Importance of Physical Activity Practice for Cardiotoxicity Risk Prevention: Systematic Review

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Importância da Prática de Atividade Física para Prevenção do Risco de Cardiotoxicidade: Revisão Sistemática

Importancia de la Práctica de Actividad Física para la Prevención del Riesgo de Cardiotoxicidad: Revisión Sistemática

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Abstract

Introduction: Cardiotoxicity can directly affect functional capacity, pulmonary ventilation and muscle strength, as well as indirectly affect other organs and systems. Exercise is suggested as an effective and inexpensive non-pharmacological strategy to minimize or prevent myocardial damage associated with anthracycline treatment. **Objective:** To discuss the effects of physical exercise in patients with cardiotoxicity following cancer treatment with chemotherapy and/or radiotherapy. **Method:** Scielo, PEDro and PubMed databases were researched, in Portuguese and English, for scientific articles published between 2007 and 2018. **Results:** We found 256 abstracts, 34 were selected for full reading because they met the inclusion criteria, 25 articles were excluded because they did not meet the inclusion criteria and only 9 presented the association of exercise effects in the presence of cardiotoxicity. **Conclusion:** The improvement in maximal oxygen uptake ($VO_{2\ max/peak}$) and 6-minute walk distance (6MWD) were more evident in continuous training and, as in resistance exercise, remained in the medium and long term. Measurements of 6WMD and maximal oxygen uptake $VO_{2\ max/peak}$ and dyspnea were the indicative parameters for improvement.

Key words: Cardiotoxicity; Exercise Tolerance; Drug Therapy; Cancer Survivors.

Resumo

Introdução: A cardiotoxicidade pode afetar de forma direta a capacidade funcional, a ventilação pulmonar e a força muscular e, também, de forma indireta, outros órgãos e sistemas. O exercício físico é sugerido como uma estratégia não farmacológica efetiva e de baixo custo para minimizar ou prevenir dano miocárdico associado ao tratamento com antraciclinas. **Objetivo:** Discutir os efeitos do exercício físico em pacientes com risco para cardiotoxicidade pós-tratamento oncológico com quimioterapia e/ou radioterapia. **Método:** Realizada pesquisa nas bases de dados SciELO, PEDro e PubMed, nos idiomas português e inglês, por artigos científicos publicados entre 2007 e 2018. **Resultados:** Foram encontrados 256 *abstracts*, 34 foram selecionados para uma leitura na integra por atenderem aos critérios de inclusão, 25 artigos foram excluídos por não se enquadrarem nos critérios de inclusão e somente nove apresentaram associação dos efeitos do exercício na presença de cardiotoxicidade. **Conclusão:** A melhora do consumo máximo de oxigênio ($VO_{2\ max/pico}$) e da distância percorrida em 6 minutos (DP6M) foi mais evidente no treinamento contínuo e, assim como no exercício resistido, permaneceu por médio e longo prazo. As medidas da DP6M e do $VO_{2\ max/pico}$ e de ausência foram os parâmetros indicativos de melhora.

Palavras-chave: Cardiotoxicidade; Tolerância ao Exercício; Tratamento Farmacológico; Sobreviventes de Câncer.

Resumen

Introducción: la cardiotoxicidad puede afectar directamente la capacidad funcional, la ventilación pulmonar y la fuerza muscular, así como afectar indirectamente a otros órganos y sistemas. El ejercicio se sugiere como una estrategia no farmacológica efectiva y económica para minimizar o prevenir el daño miocárdico asociado con el tratamiento con antraciclina. **Objetivo:** Discutir los efectos del ejercicio físico en pacientes con cardiotoxicidad después del tratamiento del cáncer con quimioterapia y/radioterapia. **Método:** Se investigaron las bases de datos SciELO, PEDro y PubMed, en portugués e inglés, para artículos científicos publicados entre 2007 y 2018. **Resultados:** Encontramos 256 resúmenes, 34 fueron seleccionados para lectura completa porque cumplían con los criterios de inclusión, 25 artículos fueron excluidos porque no cumplían los criterios de inclusión y solo 9 presentaron la asociación de los efectos del ejercicio en presencia de cardiotoxicidad. **Conclusión:** La mejora en lo consumo máximo de oxígeno ($VO_{2\ max/pico}$) y la distancia de caminata de 6 minutos (6MWD) fue más evidente en el entrenamiento continuo y, como en el ejercicio de resistencia, se mantuvo en mediano y largo plazo. Las mediciones de 6MWD y $VO_{2\ max/pico}$ y disnea fueron los parámetros indicativos para la mejora.

Palabras clave: Cardiotoxicidad; Tolerancia al Ejercicio; Tratamiento Farmacológico; Supervivientes de Cáncer.

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INTRODUCTION

The term cancer covers an ensemble of more than 100 diseases that has as main characteristic the disordered multiplication of cells[1]. According to the *Global Cancer Statistics* 2018, the estimate of cancer increased 18.1 million new cases and approximately 9.6 million deaths in 2018[2].

In Brazil, cancer is the second disease with high number of mortality after cerebrovascular and cardiovascular diseases. In 2014, approximately 395 thousand new cases; of these, 205 thousand men and 190 thousand women with bigger incidence decreasing for prostate, lung and rectum in men and breast cancer in women, cervix, rectum, thyroid and lung[3].

Along the last decades, cancer treatment evolved greatly. The development and implementation of antineoplastic treatments improved substantially the prognosis of patients with cancer[4]. Even with its clinical benefits, it is not possible to underestimate the safety of oncologic therapy. Because of its mechanisms of action, many drugs can cause important deleterious effects in the cardiovascular system. The definition of cardiotoxicity, despite being the second major of cause of death in disease remission, is still beyond a general consensus[5].

The Cardiac Review and Evaluation Committee produced one of the most accurate definitions of cardiotoxicity through clinical evaluation. It considers criteria that do not include subclinical cardiovascular injuries that can occur in the beginning of the response to some chemotherapeutic agents: (1) cardiomyopathy with reduction of the left ventricular ejection fraction (LVEF), either global or in the intraventricular septum; (2) symptoms associated to cardiac insufficiency (CI); (3) signs associated to the presence of CI as third heart sound B3, tachycardia or both; (4) reduction of LVEF of at least 5% to 55% with symptomatology of CI or a reduction of LVEF of at least 10% to 55% without signs and symptoms of CI[6-8].

Cardiac dysfunction associated to chemotherapy treatment can have three different presentations: acute, subacute and chronic. Acute and subacute cardiotoxicity appears commonly in the beginning of the treatment and until two weeks after its ending. This type is rare and can cause different kinds of arrhythmias, abnormalities in ventricular repolarization and QT interval of the electrocardiogram (ECG), acute coronary syndrome, reactions in the pericardium and alterations of the myocardium. Chronic cardiotoxicity is the most frequent type depending of the cumulative dose administered, can be characterized with two subtypes, having as base the appearance of clinical symptoms: the first subtype consists in the appearance of symptoms within one year after the last session of chemotherapy, but in the second subtype, the symptomatology appears late after one year of treatment. In its majority, the symptoms are asymptomatic left systolic and/or diastolic ventricular dysfunction that leads to congestive severe cardiomyopathy and, possibly, death[9,10].

Cardiac toxicity may also be characterized as types I and II. This classification is based in the effect of the anticancer agent on cardiomyocyte. Type I can cause death of the cardiomyocyte through necrosis or apoptosis and is irreversible. Type II causes dysfunction in the cardiomyocyte but cellular death does not occur[9]. In 1979, von Hoff et al.[11] analyzed the potential risk factors for the development of doxorubicin (DOX)-induced congestive CI through a retrospective analysis of 4,018 patient's records. The general incidence of drugs-induced congestive CI was 2.2% (88 cases). However, more recent studies concluded there was a higher risk according to the dose applied where the risk for the development of cardiotoxicity presents variations according to the dose of the drug applied. DOX is associated to 5% of the cases of CI when the dose is 400 mg/m², however, the risk can be elevated to approximately 48% when the dose ministered is 700 mg/m². In previous studies that related the schedule of patients treated weekly, the incidence of CI was lower in comparison with patients treated thrice a week. High prevalence also occurred in the oldest population or with previous cardiopathy, factors that predispose the development of CI with the use of anticancer drugs[12,13].

Several mechanisms were developed to describe the physiopathology of cardiotoxicity, even though these mechanisms are not yet very clear since anthracyclines affect the cardiomyocytes. The methodological substantiation proposal involves the lipid peroxidation and oxidative stress in the cardiomyocytes. As a consequence of the anthracyclines mechanism of action, the synthesis of DNA, RNA and proteins tend to be compromised as well as important mechanisms that are involved in the transcription and regulation of specific cardio genes. This protein degradation is related to the increase of the degradation of myofilaments, which leads to unbalance of the number of proteins of the sarcomere as titin, provoking the process of cardiac sarcopenia. However, these effects can be potentialized with the use of combined therapies as, for instance, the anthracyclines and the monoclonal antibody trastuzumab. The use of this combination can cause effects at mitochondrial levels, which can affect the transformations of energy and provoke DNA injuries. Nonetheless, the anthracyclines provoke unbalance in the dynamic regulation of the cardiac function, in the alterations of the adrenergic activity, in the cyclase adenylate and homeostasis of calcium[8].

The suggestion to minimize or prevent myocardial injury associated to DOX treatment is physical activity as a low-cost, effective non-pharmacological strategy. During and after physical activity it occurs the activation of several mechanisms to keep or restore the cellular homeostasis. Changes in the intracellular concentrations of adenosine triphosphate (ATP) with elevated levels of adenosine diphosphate (ADP) and adenosine monophosphate (AMP), reduced reserves of glycogen, changes of temperature and pH, loss of calcium, among others, are important factors to increase the formation of the reactive species of oxygen (ROS) in the myocardium during and after prolonged physical activity. Whether this situation persists, it can occur modulating effect in the defense systems of cardiac cells in contrast with the former idea that ROS serves mainly as a trigger of oxidative damages because of its role as molecular signaling[14].

Some biomarkers as the cerebral natriuretic peptide and troponins are used for early diagnosis of cardiotoxicity. Echocardiography and nuclear medicine are other key tools for early detection[15,16].

Some drugs have cardiotoxicity potential, which, depending on the dose of the chemotherapeutic, may or not present reversibility. Table 1 describes these drugs.

Consequently, this study had as objective to review the efficacy of physical activity to prevent the risk of cardiotoxicity in patients who submitted to oncologic treatment with chemotherapeutics, radiotherapeutics or both concomitantly.

METHOD

The selection of scientific articles published from August 2017 to April 2018 formed the base of the current systematic review. The electronic bases SciELO, PubMed and PEDro were searched for articles of journals published in Portuguese and in English.

The inclusion criteria of the studies were: older than 18 years, treatment for some type of cancer with chemotherapy, radiotherapy or concomitant or some of these treatments with surgery, studies that evaluated the effects of physical exercise as potential reducer of cardiotoxicity-related variables resulting from antineoplastic treatment or studies that should have presented variables of test of functional capacity, physical exercises as 6 minute walk test (6MWT), maximum rate of oxygen consumption ($VO_{2\ max/peak}$), tests of peripheral muscular strength and dyspnea. Only the studies classified as clinical trial have been included. Articles that failed to present a methodology where the intervention utilized was not well detailed or had some flaw in the execution of the functional tests as not following the criteria of the *American Thoracic Society* for 6MWT were excluded.

The search of the articles used the following descriptors: cardiotoxicity, exercise tolerance, chemotherapy, radiotherapy, cardiac function, cancer survivors for Portuguese search; and *cardiotoxicity, cardiac toxicity, cancer survivors, chemotherapy, radiotherapy, exercise tolerance, cardiac function*, for search in English and the Boolean operator "AND" for the combination of the descriptors.

Firstly, the studies were analyzed through the titles in the databases searched and further, the review of the abstracts, excluding the articles that had some kind of repetition and could not be obtained in full. The studies selected for reading and systematic review were those that satisfied all the inclusion criteria. The analysis of the level of evidence and scores of recommendations of the studies used the scale PEDro.

RESULTS

The result of the search were 256 articles; of these, 142 were from PEDro database, other 37 in SciELO and 77, PubMed. After the analysis, 36 were removed because of repetition, 220, for non-compliance with the inclusion criteria and review of abstracts and titles, 34 selected for full reading and 25 articles excluded for non-compliance with the inclusion criteria or for some bias in the tests, like not following the criteria of the *American Thoracic Society* for 6MWT. Nine articles that met the methodological

Table 1. Drugs with cardiotoxicity potential

Cardiotoxicity	Drug	Cumulative Dose	Findings in the endomyocardial biopsy (electronic microscopy)	Reversibility
Type I	Doxorubicin Cyclophosphamide	Yes	Vacuoles, destruction of sarcomeres, necrosis	No
Type II	Trastuzumab Sunitinib Sorafenib	No	Ultrastructure benign appearance	Yes (majority of the cases)

Source: Adapted from Kalil Filho et al.[17].

criteria for functional capacity testing were included. The flowchart below shows these results.

The nine essays presented in this review were randomized, but only two were blind. The sample size ranged between 16 and 272 participants with diversification in their origin: two from the United States of America, one from Denmark, one from Australia, one from Serbia, one from Turkey, one from Canada and one from The Netherlands. Table 2 presents these studies.

The qualitative analysis of the works included the nine studies of the current review utilizing the scale PEDro. None of the studies analyzed was blinded either for patients and/or therapists; with this, the higher score reached in the studies was 8/10 (Table 3).

DISCUSSION

This systematic review showed that the aerobic and muscular strength trainings are directly associated to the reduction of the deleterious effects of the cancer treatment in the cardiovascular system and improvement of the quality of life. In studies conducted after the end of the treatment, the patients improved the 6 minutes walk test, the $VO_{2\ max/peak}$, the strength and quality of life.

There are evidences that demonstrate the improvement of the functional capacity, of the result of the 6MWT with aerobic exercise in patients who underwent chemotherapy and radiotherapy, either for a short or long term as concluded in the studies of Mustian et al.[18] and Brocki et al.[25]. These randomized trials with patients with several types of tumor did aerobic exercises, low and moderate intensity exercises during four [18] and ten weeks[25], respectively, with evaluation in the initial weeks of the treatment; and in the long term for 6MWT, handgrip dynamometry and electric bioimpedance. The patients trained at 60% to 70% of the maximum cardiac frequency for a period of seven days. During this period, they received a pedometer and were encouraged to walk ten thousand steps per day during four weeks. They were also guided to do strengthening exercises with customized elastic resistance bands of low to moderate load, increasing the resistance during the sixth week of radiation post-

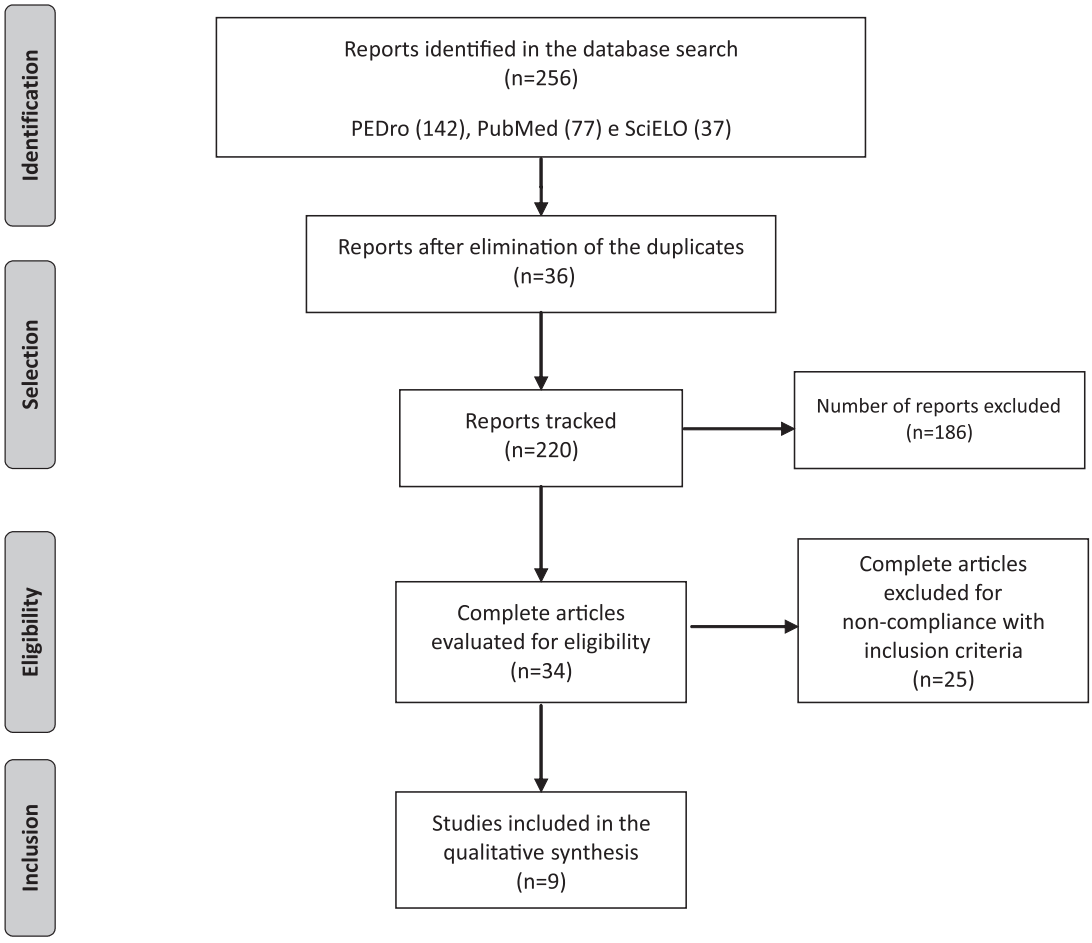

Figure 1. Result of the search

Table 2. Results of the articles listed

Author/year	Country of the study	Type of the study	Type of treatment/ Sample	Functional tests/ evaluation	Intervention	Results
Mustian et al., 2009[18]	USA	Randomized clinical trial	38 patients Post CT- training GI: Aerobic training and resistance training GC: Orientation to not perform activities 4 weeks of treatment and 3 months of follow up	6MWT, handgrip and electric bioimpedance in the beginning of the treatment, 4 weeks later and after 3 months follow up	GI: Aerobic training with 60% to 70% of the heart rate reserve MS: 1 set = 8-15 repetitions) for each one of the 11 exercises from a low to moderately challenging until 7 days a week 4 series with 15 repetitions	GI: Improvement of 6MWT and muscular strength GI after 3 months: Kept the improvement of MS and 6MTW
Toohey et al., 2016[19]	Australia	Randomized clinical essay	16 patients Training post CT, Rxt and hormone therapy GIT: aerobic interval training GCT: continuous aerobic training 12 weeks of training	6MWT: the evaluations were completed within 7 days prior to the beginning of the program and in the 7 following days	GIT: IT with 85% of the maximum CF with 7 intervals of 30 seconds GCT: Continuous training with 55% of maximum CF during 20 minutes	GIT: Increase of 18.48% in the 6na 6MWT GCT: Increase of 1.16% in 6MWT
Brdareski et al., 2012[20]	Serbia	Randomized prospective study	18 patients Post CT and Rxt training, hormone therapy or underwent surgery E1: Supervised aerobic training E2: The participants were invited to not change their life habits 3 weeks	$VO_{2\,max}$ Body weight $VO_{2\,max}$ was determined in the beginning and after 1 period of training of 3 weeks The subjective evaluation of the effort was made after each course of training in both groups	E1: ST with cycle-ergometer twice a week, during 3 weeks, with 21 minutes E2: The participants were invited to not change their habits of regular physical involvement or the nutritional habits during the study period	Increase of VO_2 (14.46%) in both groups E1 of 11.86% E2 of 17.72%
Courneya et al., 2007[21]	Canada	Randomized, controlled prospective clinical trial	242 patients Adjuvant CT to the training AET: Aerobic exercise training RET: Resistance exercise training GC: instructed to not start an exercise program 12 weeks	$VO_{2\,max}$ The patients were evaluated at baseline (1 to 2 weeks after the beginning of the chemotherapy); mid point of chemotherapy); after the intervention (3 to 4 weeks after chemotherapy); and follow up of 6 months (data not presented)	AET: Beginning with 60% of the $VO_{2\,max}$ from 1st to 6th weeks, next, 70% of $VO_{2\,max}$ in the 7th and 12th weeks and with 80% after the 12th week RET: UPPER LIMBS and LOWER LIMBS with 8 to 12 repetitions with 60 to 70% of 1MR GC: oriented to not initiate exercise program	Bigger $VO_{2\,max}$ in group AET
Vardar Yağlı et al., 2015[22]	Turkey	Randomized clinical trial	52 patients Training post-RXt and CT GI: Aerobic training with yoga consisted of group sessions of approximately 60 minutes GC: Aerobic training 6 weeks	6MWT Groups submitted to submaximum test in the first consultation, in the 3rd and in the 6th. week	The two groups were instructed to do aerobic exercises for 30 minutes per day, at 60 % to 70% of the RF_{max} expected. The yoga program consisted of sessions in group (Hope Lodge) during 60 minutes, thrice a week for 6 weeks	Aerobic training and yoga increased 6MWT in 17.09% Aerobic training had a raise of 12.58%

to be continued

Table 2. continuation

Author/year	Country of the study	Type of the study	Type of treatment/ Sample	Functional tests/ evaluation	Intervention	Results
Dolan et al., 2016[23]	Canada	Randomized pilot study	36 patients Training post CT and Rxt CMT: Moderate intensity continuous moderate training AIT: Interval training increasing intensity GC: Keeping life habits 6 weeks	VO_{2peak} Monitoring of the RHR after 5 minutes in silence and seated. After, evaluated the muscle strength of the lower limbs. 3 months after the intervention, both groups of exercises were approached by e-mail	CMT: Moderate intensity CT AIT: This group did IT increasing the intensity GC: The participants were oriented to keep their normal habits	GC, CMT and AIT increased the aerobic capacity (P=0;844) $VO_{2\ peak}$ After 3 months, 92% of the women of the group AIT reported they met or replaced the recommendations of week exercises according to the guidelines
Hornsby et al., 2014[24]	United States of America	Randomized, blind clinical trial	20 patients Training post CT GI: Supervised aerobic training GC: Receive doxorubicin plus cyclophosphamide 3 months	$VO_{2\ peak}$ Patients evaluated in the beginning of the training, in the 3rd, 6th, 9th and 12th weeks	GI: ST with aerobic exercises in cycle ergometer 3 times a week with 60%-100% of the capacity of exercise ($VO_{2\ peak}$) GC: Receive doxorubicin plus cyclophosphamide	GI increased $VO_{2\ peak}$ in 13.3% GC decrease of 8.6%
Brocki et al., 2014[25]	Denmark	Blind, randomized, evaluating clinical trial	78 patients Training post Rxt GI: Aerobic training GC: Received individual exercise training 10 weeks	6MWT, test of lung capacity Patients evaluated in the 3rd week after surgery and after 4th and 12th month	GI: ST one hour, once a week during 10 weeks. Sessions based in aerobic exercises with target-intensity of 7-12 in the classification of Borg GC: received instruction for individual exercise training	Both groups increased the 6MWT p=0.57 4 months later and p=0.93, 1 year later. No concrete change in the pulmonary function test
Kampshoff et al., 201[82]6	The Netherlands	Randomized clinical trial	272 patients Training post CT HI: Resistance exercises 70%-85% of 1MR LMI: low intensity resistance exercise 40%-55% of 1MR 12 weeks	Pulmonary function tests, handgrip	HI: Resistance exercises between 70%-85% of 1MR during 8 minutes and reaching 80% for a period of 3 to 5 minutes The group LMI did resistance exercises between 40%-55% of 1 MR and IT with 30%-45% during 8 minutes and reaching 40%-50% for 3 to 5 minutes	$VO_{2\ peak}$ LMI: increase of 1% HI: increase of 1.6% Handgrip LMI: increase of 1.5% HI: increase of 1.4%

Captions: QT: chemotherapy; GC: group control; GI: group intervention; 6MWT: six minute walk test; DC6M: distance covered in 6 minutes; $VO_{2\ max/peak}$: maximum oxygen consumption; GE: group exercises; MET: metabolic equivalent estimate; CF: cardiac frequency; RF: respiratory frequency; MS: maximum strength; VT: ventilatory threshold; MIAE: moderately intense aerobic exercise; Rxt: radiotherapy; 1MR: one maximum repetition; AT: aerobic training; CT: continuous training; IT: interval training; ST: supervised training; TLC: total lung capacity; AC: aerobic capacity; GIT: group interval training; GCT: group continuous training; E1: *exercise* 1; E2: *exercise* 2; AET: *aerobic exercise training;* RET: *resistance exercise training*; LMI: *low-to moderate intensity*; HI: *high intensity*; CMT – continuous moderate training; AIT – aerobic interval training.

intervention and there was follow up again after three months of intervention. In the randomized trial of Brocki et al.[25] with post-therapy patients, the group intervention did exercises during one hour, once a week during ten weeks. The sessions consisted of aerobic exercises with target-intensity from seven to 12 in the classification of Borg. The group control received individual instruction with exercise training. Both groups were followed up for a period of 12 months after the end of the treatment. After the follow up, only 41 patients were revaluated, since some abandoned the treatment and other because of death. Even with these involuntary losses, the aerobic training of low to moderate intensities has been fairly useful.

However, other clinical trials also evaluated the 6MWT in patients submitted to cancer treatment who developed cardiotoxicity. Toohey et al.[19] conducted a

Table 3. Escala PEDro

	Mustian et al., 2009[18]	Toohey et al., 2016[19]	Brdareski et al., 2012[20]	Courneya et al., 2007[21]	Vardar YAğLđ et al., 2015[22]	Dolan et al., 2016[23]	Hornsby et al., 2014[24]	Brocki et al., 2014[25]	Kampshoff et al., 2018[26]
Eligibility criteria	Y	Y	N	Y	Y	N	Y	Y	Y
Random assignment	Y	Y	Y	Y	Y	Y	Y	Y	Y
Sequence of random assignment	Y	N	N	Y	Y	N	Y	Y	Y
Equality between groups in pre-treatment	Y	Y	Y	Y	Y	Y	Y	Y	Y
Blinding of the patients	N	N	N	N	N	N	N	N	N
Blinding of the therapists	N	N	N	N	N	N	N	N	N
Blinding of the reviewers	N	N	N	N	N	N	Y	Y	N
Follow-up of at least 85% of the participants	Y	Y	Y	Y	N	Y	Y	Y	Y
Analysis per intent to treat	Y	Y	N	Y	N	N	Y	Y	Y
Comparison between groups	Y	Y	Y	Y	Y	Y	Y	Y	Y
Specification of the sample size of the treatment	Y	Y	Y	Y	Y	Y	Y	Y	Y
Total scores	7/10	6/10	5/10	7/10	5/10	5/10	8/10	8/10	7/10

Captions: Y: yes; N: no.

randomized clinical trial with patients with several types of tumor who did the aerobic training. The patients were divided in two groups, one with continuous and interval training during 12 weeks and underwent evaluation of 6MWT during the following seven days. The patients of the continuous training had an increase of 1.16% of 6MWT compared with the first test while the group of interval training had a raise of 18.53% when compared with the first test. Nevertheless, when comparing the two groups, the results were slightly higher in the continuous treatment group. In this study, there was a significant reduction of the risk factors for cardiovascular diseases.

In addition to measuring the 6MWT other authors did the aerobic training with different conducts to analyze the peripheral muscular strength as well as Vardar YAğLđ et al.[22] did through yoga and Mustian et al.[18] utilizing elastic bands. Vardar YAğLđ et al.[22] in their study divided the patients in two groups: one did only the aerobic training and the other, aerobic training with yoga. The patients of both groups had a significant increase of the muscular strength in the quadriceps, shoulder abductors and peripheral musculature, that was measured with a dynamometer with a perceptible raise in the group of yoga and aerobic training, unlike the study of Mustian et al.[18], where with elastic bands, the patients had a slight decrease of the muscular strength soon after the treatment period. However, after three months of follow up, the muscular strength increased[18].

$VO_{2\,MAX}$ AND $VO_{2\,PEAK}$

Two randomized clinical trials[21,24] analyzed the $VO_{2\,peak}$ using aerobic training and in only one of them[21], there were muscular strengthening exercises. The study of Hornsby et al.[24] with 20 patients who received treatment with chemotherapy assigned to two groups, one did only the DOX treatment and cyclophosphamide and the other, in addition to the treatment, also received a series of exercises in the cycle ergometer during 12 weeks and there was a significant increase of $VO_{2\,peak}$ when compared with the first evaluation; however, in the group

that underwent treatment with drugs alone, there was a drop of 8.6% of the $VO_{2\ peak}$. Corroborating the study of Hornsby et al.[24], the randomized clinical trial of Courneya et al.[21] evaluated 242 women with breast cancer who underwent chemotherapy. The protocol of exercises of this study was initiated still during chemotherapy and the patients were divided in three groups: the first performed aerobic activities; the second, resistance training and the third (group control) was asked to not initiate physical activities. For the aerobic exercises patients, the $VO_{2\ peak}$ had a significant increase in comparison to the previous evaluation and also when compared with other groups, but in the group of resistance activities alone, the 1MR test increased. Collaborating with these findings, Dolan et al.[23] conducted a study where post-menopause women and neoplasm survivors were assigned to three groups. Two, made continuous aerobic exercises, with 6 weeks interval and one, the control group, had the objective of analyzing the $VO_{2\ peak}$. For the patients who submitted to interval exercises, the $VO_{2\ peak}$ increased 11.48% when compared with the initial value, but the group with continuous exercises, the improvement was a little better, of 12.95% and the control group had a decrease of -5.97%.

Brdareski et al.[20], in a randomized clinical trial used the cycle ergometer. The patients divided in two groups, each one performed aerobic exercises with the cycle ergometer during three weeks of treatment. Kampshoff et al.[26], in a randomized clinical trial, divided the patients in two groups, one with high intensity training with resistance exercises between 70% to 85%, 1 MR during 8 minutes reaching 80% for a period of 3 to 5 minutes and the other, of moderate intensity, consisting of resistance exercises between 40% and 55%, 1MR for 12 weeks under physiotherapists supervision. Both groups underwent exercises sessions including resistance and strengthening trainings and the parameter was the 1 MR test. The two studies included patients after chemotherapy and radiotherapy treatment. In the study of Brdareski et al.[20], the patients who did the supervised training in the cycle ergometer improved their $VO_{2\ max}$. The Kampshoff et al.[26] study revealed that there was progress of $VO_{2\ peak}$ and in the muscular strength.

The 6MWT and $VO_{2\ max/peak}$ evolved in the studies analyzed in relation to aerobic training, either continuous or with interval, with more benefit for the continuous compared with interval; the resistance training corroborated the improvement of these parameters.

The current study has limitations because there are studies with involuntary loss of sample, mainly those that had the objective of a long term follow up with the patients, other that were excluded because the tests had bias in their elaboration and difficulty of finding clinical trials that complied with the inclusion criteria.

CONCLUSION

The studies analyzed demonstrated that VO_2 and 6MWT were better fulfilled in the continuous training in comparison with the interval training with the benefits continuing in medium and long term just like the resistance exercises promoted improvement of the muscular strength in the same period.

CONTRIBUTIONS

Marcos Vinicius dos Santos Corrêa, Sergio Luiz Soares Marcos da Cunha Chermont and Mônica Maria Pena Quintão contributed substantially for the conception and/or interpretation of the data and of the wording and/or critical review. Tatiana Abelin Saldanha Marinho contributed for the wording and/or critical review. All the authors approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There are no conflict of interests to declare.

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REFERENCES

1. Maia TN, Araujo GBR, Teixeira JAC, et al. Cardiotoxicity of doxorubicin treatment and physical activity: a systematic review. Int J Cardiovasc Sci. 2017;30(1):70-80. doi: http://dx.doi.org/10.5935/2359-4802.20170004
2. Ferlay J, Colombet M, Soerjomataram L, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 2018;144(8):1941-53. doi: http://dx.doi.org/10.1002/ijc.31937.
3. Barbosa IR, Souza DL, Bernal MM, et al. Cancer mortality in Brazil: temporal trends and predictions for the year 2030. Medicine (Baltimore). 2015;94(16):e746. doi: http://dx.doi.org/10.1097/MD.0000000000000746
4. Minami M, Matsumoto S, Horiuchi H. Cardiovascular side-effects of modern cancer therapy. Circ J. 2010;74(9):1779-86. doi: http://dx.doi.org/10.1253/circj.cj-10-0632
5. Sulpher J, Mathur S, Lenihan D, et al. An international survey of health care providers involved in the management of cancer patients exposed to cardiotoxic therapy. J Oncol. 2015;2015:391848. doi: http://dx.doi.org/10.1155/2015/391848
6. Albini A, Pennesi G, Donatelli F, et al. Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardio-oncological prevention. J Natl Cancer Inst.

2010;102(1):14-25. doi: https://doi.org/10.1093/jnci/djp440

7. Seidman A, Hudis C, Perri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol. 2002;20(5):1215-21. doi: https://doi.org/10.1200/JCO.2002.20.5.1215
8. Adão R, Keulenaer G, Leite-Moreira A, et al. Cardiotoxicidade associada à terapêutica oncológica: mecanismos fisiopatológicos e estratégias de prevenção. Rev Port Cardiol. 2013;32(5):395-409. doi: https://doi.org/10.1016/j.repc.2012.11.002
9. Florescu M, Cinteza M, Vinereanu D. Chemotherapy-induced cardiotoxicity. Maedica (Buchar) [Internet]. 2013 [cited 2017 Sept 2];8(1):59-67. Available from: https://www.maedica.ro/articles/2013/1/2013_Vol8(11)_No1_pg59-67.pdf
10. Dolci A, Dominici R, Cardinale D, et al. Biochemical markers for prediction of chemotherapy-induced cardiotoxicity: systematic review of the literature and recommendations for use. Am J Clin Pathol. 2008;130(5):688-95. doi: https://doi.org/10.1309/AJCPB66LRIIVMQDR
11. von Hoff DD, Layard MW, Basa P, et al. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med. 1979;91(5):710-7. doi: https://doi.org/10.7326/0003-4819-91-5-710
12. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer. 2003;97(11):2869-79. doi: https://doi.org/10.1002/cncr.11407
13. Zamorano JL, Lancellotti P, Munõz DR, et al. 2016 ESC position paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the task force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J. 2016;37(36):2768-2801. doi: https://doi.org/10.1093/eurheartj/ehw211
14. Costa TR, Tamburús NY, Souza FR, et al. Cardiotoxicity of chemotherapy drugs and possible protective effects of physical exercise: a literature review. J Resp Cardiov Phy Ther [Internet]. 2016 [cited 2018 Jan 11];4(2):37-46. Available from: https://periodicos.ufrn.br/revistadefisioterapia/article/view/8909
15. Cardinale D, Sandri MT. Role of biomarkers in chemotherapy-induced cardiotoxicity. Prog Cardiovasc Dis. 2010;53(2):121-9. doi: https://doi.org/10.1016/j.pcad.2010.04.002
16. Borges JA, Quintão MMP, Chermont SSMC, et al. Fatigue: a complex symptom and its impact on cancer and heart failure. Int J Cardiovasc Sci. 2018;31(4):433-42. doi: http://dx.doi.org/10.5935/2359-4802.20180027
17. Kalil Filho R, Hajjar LA, Bacal F, et al. I Diretriz Brasileira de Cardio-Oncologia da Sociedade Brasileira de Cardiologia. Arq Bras Cardiol [Internet]. 2011[acesso 2017 dez. 8];96(2 Supl 1):1-52. Disponível em: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0066-782X2011000700001&lng=pt&nrm=iso&tlng=pt.
18. Mustian KM, Peppone L, Darling TV, et al. A 4-week home-based aerobic and resistance exercise program during radiation therapy: a pilot randomized clinical trial. J Support Oncol [Internet]. 2009 [cited 2017 Oct 19];7(5):158-67. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3034389/
19. Toohey K, Pumpa KL, Arnolda L, et al. A pilot study examining the effects of low-volume high-intensity interval training and continuous low to moderate intensity training on quality of life, functional capacity and cardiovascular risk factors in cancer survivors. PeerJ. 2016;4:e2613. doi: https://doi.org/10.7717/peerj.2613
20. Brdareski Z, Djurović A, Šušnjar S, et al. Effects of a short-term differently dosed aerobic exercise on maximum aerobic capacity in breast cancer survivors: a pilot study. Vojnosanit Pregl. 2012;69(3):237-42. doi: https://doi.org/10.2298/VSP101117004B
21. Courneya KS, Segal RJ, Mackey JR, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. J Clin Oncol. 2007;25(28):4396-404. doi: https://doi.org/10.1200/JCO.2006.08.2024
22. Vardar Yağlı N, Şener G, Arıkan H, et al. Do yoga and aerobic exercise training have impact on functional capacity, fatigue, peripheral muscle strength, and quality of life in breast cancer survivors? Integr Cancer Ther. 2015;14(2):125-32. doi: https://doi.org/10.1177/1534735414565699
23. Dolan LB, Campbell K, Gelmon, K, et al. Interval versus continuous aerobic exercise training in breast cancer survivors--a pilot RCT. Support Care Cancer. 2016;24(1):119-127. doi: https://doi.org/10.1007/s00520-015-2749-y
24. Hornsby WE, Douglas PS, West MJ, et al. Safety and efficacy of aerobic training in operable breast cancer patients receiving neoadjuvant chemotherapy: a phase II randomized trial. Acta Oncol. 2014;53(1):65-74. doi: https://doi.org/10.3109/0284186X.2013.781673
25. Brocki BC, Andreasen J, Nielsen LR, et al. Short and long-term effects of supervised versus unsupervised exercise training on health-related quality of life and functional outcomes following lung cancer surgery: a randomized controlled trial. Lung Cancer. 2014;83(1):102-8. doi: https://doi.org/10.1016/j.lungcan.2013.10.015
26. Kampshoff CS, van Dongen JM, van Mechelen W, et al. Long-term effectiveness and cost-effectiveness of

high versus low-to-moderate intensity resistance and endurance exercise interventions among cancer survivors. J Cancer Surviv.2018;12(3):417-29. doi: http://dx.doi.org/10.1007/s11764-018-0681-0

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