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REVIEW ARTICLE

Cardiotoxicity of Doxorubicin Treatment and Physical Activity: A Systematic Review

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Abstract

The present study investigated whether the practice of exercise has a protective effect against cardiac toxicity induced by doxorubicin (DOX). A systematic review of randomized clinical trials evaluating the role of exercise in the control or prevention of DOX-induced cardiotoxicity was performed in MEDLINE and LILACS databases. Studies that did not address the main subject of this review, did not mention physical exercise or DOX, studies that evaluated other types of anthracycline-induced toxicities only (muscle, hepatic and renal toxicity) or other effects of exercise on DOX toxicity (fatigue) were excluded. With respect to the variables related to aerobic exercise prescription, there was no direct relationship between the frequency of exercise and the results of the studies. Also, intensity of exercise was not decisive for preservation of cardiac function, although a more intense exercise was associated with improvements in the antioxidant system, which was not observed in studies on lower intensity exercises. No significant differences in exercise effects were observed when it was performed before, during or after the treatment. Therefore, aerobic exercise may exert a protective effect of cardiac functions when performed before, during or after treatment with DOX. However, the mechanisms of this effect are still unknown.

Introduction

Cancer refers to a group of more than 100 diseases that have uncontrolled cell multiplication as the main characteristic.[1-3] According to the National Cancer Institute estimates,[2] the number of cases has drastically increased in the last decades. Today, neoplasms represent an important cause of morbidity and mortality, accounting for more than 12% of deaths in the world.[4]

In parallel with the increase in the number of confirmed cases of cancer, new modalities of treatment has increased cancer survival and possibilities of cure.[3] However, the treatment may cause several adverse effects,[5] including treatment-related cardiotoxicity that may lead to poorer prognosis than cancer itself, and also affect treatment continuation.[6] Depending on the therapy, users of oncology services may have a 15-fold increased chance of suffering heart failure.[7]

In this regard, it is worth mentioning the cardioprotective properties of exercise in the context of cardiovascular diseases, highlighted by previous studies,[8] as an incentive for studies on exercise and cardiotoxic chemotherapy agents. Doxorubicin (DOX) was selected for this review, since it is a chemotherapy drug used in the treatment of a wide range of cancers, with a high evidence level of cardiotoxicity.[6] Our hypothesis is that the exercise can have a protective effect against DOX-induced cardiotoxicity.

The aim of this article is to review the literature and verify whether the practice of exercises has a protective effect against DOX cardiotoxicity.

Randomized clinical trials that evaluated the role of exercise in the control or prevention of DOX-induced cardiotoxicity, published in Portuguese, English or Spanish from 2003 were included in this review. Only open access articles or those available on CAPES (Brazilian Federal Agency for Support and

Keywords

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Evaluation of Graduate Education) web search engine were considered eligible.

The Medical Literature Analysis and Retrieval System Online (MEDLINE) accessed via Public Medline (PubMed), and the Literature in the Health Sciences in Latin America and the Caribbean (LILACS) databases were used for the search.

The descriptors were selected based on direct representation of the theme and frequency of appearance in studies used for the theoretical foundation of this review. Also, all terms used for the search for articles published in Portuguese, English and Spanish were available at *Health Sciences Descriptors*, and those used for the search for articles published in English at the US Library of Medicine (NLM). The descriptors used were: *exercise* (or the corresponding *physical conditioning* for studies conducted with animals, according to DeCS' recommendations); *Anthracyclines*; *Doxorubicin*; *Adriamycin*; *cardiotoxic agents*. The descriptor *cardiotoxicity* was included in the search. Although it had not been available in the databases as an indexed term, it is widely used in articles published in the field, including the I Brazilian Guideline for Cardio-Oncology from the Brazilian Society of Cardiology.[6]

We used the advanced search tools that limit and specify all terms available at each database. The initial search yielded 145 articles. After analysis of the abstracts, 123 articles did not meet the aim of this review and three did not have an open access or were available at Capes website and were excluded. Exclusion criteria were: studies that were out of the main subject of this review (cardioprotective effect of exercise on the use of DOX), studies that did not mention physical exercise or DOX, studies on other types of anthracycline-induced toxicities (muscle, hepatic and renal toxicity), studies that evaluated other effects of exercise on DOX toxicity (fatigue), studies published before 2003, other study formats (review) and studies published in other languages.

All articles included were fully examined for a critical evaluation and data collection. Data analysis, presentation and interpretation were conducted subsequently; data were stratified and recorded in a sheet, which was used for the description of final results. Finally, the refinement and update of data was performed by a new search on May 05, 2015.

According to the inclusion criteria and the search tools, 20 randomized, clinical trials evaluating the effect of aerobic exercise on DOX-induced cardiotoxicity were identified (Chart 1).

In 20 studies evaluated, 19 were carried out on rats or mice, 14 of them on adult male rats to isolate the cardioprotective effect of estrogen estrogênio.[10-15,17,18,20,22-25,27]. A study[7] on male rats aimed to determine whether physical exercise had a cardioprotective effect on juvenile rats treated with DOX. Four studies[9,16,19,26] were performed on female animals due to protocol particularities and/or to simulate treatment conditions as similar as possible to human conditions. A study by Hornsby et al.[21] was conducted on women with operable breast cancer receiving neoadjuvant chemotherapy.

Treatment protocols

There were some differences between treatment protocols. In six studies,[15,16,20,22,23,26] the DOX dose was 10 mg/kg. Chicco et al.[9] found that exercise provides resistance against cardiac dysfunction and oxidative damage associated with DOX. Hydocket et al.,[19] using the dose of 10mg/kg (administered at 1mg/day), observed a protection against DOX acute effect for over 10 days, hence preventing cardiac dysfunction and distribution of myosin heavy chain isoforms. Using the same dose, Jensen et al.[26] observed a significant reduction of myocardial DOX accumulation in all subgroups. At 10mg/kg and especially at 20mg/kg, a protective effect of exercise was observed on cardiac biological functions related to cardiac system.[22,23]

Four studies used a single dose of 15 mg/kg.[13,14,19,24] In the study by Chicco et al.,[13] exercise attenuated cardiac dysfunction and lipid peroxidation induced by DOX, and increased HSP72 levels. This is a heat shock protein (HSP) found in cardiomyocytes in exercise, and increased HSP72 levels are associated with preservation of cardiac functions during oxidative stress.[17] Wonders et al.[14] observed that the acute effect of exercise prevented the decrease of cardiac function at this dose. Martins et al.[24] investigated the protective effect against DNA damage in cardiac cells in male rats receiving DOX, and obtained a positive result.

Studies by Chicco et al.[11] and Hayward et al.[7] used fractionated doses of 15mg/kg and 14mg/kg, respectively. The first study[11] used a fractionated dose of 2.5mg/kg three times a week; the results indicated a protection against left ventricular dysfunction and inhibition of the increase in apoptosis signaling. Also, no effect of exercise was observed on HSP levels or antioxidant metabolism.[11] The second study[7] used

Chart 1 – Clinical trials evaluated (n=19)

Authors	Population	Treatment protocol	Exercise	Protective effects identified
Chicco et al.[9]	Female rats (n=28)	10 μ DOX for 60 min	Voluntary 8 weeks before DOX	Resistance against cardiac dysfunction and oxidative damage, increase in heat shock protein (HSP72)
Ascensão et al.[10]	Male rats (n=40)	20 mg/kg single dose	Treadmill running 60 min/day, 5 days/week, 14 weeks before DOX	Maintenance of homeostasis, increase in mitochondrial defenses and reduced oxidative damage.
Chicco et al.[11]	Male rats (n=28)	2,5 mg/kg 3 x / week for 2 weeks (15mg/kg)	Treadmill 60 min/day, 5 days/week, 2 weeks during DOX treatment	Attenuated left ventricular dysfunction and apoptotic signal activation.
Ascensão et al.[12]	Male rats (n=44)	20 mg/kg single dose	Swimming 1h/day, 5 days/week for 14 weeks before treatment	Increase in cardiac muscle tolerance to DOX, with increased response of antioxidant system.
Chicco et al.[13]	Male rats (n=42)	15 mg/kg single dose	Treadmill 1h/day, 5 days/week for 14 weeks before treatment	Attenuated cardiac dysfunction and lipid peroxidation, and increased HSP72.
Wonders et al.[14]	Male rats (n=not specified)	15 mg/kg single dose	Treadmill 1 hour on a single day before DOX	Prevented cardiac dysfunction.
Hydock et al.[15]	Male rats (n=147)	10 mg/kg single dose	Voluntary and treadmill, 1h/day, 5 days/week for 8 weeks before treatment	Protected against cardiotoxicity for up to 10 days, preserving cardiac function and myosin heavy chain expression.
Wonders et al.[16]	Female rats (n=45)	DOX 10mg/kg single dose + GW2974	Treadmill 60 min/day, 5 days/week for 8 weeks before treatment	Preserved cardiac function and decreased apoptosis signaling and lipid peroxidation.
Kavazis et al.[17]	Male rats (n=28)	20 mg/kg single dose	Treadmill 60 min/day, 5 days/week for one week	Attenuated mitochondrial damage and preserved the antioxidant metabolism.
Ascensão et al.[18]	Male rats (n=20)	20 mg/kg single dose	Treadmill, 1hour on a single day before DOX	Prevented the decrease in mitochondrial function and antioxidant metabolism
Hydock et al.[19]	Female rats (n=49)	15 mg/kg single dose + goserelin acetate	Treadmill 60 min/day, for 8 weeks during treatment	Attenuated dysfunction of left ventricle and mitral and aortic valves.
Hydock et al.[20]	Male rats (n=94)	1 mg/kg/day for 10 days (10 mg/kg)	Voluntary and treadmill, 1h/day, 5 days/week for 8 weeks before treatment	Prevented cardiac dysfunction and expression of myosin heavy chain even after 1 month of treatment.
Hornsby et al [21]	Humans (n=20)	60 mg/m² + 600 mg/m² cyclophosphamide One dose every 3 weeks for 12 weeks.	Cycle ergometry 60 min/day, 3 days/week for 12 weeks during treatment.	Attenuated the increase in natriuretic peptides.
Hayward et al.[7]	Rat pups (n=64)	2 mg/kg/day during 12 days (14 mg/kg)	Voluntary for 10 weeks during and after treatment	Preserved cardiac growth curve and body mass, and attenuated cardiac dysfunction.
Ashrafi and Roshan[22]	Male rats (n=48)	10 mg/kg, 20 mg/kg	Treadmill warm up + 39 min/day, 5 days/week for 4 weeks before DOX	Protected against oxidative damage and preserved the balance between production and catabolism of oxidative agents oxidative.

Continuation

Shirinbayan and Roshan [23]	Male rats (n=48)	10mg/kg, 20mg/kg	Treadmill warm up + 39 min/day, 5 days/week for 4 weeks before DOX	Decrease the risk of cardiac disturbance and preserved the antioxidant systems.
Martins et al.[24]	Male rats (n=12)	15 mg/kg single dose	Swimming 60 min/day, 5 days/week, for over 21 days of treatment	Protection to cardiac cell DNA.
Smuder et al.[25]	Male rats (n=24)	20 mg/kg single dose	Treadmill 60 min/day, 5 days/week for one week before treatment	Inhibited the increase in lysosomal autophagy signaling.
Jensen et al.[26]	Female rats (n=77)	10 mg/kg single dose	Voluntary and treadmill, 1h/day, 5 days/week for 10 weeks before treatment	Reduced the time and the level of myocardial DOX accumulation.
Marques-Aleixo et al.[27]	Male rats (n=36)	2 mg/kg/ week for 7 weeks	Voluntary and treadmill 1 h/day, 5 days/week for 12 weeks	Improved mitochondrial bioenergetic fitness and prevented the damage caused by oxidative stress.

DOX: doxorubicin; HSP: heat shock protein

a fractionated dose of 2mg/kg/day for one week. In this study,[7] the exercise was effective in preventing the decrease in cardiac growth curve, body mass and cardiac functions. The study by Marques-Aleixo et al.[27] also used a treatment protocol with a fractionated dose of 2mg/kg (one dose per week) for 7 weeks; exercise improved mitochondrial bioenergetics and prevented oxidative stress-induced damage.

The maximal dose of DOX in the studies was 20 mg/kg, found in five studies.[10,12,17,18,25] Ascensao et al.[12] observed attenuation of cardiac muscle stress and improvement of antioxidant system. The others[10,17,18,25] demonstrated that exercise was effective in preventing oxidative stress-induced damage, preserving homeostasis and mitochondrial functions, and inhibiting the increase in apoptosis signaling induced by DOX. In addition, Smuder et al.[25] found that exercise inhibited the increase of lysosomal autophagy signaling.

With respect to the protocols that combined more than one chemotherapy agent, three studies evaluated the effect of DOC combined with other medications.[16,20,21] Wonders et al.[16] examined the combination of DOX and GW2974, a HER-2 (human epidermal growth factor receptor 2) inhibitor. The HER-2 gene is associated with normal growth and development of breasts, and its overexpression occurs in 30% of breast cancers.[16] GW2974 is a trastuzumab analog, a monoclonal antibody used in breast cancer treatment.[16] This treatment protocol is associated with increased incidence of cardiac dysfunction and heart failure.[6,16] At the end of the training period, there was a reduction in lipid peroxidation and a possible protection against apoptosis induction.[16] Hydock et al.[19] used a protocol of DOX (15 mg/kg) combined with goserelin acetate. After treatment, cardiac function was analyzed *in vivo* by echocardiography and *ex vivo*. The results indicated that cardiac dysfunction was significantly attenuated in the group subjected to exercise.[20]

The possible cardioprotective mechanisms of aerobic exercise are presented in Chart 2.

Exercise protocols according to the F.I.T.T principle

As described in Chart 1, all studies included in this review evaluated the capacity of aerobic exercises to provide cardioprotection against DOX adverse effects. Therefore, the following factors will be discussed: frequency, intensity, duration and type of exercise, following the F.I.T.T. (acronym for frequency, intensity, time and type) principle, used in aerobic exercise prescription.[28]

Frequency

With respect to how often the animals exercised, two studies[14,18] conducted two weeks of acclimation and a

Chart 2 – Cardioprotective mechanisms of aerobic exercise

Studies	Cardioprotective mechanisms
Chicco et al.[9]	Maintenance of internal pressure and attenuation of lipid peroxidation in left ventricle. Increased expression of the heat shock protein HSP7. No significant results in mitochondrial expression of superoxide dismutase (or isoforms) in the heart of trained animals.
Ascensão et al.[10]	Completely prevented the effect of DOX on state-3 respiration, respiratory control ratio, and uncoupled respiration. Decreased DOX-induced increase in calcium sensitivity, increase in mitochondrial protein carbonyl groups, malondialdehyde, Bax, Bax/BCLW ratio, tissue caspase-3 activity. Training also increased the expression of mitochondrial HSP-60 and tissue HSP-70.
Chicco et al.[11]	Low-intensity exercise did not provide a sufficiently intense stimulus to change HSP72 and SOD expression. On the other hand, exercise attenuated left ventricular dysfunction and apoptotic signal activation induced by DOX.
Ascensão et al.[12]	The levels of oxidative stress markers indicated that exercise decreased acute DOX-induced disturbances. The authors suggested that glutathione and HSP responses may have been essential for the defense against DOX-related free radicals.
Chicco et al.[13]	Attenuated the decrease in cardiac functions: heart rate, left ventricular developed pressure, left ventricular systolic function, dP/dt max, left ventricular relaxation, minimum DT/DP. Completely prevented DOX-induced MDA+4HAE increase, protecting against lipid peroxidation. No significant changes in SOD or HSP72 in left ventricle.
Wonders et al.[14]	Attenuated the decrease in the end-diastolic pressure/left ventricular diastolic pressure ratio and prevented the DOX-induced increase in MDA + 4 HAE, suggesting that exercise reduced left ventricular lipid peroxidation.
Hydock et al.[15]	Attenuated DOX-induced α-MHC upregulation
Wonders et al.[16]	Preserved cardiac functions, decreased MDA+4-HAE, caspase-3 and caspase-8 levels.
Kavazis et al.[17]	Protected against deleterious effect of DOX on cardiomyocytes, by increasing the expression of antioxidant enzymes and HSP72 in cardiomyocytes. However, a model of HSP72 isolation, tested by the authors, did not eliminate the exercise-induced cardioprotective effect, suggesting that such effect was caused by the increase in antioxidant enzymes.
Ascensão et al.[18]	Prevented the decease in cardiac mitochondrial functions, preserved mitochondrial phosphorylation capacity, attenuated the decreased tolerance to mitochondrial permeability transition pore opening, protected the activity of cardiac mitochondrial chain complexes I and V, and increased caspase 3 and 9 and mitochondrial SOD activities.
Hydock et al.[19]	Prevented a 22% reduction in left ventricular ejection fraction and depressed aortic and mitral valve blood flow. Preserved MHC, but had no effect on sarcoendoplasmic reticulum Ca2+ ATPase 2a expression.
Hydock et al.[20]	Preserved maximal and mean mitral valve blood flow.
Hornsby et al. [21]	Attenuated the increase in natriuretic peptides.
Hayward et al.[7]	Preserved diastolic and systolic function by preventing the decrease in heart rate, blood flow velocity, and isovolumetric time increase, and decreased the frequency of intrinsic depolarization. There was no significant effect on α- and β-MHC expression.
Ashraf e Roshan[22]	Increased Apelin and SOD, and decrased MDA.
Shirinbayan e Roshan[23]	Increased HSP72 and SOD, and decreased MDA.
Martins et al. [24]	Decreased DNA damage in cardiac cells without a defined mechanism. The authors hypothesized that exercise provided protection against oxidative stress and upregulation of apoptotic pathways.
Smuder et al. [25]	Prevented myofiber ultra-structure damage, inhibited Beclin-1(BCL1) increase and Beclin-2 (BCL-2) decrease, and decreased the BCL1/BCL2 ratio; reduced DOX-induced increase of TAG12, TAG4, TAG7, LC3, Cathepsin-B and Cathepsin-L.
Jensen et al.[26]	Reduced cardiac DOX by unspecified mechanisms.
Marques-Aleixo et al.[27]	Increased the percentage of normal mitochondria and mitochondrial density. Improved state 3 respiration, decreased the delay phase of ADP phosphorylation, enhanced electron transport chain activity at complex I and IV.

ADP: adenosine diphosphate; BAX: apoptosis regulator; BCL:Beclin; BCLW: Beclin W; DNA: Deoxyribonucleic acid; DOX: Doxorubicin; dP/dt max: maximal derivativves of left ventricular pressure HAE: Hydroxy alquenal; HSP: heat shock protein; LC3: autophagy marker LC3; MHC: myosin heavy chain; MDA: malonaldehyde; MHC: major histocompatibility complex; SOD: superoxide dismutase; TAG: triacilglicerol

single 60-minute exercise bout. In the study by Wonders et al.,[14] acute exercise prevented cardiac dysfunction and had no effect on change lipid peroxidation markers. Acensao et al.[18] demonstrated that the same study protocol also prevented mitochondrial dysfunction and increased antioxidant enzymes' levels.

Three studies evaluated the effect of a training period shorter than one month.[11,17,25] Chicco et al.[11] evaluated whether low-intensity exercise, practiced five days a week at 8-10 m/min-30 m/min, had a protective effect against DOX cardiotoxicity. The results suggested an attenuation of left ventricular dysfunction and inhibition of apoptosis signaling in cardiac cells. In the protocol used in the study by Kavazis et al.[17] e Smuder et al.,[25] the animals exercised on a treadmill five times a week for one week. The results of both studies[17,25] indicated that the exercise was effective in attenuating mitochondrial damage by preserving the antioxidant metabolism, and inhibiting lysosomal autophagy signaling, respectively.

Some studies included voluntary exercise on running wheels and measured the distance run.[7,9,15,20,26,27] Two of these studies used voluntary exercise only: Chicco et al.[9] detected resistance against cardiac dysfunction and increased HSP72 levels, whereas Hayward et al.[7] found that voluntary exercise preserved cardiac growth curve and body mass, and prevented cardiac dysfunction in rat pups. Four studies[15,20,26,27] compared voluntary exercise, in which the distance run was not measured, with treadmill training based on a previously established protocol of exercises five times a week for 12 weeks. The results did not show difference between the groups, except for the level of cardiac function damage, which was attenuated only in treadmill training group in the study by Hydoch et al.[15]

In the other eight studies, [10,12,13,16,19,22-24] the animals exercised five times a week for 12 week. Two were evaluated the effect of swimming[12,24] and six used motorized treadmill.[10,13,16,19,22,23] All of these studies indicated a cardioprotective effect of exercise independently of the mechanisms or other differences between their protocols.

Based on these findings, we cannot affirm that there was a direct relationship between exercise frequency and the results, since frequencies varying from acute session to exercise at random times showed evidence to exert protective effects, mainly on DOX-induced cardiac dysfunction. Although the study by Hydock et al.[15] suggests a difference in relation to the damage caused by oxygen reactive species, DOX-induced effects were evaluated at 5 and 10 days after treatment, and the intensity of exercise was different between the groups.

Intensity

There were some differences in the relationship between the intensity of exercises and the results described. The study by Chicco et al.[11] was the only one aimed to evaluate the protective effect of low-intensity exercise on DOX-induced cardiotoxicity. In this study, an aggressive exercise protocol, in terms of intensity and duration was used, starting with 5 minutes of daily exercise at 8-10 m/min and 0% inclination, followed by a 10-minute increase per day, until the duration of 60 min/day at 30 m/min was achieved on the last day of the second training week. This study indicated that this exercise modality performed during DOX treatment was capable to inhibit apoptotic signal induction and attenuation of left ventricular dysfunction. However, exercise did not provide a sufficiently intense stimulus to change HSP and superoxide dismutase (SOD) expression.[11]

Ascensao et al.[10] studied the effects of moderate exercise on treadmill on reduction of DOX-induced mitochondriopathy and apoptosis signaling. The animals were first subjected to one week of acclimation to the treadmill, followed by 14 weeks of training at 30 m/min and 0% of inclination. This mitigated changes in mitochondrial homeostasis and oxidative stress levels, and increased antioxidant metabolism and mitochondrial defenses.[10]

In another study on moderate intensity exercise, Shirinbayan and Roshan[23] subjected the animals to eight weeks of treadmill training, with 5-minute warm-up and 39 minute-running at 17 m/min. According to the authors, the results suggest that exercise decreased the risk for cardiac disturbances caused by acute DOX administration, by preservation of SOD and HSP protection systems.[23]

Two studies were conducted with swimming training programs,[12,24] but the exercise intensity was not reported. Ascensao et al.[12] evaluated whether 1 hour of daily swimming training, performed with a weight (corresponding to 4% of body weight) attached to the tail increased cardiac muscle tolerance to DOX. The results indicated protection against oxidative stress, detected by the decrease in troponin levels and increase of HSP and glutathione (GHS), an antioxidant

enzyme commonly found in the mitochondria.[12] Martins et al.[24] evaluated the effect of swimming training performed with a weight (8% of body weight) attached to the tail. The results indicated that the exercise protected cardiac cell DNA against DOX-induced damage.[24]

Only voluntary exercise on running wheel was used in the study by Chicco et al.[13] According to the references cited by the authors, in this protocol, lower exercise intensities are reached, as compared with intensity-controlled treadmill running. Eight weeks after the training period, exercise training attenuated cardiac dysfunction and oxidative damage compared with sedentary animals.[13] Hayward et al.[7] also used voluntary running wheel exercise only; ten weeks of exercise preserved cardiac growth curve, body mass and cardiac functions in trained rats in comparison with the control group.

Hydock et al.[15] and Jensen et al.[26] compared voluntary running wheel exercise with treadmill training, using the same progressive-intensity protocol, starting with 13 m/min and 5% inclination for 20 minutes, reaching the final velocity of 30 m/min and 18% inclination for 60 minutes within 4 weeks. Hydock et al.[15] evaluated the effect of exercise preconditioning on DOX-induced changes, cardiac function and myosin heavy chain isoforms. Cardiac dysfunction was attenuated only in the group subjected to more intensive treadmill training.

Jensen et al.[26] evaluated the effect of both treadmill running and running wheel on cardiac function and myocardial DOX accumulation. The animals were assessed at 1, 3, 5, 7 and 9 days after DOX administration. The results indicated a significant difference in DOX accumulation levels, and a complete elimination of the medication at 5 days, with no significant difference between the exercise modalities.[26]

Marques-Aleixo et al.[27] also used different exercise intensities to compare treadmill and running wheel training. The treadmill intensity was gradually increased from 18 m/min in the week of acclimation of the animals to the treadmill to 27 m/min in the 7th week. From this point, the velocity was adjusted at 20 m/min from the 7th to 12th week in DOX group, whereas in the placebo group (saline solution), the velocity was increased until 30 m/min. Both modalities prevented the oxidative stress.[27]

Also using a progressive intensity protocol, Hornsby et al.[21] evaluated the effect of cycle ergometry for 12 weeks, with intensities varying from 60% to 100% of maximal oxygen uptake, measured before the beginning of the exercise program. No significant differences between the interventions were detected by echocardiography.[21] Other studies[13,14,16-19,22,25] used motorized treadmill protocols that included progressive exercise intensity and duration, starting with low intensity, and velocities and inclination varying from 25-30 m/min and 5 to 18%, respectively during the training period. It is worth mentioning that in the study by Smuder et al.,[25] the animals trained at 70% of maximal oxygen uptake.

Time or Duration

Exercise duration is an important factor in aerobic exercise prescription to establish the training volume to be periodically performed, due to its direct relationship with intensity and frequency.[28] In 13 studies [10-13,15-17,19,20,24-27] the training period was one hour of exercises per day, five times a week (5 hours/week), independently of the total number of weeks in each study.

In two other studies, animals were also subjected to 60 minutes of daily exercise, in a single session though.[14,18] In the study by Ashrafi and Roshan[22] and Shirinbayan and Roshan,[23] a protocol of 39-minute daily exercise for 5 days a week (total of 3 hours and 15 minutes per week) was used. Hornsby et al.[21] used a protocol of 60-minute daily exercise, three times a week, totaling 3 hours a week. Chicco et al.[9] and Hayward et al.[7] used voluntary exercise in a running wheel and, for this reason, the duration and intensity of exercise were not quantified and could not be analysed.

In general, the studies analyzed here[9-27] did not aim to specifically evaluate the cardioprotective effects of training-related variables against DOX, but rather investigate the mechanisms involved in this protection. Although many studies have systematically elaborated the exercise protocols, none of them evaluated the cause/effect relationship of each exercise-related variable.

In this context, exercise duration is important to be considered. In addition to its direct relationship with total training volume,[7] one of the major difficulties faced by cancer patients is to perform long-duration exercise[3] due to fatigue and other adverse effects that hamper the desire and possibilities to exercise.[3]

Type

Different types of exercise or sports modalities may exert different effects on individuals, and thereby directly influence the objectives of exercise prescription.[28] In this review, only aerobic exercise was identified in the studies, with variations of modalities, intensity, frequency and time.

Fifteen studies were performed with at least one group subjected to treadmill running, and all of them included one week of acclimation of the animals to this procedure. [10,11,13-20,22,23,25-27]

The results indicated that treadmill training protected against DOX-induced cardiac dysfunction in all eight studies in which this outcome was one of the main objectives.[13-16,19,20,23] Exercise was also effective in preventing lipid peroxidation and oxidative damage in four studies.[10,13,16,22] Regarding the oxidative stress, exercise protected, or even improved antioxidant activity.[10,17,18,22,23]

Four studies investigated the effect of exercise on mitochondrial function, defenses and apoptosis. The results indicated that treadmill training had a protective effect against damage and dysfunction, attenuated the increase in DOX-induced apoptosis, and increased mitochondrial defenses.[10,17,18,27] With respect to programmed cardiomyocyte death, exercise inhibited the increase in DOX-induced apoptosis signaling in three studies.[11,16,25] Other beneficial factors included the increase in HSP72 levels,[13] and preservation of HCM isoforms.[15,19]

Voluntary exercises in running wheels were used in four studies,[7,9,15,26] due to their lower intensity as compared with preprogrammed treadmill exercises, and to the possibility for the animals to perform the exercises by their will. These aspects have a connection with oncologic patients, who may have difficulties in adhering to exercise programs at pre-established schedules and high intensities.[3]

Chicco et al.[9] suggested that regular voluntary exercise may provide resistance against DOX-induced cardiac dysfunction and oxidative damage in long term, and increase HSP72 levels. Hayward et al.[7] concluded that exercise was effective in preventing changes in cardiac growth curve, systolic and diastolic dysfunction, and depolarization velocity decrease, and had no effect on body mass loss. This was the only study to evaluate cardiac functions during exercise.

Hydock et al.[15] compared groups of animals subjected to running wheel and treadmill running. In this study, attenuation of cardiac dysfunction was observed only in the group that underwent high-intensity, treadmill testing. Finally, Jensen et al.[26] evaluated the effect of pre-treatment exercise in both treadmill and running wheel. Both modalities led to significant reductions in DOX accumulation and significant increase in total elimination of DOX after five days, with no significant difference between them.[26]

Two studies evaluated the possible effect of swimming against cardiotoxicity.[12,24] Ascensao et al.,[12] after treatment and analysis of data, found a cardiomyocyte protection in exercised animals by reduction of cardiac stress, which may be associated with the reduction in stress markers, and by preservation of antioxidant enzyme levels as compared with sedentary animals. Martins et al.,[24] using a pre-treatment swimming program, demonstrated a protective effect against DNA damage in cardiac cells.

The study by Hornsby et al.[21] was the only study to use cycle ergometry, and the only statistically significant result was the attenuation of the natriuretic peptide increase in the exercised group as compared with the control group.

In humans

Hornsby et al.[21] evaluated the safety and efficacy of aerobic training in improving chemotherapy adverse effects, and Jones et al.[29] evaluated its cardioprotective effect on DOX-induced cardiotoxicity. According to Jones et al.,[29] aerobic exercise had no cardioprotective effect in humans. It is worthy of note that this was the only study to use this protocol. Also, cyclophosphamide has a high level of evidence for cardiotoxicity.[6]

The studies by Hornsby et al.[21] and Jones et al.[29] evaluated 20 women with stage IIB and IIIC operable breast cancer, receiving neoadjuvant therapy with DOX 60 mg/m^2 and cyclophosphamide 600 mg/m^2 in four cycles (one cycle every 21 days for three months). Patients were randomized to one of the two groups: DOX + cyclophosphamide and cyclophosphamide + aerobic training. Aerobic training was performed by cycle ergometry, 3 times a week for 3 months, following an individualized program with progressive intensity, prescribed based on ergospirometry performed in the beginning of the study (Chart 3).

Chart 3 – Aerobic training performed in the studies analyzed

Week	Duration	Intensity	Incremental training from the fifth week onwards
	3 sessions of 15-20 min	60% VO_2max.	-
2nd to 4th	3 sessions of 30 min	65% VO_2max	-
5th and 6th	2 sessions of 30-45 min	60-65% VO_2max	1 session of 20-25 min at ventilator threshold determined by a systematic increase in the VE/VO_2 ratio while VE/VCO_2 remained constant.
7th to 9th	2 sessions of 60 min	65-70% VO_2max	1 session of 20-25 min at ventilator threshold determined by a systematic increase in the VE/VO_2 ratio while VE/VCO_2 remained constant.
10th to 12th	2 sessions of 60 min	60-70% VO_2max	Interval trainings of 30 seconds at 100% VO_2max, followed by 60 s of active recovery (total of 10-15 cycles).

The effects of aerobic training were analyzed by ergospirometric test and transthoracic echocardiography. The results reported in both studies[21,29] indicated that there were no significant differences in protection against DOX-induced cardiotoxicity after training or between the groups. However, Hornsby et al.[21] demonstrated that high intensity interval aerobic training is safe and well tolerated by participants; it reduces therapy adverse effects, and attenuates the increase in natriuretic peptide levels, cardiopulmonary dysfunction and VO_2max.

In summary, the results of the studies indicated that aerobic exercise can exert a protective effect on cardiac functions when performed before, during or after training, and may be an adjuvant therapy to DOX. Nevertheless, the mechanisms associated with this protective effect are controversial and have been associated with several hypothetical mechanisms, thus requiring further research. In general, the studies analyzed differed in protocols: intensity, time of training in relation to the treatment, methods and objective of study.

Concerning the variables related to aerobic exercise prescription, no relevant differences in cardioprotective effects were observed between the time of training – before, during or after treatment. However, some results in relation to the total training time may be pertinent if extended to the oncologic treatment reality, since acute training sessions or only one week of exercises before DOX administration showed effective results. There was no direct relationship between the frequency of exercise and the results of the studies; regardless of frequency variation, there was evidence of protective effect of exercise, especially on DOX-induced cardiac dysfunction. The intensity of exercise was also not decisive for preservation of cardiac function, although a more intense exercise was associated with improvements in the antioxidant system, which was not observed in studies on lower intensity exercises.

New studies including different populations and types of exercise prescriptions are needed before concluding that the exercise would be effective against cardiotoxicity induced by treatment with DOX.

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Statistical analysis, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Maia TN, Araujo GBR, Teixeira JAC, Alves Junior ED, Dias KP.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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References

1. Instituto Nacional de Câncer. Ações de enfermagem para o controle do câncer: uma proposta de integração ensino-serviço. 3a ed. Rio de Janeiro: INCA; 2008.
2. Instituto Nacional de Câncer. ABC do câncer: abordagens básicas para o controle do câncer. 2a ed. Rio de Janeiro: INCA; 2012.
3. Sanft T, Irwin ML. Side effects and persistent effects of cancer surgery and treatment. In: American College of Sports Medicine, Irwin ML, eds. ACSM's guide to exercise and cancer survivorship. Champaign (IL): Human Kinetics; 2012.p.15-25
4. Korde LA. Diagnosis and treatment of cancer. In: American College of Sports Medicine, Irwin ML, eds. ACSM's guide to exercise and cancer survivorship. Champaign (IL):Human Kinetics; 2012.p.1-12
5. ACSM's guide to exercise and cancer survivorship / American College of Sports Medicine;Irwin ML (ed). Guide to exercise and cancer survivorship. Champaign (IL):Human Kinetics; 2012.
6. Kalil Filho R, Hajjar LA, Bacal F, Hoff PM, Diz M del P, Galas FR, et al; Grupo de Estudos em Insuficiência Cardíaca da Sociedade Brasileira de Cardiologia (GEIC/SBC); Sociedade Brasileira de Oncologia Clínica; Instituto do Coração – Faculdade de Medicina da Universidade de São Paulo; Instituto do Câncer do Estado de São Paulo – Faculdade de Medicina da Universidade de São Paulo. [I Brazilian Guideline for Cardio-Oncology from Sociedade Brasileira de Cardiologia]. Arq Bras Cardiol. 2011;96(2 Suppl. 1):1-52.
7. Hayward R, Lyen CY, Jensen BT, Hydock DS, Schneider CM. Exercise training mitigates anthracycline–induced chronic cardiotoxicity in a juvenile rat model. Pediatr Blood Cancer. 2012;59(1):149-54.
8. Scott JM, Khakoo A, Mackey JR, Haykowsky MJ, Douglas PS, Jones LW. Modulation of anthracycline-induced cardiotoxicity by aerobic exercise in breast cancer: current evidence and underlying mechanisms. Circulation. 2011;124(5):642-50.
9. Ascensão A, Magalhães J, Soares JM, Ferreira R, Neuparth MJ, Marques F, et al. Moderate endurance training prevents doxorubicin-induced in vivo mitochondriopathy and reduces development of cardiac apoptosis. Am J Physiol Heart Circ Physiol. 2005;289(2):H722-31.
10. Chicco AJ, Hydock DS, Schneider CM, Hayward R. Low-intensity exercise training during doxorubicin treatment protects against cardiotoxicity. J Appl Physiol (1985). 2006;100(2):519-27.
11. Ascensão A, Magalhães J, Soares J, Ferreira R, Neuparth M, Marques F, et al. Endurance training attenuates doxorubicin-induced cardiac oxidative damage in mice. Int J Cardiol. 2005;100(3):451-60.
12. Chicco AJ, Schneider CM, Hayward R. Exercise training attenuates acute doxorubicin-induced cardiac dysfunction. J Cardiovasc Pharmacol. 2006;47(2):182-9.
13. Wonders KY, Hydock DS, Schneider CM, Hayward R. Acute exercise protects against doxorubicin cardiotoxicity. Integr Cancer Ther. 2008;7(3):147-54.
14. Hydock DS, Lien CY, Schneider CM, Hayward R. Exercise preconditioning protects against doxorubicin-induced cardiac dysfunction. Med Sci Sports Exerc. 2008;40(5):808-17.
15. Kavazis AN, Smuder AJ, Min K, Tümer N, Powers SK. Short-term exercise training protects against doxorubicin-induced cardiac moticondrial damage independent of HSP72. Am J Physiol Heart Circ Physiol. 2010;299(5):H1515-24.
16. Ascensão A, Lumini-Oliveira J, Machado NG, Ferreira RM, Gonçalves IO, Moreira AC, et al. Acute exercise protects against calcium-induced cardiac mitochondrial permeability transition pore opening in doxorubicin-treated rats. Clin Sci (Lond). 2011;120(1):37-49.
17. Hydock DS, Lien CY, Jensen BT, Schneider CM, Hayward R. Exercise preconditioning provides long-term protection against early chronic doxorubicin cardiotoxicity. Integr Cancer Ther. 2011;10(1):47-57.
18. Ashraf J, Roshan VD. Is short-term exercise a therapeutic tool for improvement of cardioprotection against DOX-induced cardiotoxicity? An experimental controlled protocol in rats. Asian Pac J Cancer Prev. 2012;13(8):4025-30.
19. Shirinbayan V, Roshan VD. Pretreatment effect of running exercise on HSP70 and DOX-induced cardiotoxicity. Asian Pac J Cancer Prev. 2012;13(11):5849-55.
20. Martins RA, Minari AL, Chaves MD, Santos RW, Barbisan LF, Ribeiro DA. Exercise preconditioning modulates genotoxicity induced by doxorubicin in multiple organs of rats. Cell Biochem Funct. 2012;30(4):293-6.
21. Smuder AJ, Kavazis AN, Min K, Powers SK. Doxorubicin-induced markers of myocardial autophagic signaling in sedentary and exercise trained animals. J Appl Physiol (1985). 2013;115(2):176-85.
22. Marques-Aleixo I, Santos-Alves E, Mariani D, Rizo-Roca D, Padrão AI, Rocha-Rodrigues S, et al. Physical exercise prior and during treatment reduces sub-chronic doxorubicin-induced mitochondrial toxicity and oxidative stress. Mitochondrion. 2015;20:22-33.
23. Chicco AJ, Schneider CM, Hayward R. Voluntary exercise protects against acute doxorubicin cardiotoxicity in the isolated perfused rat heart. Am J Physiol Regul Integr Comp Physiol. 2005;289(2):R424-31.
24. Wonders KY, Hydock DS, Greufe S, Schneider CM, Hayward R. Endurance exercise training preserves cardiac function in rats receiving doxorubicin and the HER-2 inhibitor GW2974. Cancer Chemother Pharmacol. 2009;64(6):1105-13.
25. Hydock DS, Parry TL, Jensen BT, Lien CY, Schneider CM, Hayward R. Effects of endurance training on combined goserelin acetate and doxorubicin treatment-induced cardiac dysfunction. Cancer Chemother Pharmacol. 2011;68(3):685-92.
26. Jensen BT, Lien CY, Hydock DS, Schneider CM, Hayward R. Exercise mitigates cardiac doxorubicin accumulation and preserves function in the rat. J Cardiovasc Pharmacol. 2013;62(3):263-9.
27. Hornsby WE, Douglas PS, West MJ, Kenjale AA, Lane AR, Schwitzer ER, 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.
28. American College of Sports Medicine. Diretrizes do ACSM para os testes de esforço e sua prescrição. 8a ed. Rio de Janeiro: Guanabara-Koogan; 2010.
29. Jones L, Dolinsky V, Haykowsky M, Patterson I, Jones L, Allen J, et al. Effects of aerobic training to improve cardiovascular function and prevent cardiac remodeling after cytotoxic therapy in early breast cancer [abstract]. In: Proceedings of the 102nd Annual Meeting of American Association of Cancer Research; 2011 Apr 2-6; Orlando, FL, USA. Philadelphia: AACR; Cancer Research.2011;71(8 Suppl):5024.