between 12-48h), and 30 and 60 days afterward at the outpatient clinic or during the hospitalization stay.

Outcome measures

Data collection included participant characteristics, clinical history and cancer treatment. Height and body mass were measured and the Body Mass Index – BMI (kg/m^2) was calculated. Pain and perceived exertion were assessed using McGill questionnaire and Borg Scale of Perceived, respectively[19,20] Any postoperative respiratory or surgical complications were registered during hospitalization. Surgery duration was obtained from medical records.

Pulmonary function was evaluated using a portable spirometer (*Easy One, NDD Medical Technologies, Switzerland*). Full calibration and verification of the equipment were carried out prior to each test. Once our intention was to evaluate the participants in the 48h postoperative period, we choose to perform the slow vital capacity (SVC) maneuver instead of the forced vital capacity (FVC) maneuver, in order to avoid inadequate efforts. The SVC was performed according to the methods and criteria of the American Thoracic Society/European Respiratory Society[21,22] and the follow measures were analyzed: tidal volume (TV) – amount of air inhaled during a normal breath; vital capacity (VC) – maximal amount of air exhaled after deep inspiration; and inspiratory capacity (IC) – amount of air that can be inhaled after the end of a normal expiration.

Respiratory muscle strength was evaluated by measuring maximal inspiratory (MIP) and expiratory (MEP) pressures at the mouth (in cmH_2O), using a digital manovacuometer (Global Med MVD 300®, Brazil). The MIP was measured at a volume close to the residual volume, while the MEP was obtained at a volume close to the total lung capacity. The best value of three reproductible maneuvers was considered for the analysis. The recommendations and criteria of the ATS/ERS[21] were adopted and predicted values were calculated using the equations proposed by Neder *et al.*[23].

Data analysis

For the sample size calculation, we considered a statistical power of 80%, an alpha of 5% and a potential loss to follow-up of 10%. The sample size calculation indicated that a minimum of 26 participants would be required to detect any difference between the four measures for the five variables of interest (IC, VC, TV, MIP and MEP)[24].

Missing data were processed with a multiple imputation method[25,26] using the SPSS software version 20.0. Twenty imputed data sets were created using the pulmonary function and respiratory muscle strength data at the baseline and follow-up assessments to predict the missing data[25,26]. The Shapiro-Wilk test confirmed normal distribution of the data. One-way analysis of variance (ANOVA) for repeated measures and post hoc pairwise comparisons using Bonferroni correction were used to investigate the effect of breast surgery on pulmonary function and respiratory muscle strength parameters over the post-surgical period (time point after baseline: the day after, 30 days and 60 days after surgery). The baseline values were adopted as references. Additionally, an independent t-test was used to compare the respiratory parameters considering the type of surgery (conservative *versus* non-conservative) and immediate breast reconstruction or not at each time point. Pearson's correlation test was used to assess the effect of BMI on pulmonary function and respiratory muscle strength. All analyses were performed (SPSS Inc. Version 20.0, Chicago, IL, USA) accepting statistical significance at p<0.05.

RESULTS

Thirty-five women with clinical diagnosis of breast cancer who underwent surgical interventions were assessed for eligibility. Of these, three were excluded: one presented cardiorespiratory failure after the surgery, another opted to take the surgery at another hospital and the other related weakness and/or post-chemotherapy fatigue (as neoadjuvancy). Seven participants were not evaluated at some point due to impossibility of attending the outpatient clinic, some equipment failure or the refusal to take the test based on discomfort and/or insecurity. Multiple imputation method was used for all missing data.

The 32 participants presented ages between 24 and 70 years old (mean=50.34; SD = 11.32) and BMI of 27.48 kg/m² (SD=4.06). None of the participants had known distant metastases on routine screening and physical examination. Eight (25.0%) were smokers or former-smokers, with an average tobacco load of 29.71 pack-years (SD=19.88). The surgical procedure was performed according to the core needle biopsy, immunohistochemical analysis, as well as to the stage of the tumor (TNM staging system) and was classified as conservative (n=10) or non-conservative/mastectomy (n=22) surgery, considering the mammary gland. None of them had any muscle resection. The average time for surgery was 3.38 hours (SD=1.85), varying from 1.50 to 6.5 hours. None have received any kind of physiotherapy intervention during the study protocol. General characteristics of the sample, tumor and surgery performed can be viewed in Table 1.

The means of VC and IC were significantly diminished in the 48h postoperative period 20.43% and 21.91%, respectively; p<0.05). After 30 and 60 days, both IC and VC reached values similar to the baseline (p>0.05). A decreasing trend at 48h postoperative values was observed for the tidal volume (TV) compared with baseline values, but statistically significant differences were observed only when comparing 60 days after surgery to the 48h postoperative period values (p<0.05) (Table 2).

Both the MIP and MEP presented statistically significant reductions in the 48h postoperative period (23.46% and 30.9%, respectively; p<0.05), with a return to baseline values at 30 days, and their maintenance 60 days after surgery (p>0.05) (Table 2). Respiratory muscle strength was below predicted values in all the assessments (Table 2).

No participant presented pulmonary complications during the 48h postoperative hospital stay, therefore, the period of hospitalization varied between 24 and 72 hours. Additionally, none reported dyspnea or respiratory discomfort between evaluations. The occurrence of pain at the surgical site (thoracic) was controlled during the preoperative evaluations so that it did not affect the performance of the tests. Complaints of pain were restricted to peripheral venous access in the upper limb.

A post-hoc analysis showed no statistically differences between the values for pulmonary function and respiratory muscle strength variables when comparing the type of surgery (conservative *versus* non-conservative) in any assessment time

Table 1: Demographic and treatment-related characteristics of the participants (n=32).

	n (%)
Race	
White	29 (90.6)
Multiracial	2 (6.3)
Black	1 (3.1)
Educational level	
Less than 8 years	8 (25.0)
More than 8 years	24 (75.0)
Marital status	
With mate	20 62.5)
Without mate	12 (37.5)
Physical activity*	
Inactive	25 (78.1)
Regular practice	7 (21.9)
Smoking	
Non-smoker	24 (75.0)
Smoker/former-smoker	8 (25.0)
Laterality	
Left	18 (56.3)
Right	11 (34.4)
Bilateral	3 (9.4)
Histological type	
Invasive ductal carcinoma	21 (65.6)
Intraductal in situ	8 (25.0)
Other types	3 (9.4)
Clinical stage of the tumor**	
Early stage	26 (81.3)
Advanced	6 (18.8)
Surgery	
Modified radical mastectomy + AL	13 (40.6)
Modified radical mastectomy + SLB	10 (31.3)
Quadrantectomy + AL	5 (15.6)
Quadrantectomy + SLB	4 (12.5)
Breast reconstruction	
None	19 (59.4)
Tissue expander implant	7 (25.0)
Definitive implant	6 (21.9)
Neoadjuvancy	
No indication	27 (84.4)
Clinical treatment (chemotherapy)	5 (15.6)
Adjuvant treatment indication***	
No indication	8 (25.0)
Clinical treatment****	9 (28.1)
Radiotherapy	3 (9.4)
Clinical treatment**** + radiotherapy	10 (31.3)
No information	2 (6.3)

AL: Axillary lymphadenectomy; SLB: Sentinel lymph node biopsy for intraoperative histological study. *Based on self-report. **Based on TNM Staging System. ***Initiated after the study period ****Chemotherapy and/or targeted therapy and/or hormone therapy.

point (p>0.05, Table 3). When taking into account immediate breast reconstruction or not, it was observed statistical differences with lower values for respiratory muscle strength only in the 48h postoperative period for those submitted to the procedure (Table 4). No correlation was found between the respiratory measures evaluated and the BMI of the participants (p>0.05, data not shown).

DISCUSSION

This study was innovative in monitoring the pulmonary function and respiratory muscle strength of patients who underwent surgery for breast cancer from the preoperative period until 60 days after it. The main findings of this longitudinal study are that breast cancer surgery does not impact long-term respiratory outcomes. There were transitory changes in pulmonary function and respiratory muscle strength in the 48h postoperative period, with a return to baseline values after 30 days, and their maintenance at 60 days. Our findings are similar to a previous study[27] which reported that patients after breast cancer surgery present reduction of forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC) and of respiratory muscles strength immediately after axillary lymphadenectomy, with a return to baseline values 30 days after surgery. The authors attributed these alterations to the presence of a surgical drain, superficial breathing, fear of experiencing pain and/or use of analgesics.

The occurrence of lesions or the removal of serratus, pectoralis major and pectoralis minor muscles may diminish thoracic expansion altering respiratory mechanics[9]. However, the participants of our study did not have any kind of muscle resection due to the type of surgeries which were modified radical mastectomies based on Madden technique, or quadrantectomies, supposed to be even more conservatives. Of note Cortes-Flores *et al.*[28] described that respiratory function is often compromised after a major surgical procedure, especially those performed under general anesthesia in the head, thoracic and abdominal areas. Besides that, the presence of pain and chest dressing cause limited chest movement and

Table 3: Comparison of pulmonary function and respiratory muscle strength variables considering conservative surgery or not in the four evaluation periods (n=32).

	Conservative surgery (n= 9)	Non-conservative surgery (n = 23)	p
	$\bar{\chi}$ (sd)	$\bar{\chi}$ (sd)	
IC_PRE	2.21 (0.42)	2.19 (0.56)	0.917
IC_PO48h	1.90 (0.40)	1.64 (0.51)	0.180
IC_PO30	2.37 (0.27)	2.08 (0.65)	0.215
IC_PO60	2.23 (0.32)	2.06 (0.71)	0.509
TV_PRE	2.72 (0.53)	2.75 (0.56)	0.909
TV_PO48h	2.21 (0.46)	2.18 (0.70)	0.897
TV_PO30	2.80 (0.50)	2.75 (0.65)	0.864
TV_PO60	2.68 (0.22)	2.63 (0.71)	0.828
VC_PRE	0.69 (0.33)	0.74 (0.29)	0.695
VC_PO48h	0.61 (0.21)	0.66 (0.20)	0.834
VC_PO30	0.68 (0.28)	0.72 (0.32)	0.755
VC_PO60	0.82 (0.24)	0.86 (0.42)	0.820
MEP_PRE	55.00 (25.43)	58.48 (23.52)	0.712
MEP_PO48h	45.57 (25.27)	37.43 (19.34)	0.462
MEP_PO30	55.08 (30.57)	61.73 (22.56)	0.503
MEP_PO60	54.23 (27.96)	64.58 (21.45)	0.269
MIP_PRE	46.9 (19.72)	43.26 (17.29)	0.614
MIP_PO48h	36.62 (10.69)	32.83 (13.83)	0.466
MIP_PO30	55.82 (28.72)	47.9 (17.80)	0.456
MIP_PO60	50.85 (26.89)	50.76 (16.16)	0.438

Conservative surgery: limited procedures allowing the removal of only the tumor with a margin of security around the lesion; Non-conservative surgery: modified radical mastectomies based on Madden technique (resection of the mammary gland); IC: Inspiratory capacity; TV: Tidal volume; VC: Vital capacity; MIP: maximum inspiratory pressure; MEP: maximum expiratory pressure; PRE: preoperative period; PO48h: 48h postoperative period; PO30: 30 days postoperative; PO60: 60 days postoperative.

Table 4: Comparison of respiratory muscle strength variables considering immediate breast reconstruction or not in the four evaluation periods (n=32).

	No breast reconstruction	Immediate breast reconstruction	p
	$\bar{\chi}$ (sd)	$\bar{\chi}$ (sd)	
MEP_PRE	60.98 (23.15)	52.38 (24.50)	0.32
MEP_PO48h	46.48 (22.43)	29.85 (14.62)	0.04*
MEP_PO30	65.15 (27.40)	52.12 (18.54)	0.14
MEP_PO60	63.65 (25.35)	58.77 (21.04)	0.57
MIP_PRE	45.52 (18.65)	42.46 (16.92)	0.64
MIP_PO48h	38.24 (14.21)	27.54 (7.60)	0.01*
MIP_PO30	53.44 (24.26)	45.23 (15.39)	0.29
MIP_PO60	52.16 (21.34)	48.77 (16.43)	0.63

MIP: maximum inspiratory pressure; MEP: maximum expiratory pressure; PRE: preoperative period; PO48h: 48h postoperative period; PO30: 30 days postoperative; PO60: 60 days postoperative. *p<0.05.

Table 2: Comparison of respiratory variables in the four evaluation periods (n=32).

	Preoperative	48h postoperative	Postoperative 30 days	Postoperative 60 days
	$\bar{\chi}$ (sd)	$\bar{\chi}$ (sd)	$\bar{\chi}$ (sd)	$\bar{\chi}$ (sd)
Pulmonary function				
Inspiratory capacity	2.19 (0.51)	1.71 (0.49)*	2.16 (0.57)#	2.11 (0.62)†
Tidal volume	0.72 (0.29)	0.64 (0.19)	0.71 (0.30)	0.84 (0.37)†
Vital capacity	2.74 (0.54)	2.18 (0.63)*	2.76 (0.60)#	2.64 (0.60)†
Respiratory muscle strength				
MIP, cmH_2O	-44.28 (17.7)	-33.89 (12.9)*	-50.1 (21.2)#	-50.78 (19.2)†
MIP, % pred	51.53 (20.5)	39.56 (15.5)	58.05 (23.7)	58.91 (21.4)
MEP, cmH_2O	57.49 (23.7)	39.72 (21.0)*	59.86 (24.7)#	61.67 (23.4)†
MEP, % pred	67.91 (28.6)	47.09 (25.2)	70.35 (29.6)	72.26 (27.2)

MIP: maximum inspiratory pressure; MEP: maximum expiratory pressure; % pred: percentage of the predicted value; c- mean; sd- standard deviation; *p<0.05 48h postoperative *versus* preoperative; # p<0.05: 30 days postoperative *versus* 48h postoperative; † p<0.05 60 days postoperative *versus* 48h postoperative.

lung restriction, which seems to explain the transitory changes found in the present study.

The pulmonary function can also be altered due to antalgic posture or scar adhesions, frequently reported after breast cancer treatment. Bregagnol and Dias[27] demonstrated that shoulder ROM in mastectomized patients is reduced in the immediate postoperative period. Additionally, Nagato *et al.*[29] demonstrated that a upper limb elevation above shoulder level causes an increase in the minute volume and VT. Therefore, increasing shoulder ROM and improving posture likely lead to improvements in pulmonary function[29].

The reduction of inspiratory and expiratory muscle strength observed in the 48h postoperative period could be explained by the surgical incision in the thorax, that affects its capacity to generate pressure, with a consequent alteration of the mechanics of the thoracic wall[11]. Additionally, the expiratory pressure can diminish during the immediate postoperative period due to the presence of pain or even the fear of experiencing it[27].

Despite the reduction of respiratory muscular strength during the 48h postoperative period, the 30-day evaluation demonstrated its re-establishment. Gastaldi *et al.*[30] reported a faster recovery. The respiratory muscle strength returned to the preoperative values after four days of the surgery with the performance of respiratory exercises. The evaluation of respiratory muscle strength is important to manage the surgical patient, given that vital capacity only begins to diminish when there is a decline in respiratory muscle strength of at least 50% of the predicted value. Additionally, a MEP of at least 40 cmH_2O is necessary to promote an effective cough and eliminate sputum[31].

The sample studied presented a reduction in the predicted values for respiratory muscle strength during all the assessments. A study with patients who underwent thoracotomies (non-cardiac) and elective upper laparotomies suggested that MIP or MEP values below 75% of those predicted have an association with higher risk of postoperative pulmonary complications[32]. However, no patient in the present study showed pulmonary complications during their postoperative hospital stay.

Although no significant difference in pulmonary function and respiratory muscle strength was observed when comparing patients submitted or not to conservative surgery, a worse performance would be expected in the second group. Extensive surgeries involve a longer period under anesthesia, an increase in the size of the surgical incision and subsequent placement of adherences on the thoracic wall, antalgic posture and a reduction in should ROM resulting in greater respiratory changes[27,29]. Particularly in mastectomies, there is the complete removal of the mammary gland, some lymph nodes and the pectoral fascia, while conservative surgeries involve a limited procedure allowing the removal of only the tumor with a margin of security around the lesion. The difference observed between those submitted to immediate reconstruction or not reinforces this hypothesis, since this type of surgery involves the manipulation of muscle to place breast implant and larger tissue flaps. Anyhow, the discrepancy in our sample size between the groups that underwent conservative surgery and mastectomy does not permit further conclusions.

The reduction in breast size could increase chest compliance, which interferes on pulmonary ventilation. Although Turhan-Haktanir *et al.*[33] have observed no correlation between breast size and pulmonary function in a study performed with 100 healthy volunteers women, some previous studies have suggested the improvement in breathing following bilateral breast reduction in cases of macromastia[34-36]. Besides macromastia, pulmonary function tests may be affected by patient weight. Indeed, as hypothesized by Turhan-Haktanir *et al.*[33], macromastia associated with obesity may lead to a relative restriction in chest wall compliance, so breast size reduction is supposed to enhance chest wall compliance and lead to improved ventilation. However, a post-hoc analysis showed no correlation between the pulmonary variables and the BMI of the participants of the present study.

Long-term toxicity of chemotherapy, specially anthracyclines and taxanes, can lead to a decrease in pulmonary diffusion capacity and significant dyspnea that persists after treatment completion[17]. In the present study, five participants were submitted to neoadjuvant chemotherapy before surgery. However, no difference for the studied variables was observed, probably due to an insufficient sample size.

A moderate exercise program is supposed to improve pulmonary function in women with adverse sequelae from breast cancer surgery[37]. O'Donnell *et al.*[18] observed a reduction in inspiratory capacity and static inspiratory muscle strength, a faster and shallow breathing pattern, and more intense dyspnea during exercise, which were consistent with the presence of significant inspiratory muscle weakness in breast cancer survivors compared to healthy people. Therefore, it would be interesting to detect as early as possible those patients who would benefit from such an exercise program. Taking into account the patients with indication of subsequent radiotherapy, exercise interventions since the preoperative period – such as the inspiratory muscle training –, is important to prevent or reduce postoperative pulmonary complications (PPC) and length of hospital stay[38]. Furthermore, inspiratory muscle training after surgery, with or without other type of rehabilitation interventions such as physical exercise or breathing and coughing, is supposed to be more effective to prevent pulmonary complications[38,39].

Despite the clinical relevance of our findings, they should be interpreted with consideration to some limitations. Firstly, some data should be carefully analyzed because of imputation performed. However, in a qualitative analysis, the imputed data did not differ from the originals. Also, it can be argued that the evaluation of pulmonary function using SVC method may not be as adequate as the FVC maneuver. However, it is known that the FVC maneuver is more difficult to perform due to the rapid and forced expiration. Additionally, no difference between FVC and SVC maneuvers was found in healthy individuals[40]. The choice of SVC was made given that patients may feel insecure about performing an effort and strength-dependent technique during the immediate postoperative period. This could happen due to fear of experiencing pain, performing movements, effort or deep breathe. And because all pulmonary function and respiratory muscle strength tests are effort-dependent[33,35], a learned skill with improved scores over time could be achieved, so we attempted to standardize each patient's testing as possible according to the American Thoracic Society/European Respiratory Society protocols and recommendations[21,22].

Even though none of the participants had any worsening in pulmonary function or respiratory muscle strength after breast cancer surgery, several studies have suggested that most of the patients are asymptomatic regarding pulmonary impairment[12], and for that reason pulmonary function tests shall be performed in all breast cancer patients for early detection of any complication.

In summary, breast cancer surgery promotes a transitory reduction in pulmonary function and respiratory muscle strength during the 48h postoperative period after breast cancer surgery, with a subsequent return to baseline values after 30 days and their maintenance at the 60-day postoperative mark.

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