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AKADÉMIAI KIADÓ

Effects of multimodal training program on muscle deoxygenation in women with breast cancer: A randomized controlled trial

MOUADH HIRAOUI[1,2,3], NABIL GMADA[4,5*], BADRIA AL-HADABI[4], AMEL MEZLINI[2], MAJID AL BUSAFI[4], PIERRE LOUIS DOUTRELLOT[1], EZDINE BOUHLEL[6] and SAID AHMAIDI[1]

[1] EA-3300: APERE, Exercise Physiology and Rehabilitation Laboratory, Sport Sciences Department, Picardie Jules Verne University, Amiens Cedex, France

[2] Medical Oncology Department, Salah Azaiez Oncologic Hospital, Tunis, Tunisia

[3] Bizerte Sciences Faculty, Carthage University, Bizerte, Tunisia

[4] Physical Education and Sport Sciences Department, College of Education, Sultan Qaboos University, Muscat, Sultanate of Oman

[5] Research Unit, "Sportive Performance and Physical Rehabilitation," High Institute of Sports and Physical Education, Kef, University of Jendouba, Jendouba, Tunisia

[6] Laboratory of Physiology, Faculty of Medicine of Sousse, University of Sousse, Sousse, Tunisia

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ABSTRACT

Purpose: Chemotherapy and/or radiation are the most often delivered treatments to cancer patients. Usually during the adjuvant treatment, patients complain about fatigue. In addition, physical exercise during adjuvant treatment of cancer seems to have beneficial effects. The aim of this investigation was to assess the effects of multimodal aerobic and strength exercises programs on muscle deoxygenation of patients with breast cancer undergoing adjuvant chemotherapy treatment. *Methods:* Thirty-two women with breast cancer (20 patients as the training group and 12 patients as the control group) undergoing adjuvant chemotherapy participated in the study. The training group took part in 6 weeks of supervised intermittent aerobic cycling, home-based walking, isometric and electrical muscle stimulation (EMS)

* Corresponding author. Physical Education and Sport Sciences Department, College of Education, Sultan Qaboos University, 123 Muscat, Sultanate of Oman. Tel.: +968 91350154. E-mail: ngmada@squ.edu.om; ngmada@yahoo.fr

exercise training programs. The Outcome measures were muscle deoxygenation (ΔHHb), Maximal Voluntary isometric Contraction (MViC) and Endurance Time (ET) before and after the training period. *Results:* Compared to the control group, a significant increase in ΔHHb ($P < 0.01$) accompanied with an increase in ET ($P < 0.01$) and MViC ($P < 0.01$) of the quadriceps was obtained in the training group. However, no significant differences of MViC, ET and ΔHHb were observed in the control group. *Conclusion:* Multimodal aerobic and strength exercise programs enhance muscle oxygen utilization, which may partly explain the improvement in muscular strength and endurance, and the reduction of muscle fatigue in patients with breast cancer during an adjuvant chemotherapy period.

KEYWORDS

multimodal training, breast cancer, muscle deoxygenation, muscle fatigue, strength exercise

INTRODUCTION

Cancer-Related Fatigue is a common problem in cancer patients undertaking chemotherapy [1, 2]. It was reported that fatigue affects up to 70% of cancer patients during chemotherapy [3]. Changes in neuromuscular function were potential contributors to cancer-related fatigue [4, 5].

Yavuzsen et al. [5] showed impaired neuromuscular junction conduction and greater central fatigue in a cancer patient group undergoing palliative care, compared to a healthy control group.

Furthermore, Bruera et al. [6] showed several muscular alterations, including reduced relaxation velocity, lower maximum strength after supramaximal stimulation and a higher loss of contractile strength, after 30 s of stimulation of advanced breast cancer patients.

Thus, these data show that cancer and the treatment of cancer have negative effects on muscular functional capacity. Muscle wasting is the essential consequence of cancer cachexia, inducing in particular muscle fatigue and respiratory disorders [7].

Moreover, the lack of physical activity during cancer treatment, prolonged bed rest and treatment with high-dose corticoids can aggravate the decline of muscular function by a substantial loss of muscle mass as well as reduction of plasma volume and cardiac output that further impairs exercise tolerance [8]. Otherwise, immunosuppression with cyclosporine may induce mitochondrial myopathy [9], loss of capillary density and exercise ability [10].

The study of Ederer et al. [11] is the first evidence of potential muscle microvascular toxicity in cancer survivors treated with adjuvant treatments. These authors observed a significant decrease of skeletal microvascular muscle during dynamic exercise on cycle ergometer in cancer survivors compared to healthy subjects. This decrease suggests that muscle oxygen extraction and muscle microvascular hemoglobin concentration were lower in the cancer survivor group [11]. In this context, fatigue mechanisms of the whole body in cancer patients could be related both to central and peripheral factors. Chemotherapy combined with prolonged physical inactivity will impact oxygen delivery, oxygen utilization, and consequently the functional capacity of the patient.

Some studies have shown that aerobic and resistance exercise improved self-esteem, physical fitness, body composition, and chemotherapy completion rate without causing lymphedema or significant adverse events, during adjuvant chemotherapy [12] and after treatment [13].

Andersen et al. [14] demonstrated that six-weeks of supervised multimodal exercise intervention comprising high-intensity aerobic and heavy resistance training, relaxation and body awareness training and massage could provide a significant reduction in self-reported cancer-related fatigue in cancer patients undergoing chemotherapy.

Battaglini et al. [15] showed that strength training decreases muscle fatigue and improves muscular strength in women with breast cancer. Furthermore, Steindorf et al. [16] indicated that resistance training is safe and efficient in improving cancer-related fatigue in breast cancer patients during adjuvant treatment. Strength exercise is often suggested in dynamic form using the estimated one repetition maximum in cancer patients [3, 14, 17], nevertheless no study has proposed isometric strength exercise in such patients.

Near-infrared spectroscopy (NIRS) is a non-invasive method for measuring tissue oxygenation [18]. The deoxygenation of hemoglobin and myoglobin measured by NIRS gives a reproducible estimate of the fraction of oxygen used at the level of microcirculation [19, 20].

To decrease muscular fatigue caused by cancer treatment and physical inactivity, the purpose of this study was to assess the effects of supervised and individualized multimodal aerobic and strength exercise programs on muscle deoxygenation in patients with breast cancer undergoing adjuvant chemotherapy.

MATERIAL AND METHODS

Patients

A randomized controlled trial was performed to examine the effect of a multimodal training program on muscle deoxygenation. Sample size was calculated based on the primary outcome of this study, muscle deoxygenation. Given the pioneer character of the present study, the effect size was arbitrarily fixed high at 0.80 and a power of 80% ($\alpha = 0.05$), assuming approximately 10% dropout rate. The total sample size calculated using the software G*Power 1.3.9.4 was 24 (12 participants in each group).

At the beginning, thirty-nine patients were selected to participate in this study. They were recruited from the medical oncology department of hospital. They represented a subgroup from a population of 730 patients followed in the oncology department. Recruited patients were randomly divided (sealed envelope method without replacement) into 2 homogeneous groups: one "training" group ($n = 20$) and one control group ($n = 19$). At the end of the experiment, seven patients in the control group were eliminated, because they changed their hospitals and therefore they did not perform the retest (Fig. 1). Only the group of trained patients participated in the rehabilitation program. Subjects from the control group maintained taking their adjuvant chemotherapy during the 6-week period without taking part in any exercise or rehabilitation program.

The women's inclusion criteria were: age between 18 and 65 years, lack of a known history of chronic respiratory or neuromuscular diseases, diagnosis with non-metastatic breast cancer (stage I-IIIA), mastectomy, and being in the process of adjuvant chemotherapy (postoperative). The chemotherapy sessions lasted 3 h and were carried out in the hospital every three weeks. The protocols used were FEC 100 (5 Fluouracil, Epirubicin, Cyclophosphamide) alternated with Docetaxel. The first chemotherapy session was realized 6 weeks after the surgical procedure, and the first training session was performed 2 weeks after the first chemotherapy session.

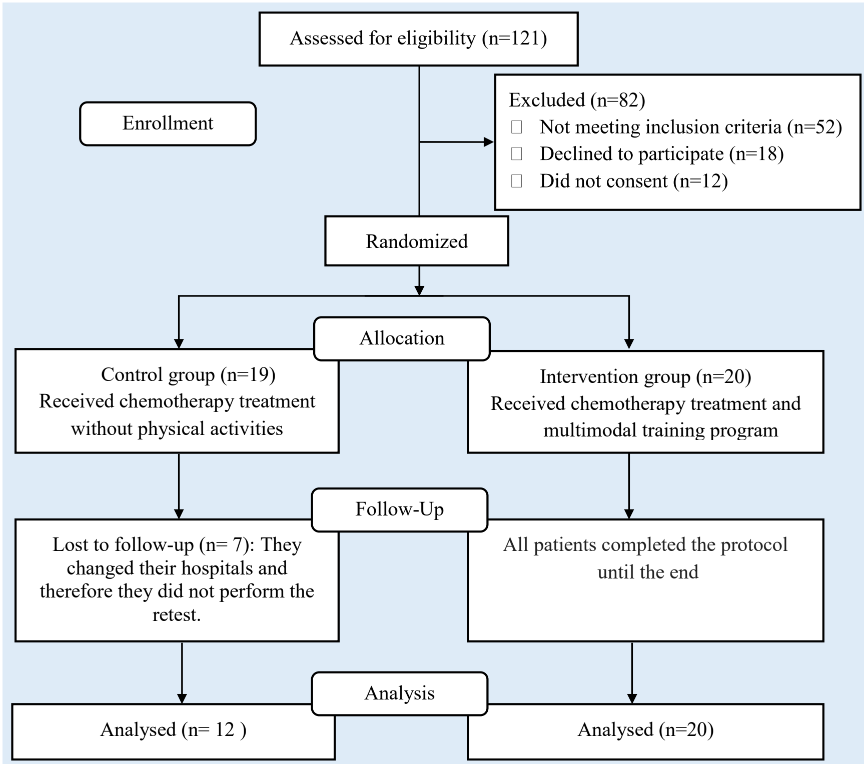

Fig. 1. Flow diagram of randomization procedure

The exclusion criteria were: the practice of physical activity, malnutrition (BMI <20; [21]), chronic diseases that can be exacerbated by exercise (coronary artery disease, chronic obstructive pulmonary disease, osteoarthritis), haemoglobin concentration <8 g dL^{-1}, chronic infection, platelet count <20 nL^{-1}, obesity (BMI >30), treatment with high-dose corticoids (prednisone >50 mg day^{-1} or equivalent dose of related agents), neurologic or muscular impairment, skeletal metastases resulting in bone instability, or progressive disease with indication of new or additional therapy. Patients who had metastases were excluded, because they had general weakness and did not follow the same treatment as non-metastatic patients. In addition, women with non-communicable diseases such as hypertension, diabetes, cholesterol, and triglycerides were excluded from our investigation. Thirty-two eligible patients were enrolled in this study after providing informed consent. All were also non-smokers, and none abused alcohol. Patients didn't take any medication. The characteristics of the subjects are summarized in Table 1. The study was approved by the Ethics Committee of the Oncology Hospital in accordance with the Declaration of Helsinki. All patients were advised in detail of the procedures and risks associated with the various experiments as well as the expected benefits, and gave their informed consent. Confidentiality was maintained throughout the study period.

Table 1. Characteristics of patients in both groups

	Training group	Control group
N	20	12
Gender	Female	Female
Age (years)	49.71 ± 5.41	48.93 ± 4.76
Q_{25}	45.25	44.25
Q_{50} (Med)	47.5	49.5
Q_{75}	55.75	53
Weight (kg)	73.1 ± 6.63	70.25 ± 5.03
Q_{25}	67.25	65.5
Q_{50} (Med)	71.5	71
Q_{75}	80.75	73.5
Height (cm)	160.47 ± 4.75	159.87 ± 3.25
Q_{25}	155.25	157
Q_{50} (Med)	162.5	159.5
Q_{75}	164	163
BMI (kg m^{-2})	28.42 ± 2.55	27.55 ± 2.62
Q_{25}	26.45	24.83
Q_{50} (Med)	28.32	27.79
Q_{75}	30.02	29.26
HRrest at baseline (bpm)	84.45 ± 7.98	88.08 ± 6.17
Blood Pressure Systolic (mm Hg)	124.1 ± 12.12	123.92 ± 11.95
Blood Pressure Diastolic (mm Hg)	84.55 ± 8.73	84.58 ± 7.97
Postmenopausal patients	3	2
Type of Tumor	Breast cancer	Breast cancer
Side of the operated breast		
Right	11 (55%)	7 (58.33%)
Left	9 (45%)	5 (41.67%)
Treatment	Adjuvant Chemotherapy	Adjuvant Chemotherapy

Data are expressed as mean ± standard deviation and Quartiles 25, 50, 75.

Protocol

After recruitment, pretest and posttest trials of muscular performance were carried out. These consisted of an isometric test to measure the Maximal Voluntary isometric Contraction (MViC) and endurance time (ET) of the quadriceps muscle. Muscle deoxygenation changes (ΔHHb) during hold to 50% of MViC using NIRS was assessed during the endurance time test.

Quadriceps muscle strength

Quadriceps muscle strength was assessed using a universal dynamometer (Electronic Council, France) mounted on a platform. Patients were seated comfortably with the back supported in a sturdy chair, hips and knees at 90°. A strap was positioned 2 cm above the lateral malleolus of the ankle of the dominant leg; the other end of the strap was attached to the strain gauge dynamometer. During contractions, the direction of force generation was perpendicular to the axis of the leg. Patients pushed as hard as possible during three seconds. After a familiarization test, the patients began three attempts, interspersed with a passive recovery of two minutes, with verbal encouragement to develop maximal force. To determine the MViC, the average of the values of the three MViCs obtained during the three maximum extensions was calculated.

After the three maximum extensions, a 5-min recovery period was proposed for patients before starting the holding to 50% of MViC. To measure endurance time, patients held 50% of MViC as long as possible.

To measure MViC and ET, we used an electronic card with its associated software on a computer. A strength sensor had been connected to the measuring card. The kinetics of the developed force and the holding time was displayed on the computer screen visible to the patients.

NIRS signal acquisition and analysis

The probe infrared spectroscopy "NIRS" (Portamon, ARTinis, Medical System, Zetten, Netherlands) was placed at the Rectus Femoris muscle. The sensor was applied to 12 cm of the patella in the longitudinal axis of the muscle (after the muscle had been localized via a voluntary knee flexion at 90°). In order to minimize the possible effects of muscle perfusion heterogeneity, the probe was placed over the belly of the muscle. The probe was protected with medical adhesive and covered with a black bandage to prevent signal contamination by ambient light. Skinfolds were measured at the location of the probe using a skinfold caliper (Harpenden HSK-BI, United Kingdom), to ensure that skinfold was lower than 1.5 cm as recommended to avoid signal alterations [22].

After calibration of the NIRS device and rest measurements, the curves of MViC were instantly displayed on the screen and recorded in "line" for further analysis. ΔHHb was measured using the differences in characteristics of light absorption at 750 and 850 nm because of uncertainty in differential path length factors for the quadriceps muscle.

During acquisition, the receiving system of the NIRS was connected to a PC computer to transfer data from the sensor to the receiver via Bluetooth for acquisition and data archiving at a frequency of 10 Hz.

The NIRS derived reflected changes in muscle deoxygenation within venules, capillaries, the small arterioles and of intracellular myoglobin [18]. The distinction between myoglobin and hemoglobin cannot be regularly made due to the similar absorption properties at the NIRS light wavelengths [23]. ΔHHb changes relative to baseline were computed as the difference between the average baseline value and the average contraction value of 50% MViC.

Training program

The training program lasted for a period of six weeks and consisted of combined supervised intermittent aerobic, muscle strength and home-based walking training programs. The aerobic training consisted of home-based walking and a cycling training program.

Patients of the training group were equipped with a Polar heart rate monitor (Polar Electro, Port Washington, NY, USA) during each walking and cycling exercise-training session to monitor their heart rates. The mean heart rate values were calculated weekly from the data of the heart rate monitor recorder. We read and calculated the patients' mean exercise heart rates weekly using a heart rate monitor to adjust and control the training load. In addition, we increased the walking exercise intensity every two weeks by 5% compared to the average exercise heart rate calculated each week.

The home-based walking program consisted of walking continuously for 20 min, 5 days per week during the two first weeks, 25 min during the 3rd and the 4th weeks and 30 min during the last 2 weeks. The supervised home based walking program was coupled to an isometric exercise training of the knee extensor muscles (10*10 contractions of 3 s in the first week, 15*15 contractions of 4 s for 2 weeks and 20*20 contractions of 5 s in the last 3 weeks, 5 days week^{-1}).

The intermittent cycling training program consisted of exercises on cycle ergometer twice a week. The cycling exercise program started with 5 min of warming-up at an intensity of 50% of the theoretical maximal heart rate (THRmax). The THRmax was calculated using the formula of Gulati et al. [24]: (206 – [0.88 x age]). This formula was obtained in a fragile sample of 5,437 asymptomatic women with chronotropic incompetence and increased risk of death.

During the 1st week, patients carried out two cycling training sessions of 2 x 10 min at an intensity of 55% of THRmax. During the 2nd week, the exercise intensity was increased to 60% of THRmax with 2x 12 min training duration. During the 3rd week, the exercise intensity was 65% of THRmax for 2 x 15 min duration.

In the last 3 weeks, the patients performed six cycling training sessions of 2x 20 min at 70% of THRmax for the 4th week, 75% of THRmax for the 5th week and 80% of THRmax for the last training week.

The training load was increased lightly and progressively during the training period, to have a number of repetitions, a time of cycling, and a recovery between bouts of 2*10′ (3′); 2*12′ (3′30); 2*15′ (5′); 2*20′ (7′), respectively; using passive recovery between bouts, the cadence of cycling was between 50 and 70 rpm. We used the Borg scale after each training session. In addition, we read and calculated the patients' mean exercise heart rates weekly from their heart rate monitor data to adjust and control the training load.

In all cycling training sessions, we suggested a passive recovery with electrical muscle stimulation (EMS) that was applied to knee extensor muscles using EMS devices (Compex-P, Vista, CA 92081-8553, USA) producing biphasic symmetric impulses with a 50 Hz frequency, a pulse width of 0.35 ms (stimulus regime: 8 s on/24 s off; session time 30 min day^{-1} in the first 2 weeks, increased to 40 min day^{-1} in the last 4 weeks, 2 days week^{-1}). We used a pre-established electrostimulation protocol in the Compex system. Stimulation intensity was individually adjusted for each limb in order to obtain tetanic contraction or maximum tolerated intensity.

The device provided 4 output channels with the possibility to adjust intensity. The device was provided with self-adhering surface electrodes (2″ × 2″ and 2″ × 4″, Compex, Medi-Konzept GmbH). To stimulate the quadriceps muscle, the electrodes were placed bilaterally, medially and laterally, 3 cm proximal to the upper border of the patella and 5 cm distal to the inguinal fold [25]. The perceived rate of exertion (PRE) was assessed using the Borg scale at the end of each training session.

Statistical analysis

Normality and homogeneity of variances were examined by Shapiro–Wilk and Levin tests, respectively. To compare changes in ΔHHb, ET and MViC in the training and control groups, a two-way (groups vs pre-post training) analysis of variance with repeated measures was used. When a difference was found, a Bonferroni post hoc test was applied. Effect sizes (ES) were also calculated for each output. The following scale proposed by Hopkins [26] was used for the interpretation: <0.2:[trivial]; 02-06: [smal]; 06-1.2:[moderate]; 1.2-2:[large]; and >2.0:[very large]. All statistical analyses were performed using the SPSS Statistics version 22 (SPSS Inc., Chicago, IL, USA). All data are presented as mean ± standard deviation (SD), and the value of $P < 0.05$ was accepted as the minimal level of significance.

RESULTS

Neither the Shapiro–Wilk nor the Levin tests were significant ($P > 0.05$), suggesting a normal distribution with homogeneous variance for all measured variables. Descriptive data for anthropometric characteristics of all patients are summarized in Table 1.

No significant differences were observed in ΔHHb in the control group (2.37 ± 0.6AU vs 2.06 ± 0.43AU, respectively in test and retest; $P > 0.05$). However, the ΔHHb values of the training group increased by 51.68% following the six-week training program (2.20 ± 1.19AU vs 3.00 ± 1.12AU, respectively in test and retest; $P < 0.01$, ES = 0.69) (Fig. 2).

MViC values of the training group also increased significantly by 16.66% following the 6-week training intervention (14.79 ± 2.58 kg vs 17.06 ± 2.61 kg, respectively in test and retest; $P < 0.01$, ES = 0.87). However, no significant differences were observed in the control group (15.12 ± 1.19 kg vs 14.39 ± 1.38 kg, respectively in test and retest; $P > 0.05$) (Fig. 3).

No significant differences were observed for ET in the control group (51 ± 14.06 s vs 48.17 ± 9.45 s, respectively in test and retest; $P > 0.05$). However, the ET values of the training group increased by 47.36% following the six-week training program (50 ± 24.58 s vs 69.25 ± 29.75 s, respectively in test and retest; $P < 0.01$, ES = 0.71) (Fig. 4).

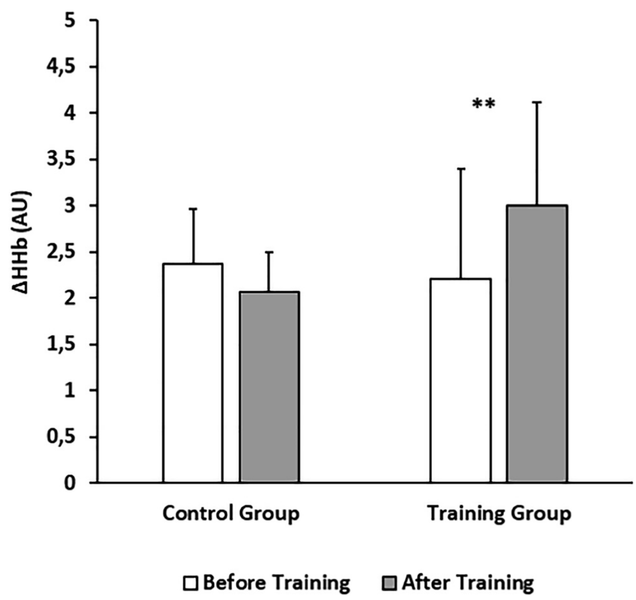

Fig. 2. Changes in muscle deoxygenation in training and control groups. Data are expressed as mean ± SD.
**: Significance at $P < 0.01$

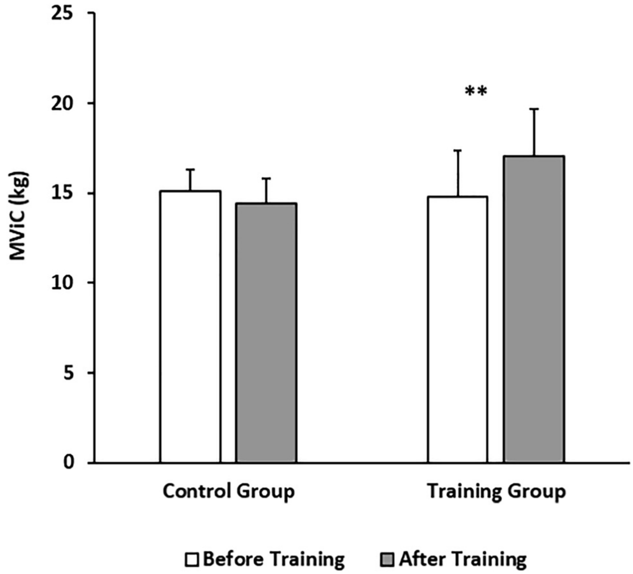

Fig. 3. Changes in maximal voluntary isometric contraction in training and control groups. Data are expressed as mean ± SD. **: Significance at $P < 0.01$

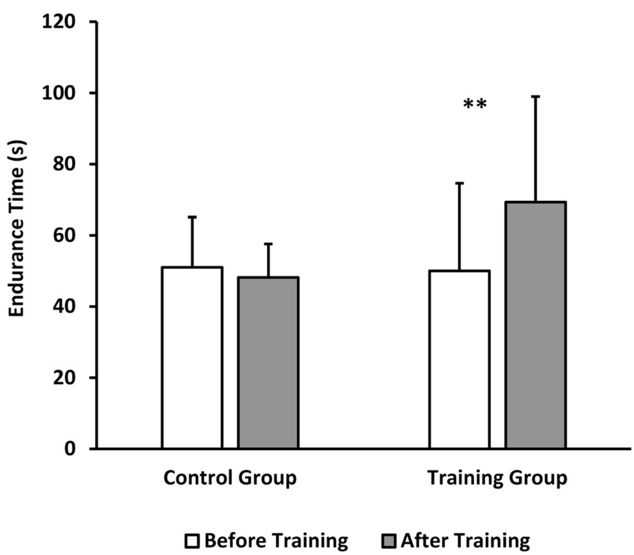

Fig. 4. Changes in endurance time in training and control groups. Data are expressed as mean ± SD. **: Significance at $P < 0.01$

A significant improvement was observed for PRE in the training group (6.35 ± 0.93 vs 5.7 ± 0.12, respectively in test and retest; $P < 0.05$, ES = 1.24). However, no difference was shown in controls (6.17 ± 0.94 vs 6.42 ± 0.90, respectively in test and retest).

DISCUSSION

The objective of this study was to investigate the effects of combined supervised intermittent aerobic, muscle strength and home-based walking training programs on muscle deoxygenation and muscle performance in patients with breast cancer undergoing adjuvant chemotherapy.

The main finding of the present study was that six weeks of combined aerobic, resistance, and muscle stimulation training program induced improvements of muscular performance in patients with breast cancer undergoing adjuvant chemotherapy. In fact, we found increases in MViC and ET during isometric tests, accompanied by an increase in muscle deoxygenation in the training group.

Our findings seem to be interesting, because we showed that multimodal aerobic and strength exercise programs enhance muscle oxygen utilization, which may partly explain the improvement in muscular strength and endurance, and the reduction of muscle fatigue in patients with breast cancer during adjuvant chemotherapy period.

It is important to note that the training protocol used in this study was varied and progressive in terms of type, intensity, and duration of exercises. For this reason it was well tolerated by our subjects. In this context, we exported the data daily to track the adherence rate of our patients. Our training protocol seems to be relevant, because the adherence of our patients was high even for unsupervised attendance rate. The rate of patient adherence to unsupervised sessions was around 98%. Furthermore, the effective rate of wearing the Polar heart rate monitor during walking sessions reached 90%. In addition, we reported no discomfort or discouragement of our patients during the intervention.

Our data are of importance, because in such a population cancer treatment by chemotherapy leads to fatigue, and improvements of muscle endurance related to training could counteract fatigue mechanisms [27, 28]. Ng [27] suggested that exercise could be one of the few effective tools to manage unexplained cancer-related fatigue, especially in cases of absence of cachexia or anemia. According to the author, exercise could induce the preservation of muscle functional capacity, preventing deterioration.

In our study, we used a near-infrared spectroscopy (NIRS) device. This device could provide accurate information related to local muscle oxygenation, and thus to muscle fatigue during exercise [29]. Felici et al. [30] reported that a decrease in muscle activity could reflect a reduction in muscle oxygen consumption. Other physiological variables could be appreciated including oxygen consumption and oxygen delivery [31]. Quaresima et al. [32] pointed out that there are other parameters, such as intramuscular pressure, local blood supply, and fiber type recruitment that may account for differences in NIRS signal responses, both within and between the muscles involved during exercise.

After the multimodal training program, we found a significant increase in ΔHHb, explaining an increase in oxygen consumption during the muscular endurance test at 50% of MViC. Kahn et al. [33] found that the peak deoxygenation level was produced at 50%

MViC in the brachioradialis muscle. They showed that at 50% MViC, type I muscle fibers are involved, and some type II fibers are also solicited in order to maintain the desired force.

Inadequate oxygen consumption and/or inadequate blood supply can influence the ability of muscles to sustain muscle contraction [34, 35]. Ederer et al. [11] explained the decrease of muscle deoxygenation by an alteration in the balance between oxygen delivery and oxygen utilization during exercise in cancer survivors.

In our training program, we also used the electrical muscle stimulation method (EMS). This method is widely used both in patients and in trained subjects. EMS delivers a controlled contractile stimulus to underlying muscles via surface electrodes placed on the skin. For example, in pathological patients, EMS is often used to assist with rehabilitation following joint surgery [36], by helping to speed up strength muscle recovery and joint function. In this context, Stevens et al. [37] used electrical stimulation of the muscle in combination with voluntary contraction exercises in order to strengthen the muscles of the limbs after knee replacement surgery. Our intervention based on the combination of aerobic exercise, resistance exercise and EMS was effective, involving increased strength and muscular endurance.

Studies using electrical muscle stimulation have highlighted the importance of this technique in improving muscle function [38–41], particularly in subjects unable to perform dynamic exercises [37–40].

Aerobic training induces muscle adaptations, such as improving myoglobin and mitochondria content, and increases in capillary density, the percentage of slow fibers, and the activity of oxidative enzymes [42], thus involving enhancement in muscle strength and endurance [43].

Training using resistant or intense exercises optimizes the mechanism of muscle recruitment, regarding adaptation affecting both anaerobic and aerobic muscular metabolism [44, 45]. The reduction of effort perception (PRE) that we found in our intervention group could be related to such adaptations.

Mijwel et al. [46] showed that high-intensity interval training (HIIT) combined with aerobic training, and HIIT combined with resistant training induced improvements in skeletal muscle function, such as citrate synthase activity, capillaries per fiber, and muscle fiber cross-sectional area in breast cancer patients. In addition, the authors suggested the inclusion of high interval training to aerobic training during the chemotherapy period. Recently, Schutz et al. [47] concluded that HIIT associated with resistance training, with an intensity of 70–80% of 1 RM, or HIIT combined with aerobic exercise provided positive effects on quality of life, muscle strength, handgrip, body weight stabilization and fatigue in addition to reducing pain and symptoms related to breast cancer.

In their review, Kim et al. [48] confirmed that combined training is more efficient than aerobic or resistant training alone in physical fitness and biomarker levels in breast cancer patients. In the same context, Hiraoui et al. [49] pointed out the importance of supervised combined intermittent aerobic, muscle strength and home-based walking training programs on cardio-respiratory fitness in women with breast cancer during adjuvant chemotherapy treatment. The authors reported that using a training program improves cardio-respiratory responses and reduces the perception of fatigue in women with breast cancer.

STUDY LIMITATIONS

This study has obvious limitations. The sample size is relatively small and the groups showed an imbalance in size between groups (20 vs 12, respectively for experimental and control groups). But despite this imbalance, both groups were homogenous for age, BMI, type of tumor, treatment, and especially in baseline values of ΔHHb, MViC and ET that were measured before and after training.

CONCLUSION

Our study showed that multimodal aerobic and strength exercise programs enhance muscle oxygen utilization, which may partly explain the improvement in muscular strength and endurance, and the reduction of muscle fatigue in patients with breast cancer during the adjuvant chemotherapy period. Our data have important clinical implications, showing that a well-adjusted and varied exercise protocol combined with muscle electrostimulation has beneficial effects, in particular on reducing fatigue, improving physical fitness and autonomy during the chemotherapy treatment period in women with breast cancer.

Conflict of interest: The authors declare that they have no conflict of interest.

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Ethical approval: The article has received ethics approval from the Institutional Review Board of the Medical Center Salah Azaiez of Tunisia (Ref: ISA/2016/01bis) in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration. Written informed consent was obtained from all participants and confidentiality was maintained throughout the study.

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