Journal of Respiratory and CardioVascular Physical Therapy

LITERATURE REVIEW

CARDIOTOXICITY OF CHEMOTHERAPY DRUGS AND POSSIBLE PROTECTIVE EFFECTS OF PHYSICAL EXERCISE: A LITERATURE REVIEW

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Received March 3, 2016; accepted November 20, 2016

KEYWORDS: Cardiotoxicity, doxorubicin, anthracyclines, cardiomyopathie, exercise

This review was designed to summarize the main pathophysiological mechanisms of doxorubicin cardiotoxicity and the positive effects of physical exercise. **Objective**: To characterize a literature review on the main cardiotoxicity mechanisms already described and what possible strategies attenuate and/or prevent these side effects, with a focus on physical exercise. **Methods**: A literature search using PubMed (MEDLINE) and SciELO databases was conducted covering the articles published between 2000 and 2015. These studies were selected for posterior analysis, according to pre-established criteria. **Results**: Fifty-eight (58) articles based on references and according to the descriptors were found and 45 articles were included: 18 reviews, 19 articles developed with animal experiments, 07 articles with studies in humans and 01 guideline. **Conclusion**: Data analysis led us to understand that although there is no consensus about the doxorubicin mechanism of action that causes toxicity, the generation of reactive oxygen species and changes in intracellular calcium are the most studied mechanisms and provide the most evidence in literature. Other studies are still needed to elucidate the complex cardiotoxicity mechanisms and which strategies would be the best for cardioprotection. A possible therapeutic strategy that has been studied is implementing exercise, but some questions still arise, including: 1) What would be the best time to implement an exercise program, before or during chemotherapy? And 2) Could exercise play a cardioprotective role in preventing or attenuating toxic effects on the heart?

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INTRODUCTON

Cancer causes more than 500 deaths annually in the United States, which corresponds to almost a quarter of all deaths[1]. It is estimated that there are 10 million cancer survivors in the US and Europe, and the risk of cardiovascular death in this population can be greater than the risk of tumor recurrence[2]. In Brazil, the estimate for the years 2014 and 2015 points to the occurrence of approximately 576,000 new cases, thus enhancing the magnitude of this problem in the country[3].

Over the past decades, cancer treatment has substantially evolved due to the development of more potent drug therapies that improve prognosis[2,4,5]. However, the discovery of such new agents has also resulted in the appearance of adverse effects, and the manifestation of cardiotoxicity has been a major limitation in their use[2].

A class of anthracycline drugs has become one of the most important strategies for the treatment of hematological and solid tumors[6]. In the class of anthracyclines, doxorubicin (DOX) is the main anti-tumor agent[7,8] with wide application across the clinical spectrum[9,10], but its use is limited due to causing dose-dependent cardiotoxicity which may eventually lead to heart failure and increase the risk of death[11-13].

Despite pharmacological interventions minimizing DOX induced cardiotoxicity, exercise has been extensively studied as part of a comprehensive monitoring program in these patients. According to the authors, exercise is an important non-pharmacological measure able to increase DOX cardiotoxicity tolerance, providing parallel protection and mitigating some of its toxic effects[14]. The mechanisms by which exercise demonstrates its cardioprotective effects are still not clear; however, it is known that it positively modulates several important cardiac defense systems that appear to antagonize some toxic effects caused by DOX treatment[15-16].

Given that the molecular mechanisms involved in cardiotoxicity induced by DOX are still poorly understood in literature, in addition to the cardioprotective effects of exercise in this condition, this critical review aims to summarize the main mechanisms involved in cardiotoxicity induced by DOX and highlight which cardioprotective strategies have been proposed to minimize these effects on the heart, with emphasis on the effects of physical exercise.

METHODS

This study used the PubMed (MEDLINE) and SciELO databases combining the descriptors in Health Sciences in English of *cardiotoxicity, doxorubicin, anthracyclines, cardiac alterations,* and *exercise*. The searches were conducted by restricting the date for articles published to between 2000 and 2015; it included review articles and studies in humans and in experimental animals which only addressed chemotherapy doxorubicin as a cause of cardiotoxicity, and those that described cardiotoxicity mechanisms and cardioprotective strategies, with an emphasis on the role of physical exercise. Articles outside the scope of interest or studies that addressed other types of chemotherapy regimens were excluded.

RESULTS

Based on the references found and according to the descriptors used in the search strategy, 58 articles were located and of these, 45 articles were included, being 18 reviews, 19 articles developed with animal testing, 07 articles of studies involving humans and 01 guideline. Below are the main points related to the discovery of the anthracyclines, the mechanisms of cardiotoxicity by doxorubicin, and current strategies proposed to attenuate and/or prevent its toxic effects, highlighting the role played by exercise.

Anthracyclines: In 1950, daunorubicin was identified from *Streptomyces peucetius* bacteria, giving rise to the anthracycline drug class[17]. Within this group, the two most prescribed forms in practice are doxorubicin (DOX) and daunorubicin. Its anti-tumor effects include interleaving into cellular DNA leading to inhibition of macromolecular biosynthesis, the generation of reactive oxygen species (ROS) and irreversible damage to DNA by inhibiting topoisomerase II[18].

Secondary cardiotoxicity continues to be a limiting factor in their use being generally related to dose-response and mainly manifested as heart failure[19]. The National Cancer Institute defines cardiotoxicity in simple terms as "toxicity that affects the heart." According to the First Brazilian guidelines on cardio-oncology (*I Diretriz de Cardioncologia*), cardiotoxicity is defined according to changes in the left ventricular ejection fraction (LVEF) obtained by echocardiography, namely: Grade I:

asymptomatic decrease in LVEF between 10% and 20%; Grade II: LVEF decrease below 20% or below normal; and Grade III: symptomatic heart failure[20].

Cardiotoxicity can be manifested in three forms: acute, subacute or chronic. The acute or subacute form is characterized by changes occurring in ventricular repolarization, electrocardiographic abnormalities of QT interval arrhythmias, acute coronary syndromes, pericarditis and/or myocarditis, observed since the beginning of therapy until 2 weeks after completion of treatment[21].

The most common manifestation of chronic cardiotoxicity is the systolic and/or diastolic ventricular dysfunction which leads to congestive heart failure and can lead to death[21,22]. Regarding morphological changes of the myocardium resulting from the use of DOX, the following classic findings are described: vacuolar degeneration, disruption or loss of myofibrils, interstitial fibrosis, dilation of the sarcoplasmic reticulum[23] and T-tubules, mitochondrial lesion characterized by swelling and disruption of mitochondrial crests, and disorganization of nuclear chromatin impairing adhesion proteins[24].

In general, the main proposed cardiotoxicity mechanisms are: increased oxidative stress[25,26] due to increased ROS levels[23,27], changes in sarcolemmal transport of calcium (Ca^{+2})[16,25,28], reduction in the expression of important cardiac structural proteins such as dystrophin and contractile proteins[29,30], cardiomyocyte apoptosis[8,17,25,31], changes in the sarcomeric structure, changes in the high energy phosphate complex and iron metabolism[19], and the influence of age and gender[32-35].

Influence of age and gender: The probability of developing cardiotoxicity may also occur at lower doses, probably due to individual susceptibility[32]. Some risk factors have been suggested to explain this susceptibility, such as gender difference and age[33]. In the review by Puma et al.[34], women had more severe cardiotoxicity evidenced by the loss of cardiac contractility, and they also had a higher risk in subclinical cardiotoxicity when compared to males[34]. Older adult patients over 65 years and children under the age of four[33] have an increased risk of doxorubicin-induced cardiotoxicity [35].

Oxidative stress: The production of free radicals is one of the main mechanisms described in cardiac injury induced by DOX. From the study by Chatterjee et al., DOX induces damage to mitochondria in cardiomyocytes and increases the production of enzymes such as NADH dehydrogenase, cytochrome P450 reductase and xanthine oxidase which are involved in generating free radicals and ROS. DOX increases the formation of superoxide anion, endothelial nitric oxide synthase (eNOS), and it induces intracellular hydrogen peroxide formation that leads to cell membrane damage and increased permeability[7]. A study by Salazar-Mendiguchía et al.[19] described that myocardium is highly prone to oxidative damage due to its low levels of superoxide enzyme activity compared to other tissues. As the metabolism of anthracyclines involves reducing the quinone fraction of its semiquinone formula, the rapid transfer of its unpaired electron to an oxygen molecule may occur, returning to its original quinone form, and thus completing the redox cycle and inducing the formation of ROS[19].

Intracellular Ca^{2+}: DOX-induced cardiotoxicity is also accompanied by an increase in intracellular Ca^{2+} levels. Dysregulation in the intracellular Ca^{2+} concentration can be the final route or cause for the increased generation of ROS. The generated ROS and hydrogen peroxide alter the normal Ca^{2+} homeostasis by inhibiting the Ca^{2+} ATPase pump. DOX induces Ca^{2+} release from the sarcoplasmic reticulum, increasing the likelihood that the channel becomes more permeable[16,28].

Deregulation of Ca^{2+} plays an important role in the pathogenesis of cardiomyopathy induced by DOX through the activation of proteases such as calpains. As a large part of the intracellular calcium of cardiomyocytes is in the sarcoplasmic reticulum, oxidative stress may result in leakage of Ca^{2+}, the activation of calpain and also of caspase-12, cleaving intracellular proteins and activating the apoptosis process. Furthermore, this increase in cytoplasmic Ca^{2+} concentration in DOX-induced injury is associated with deterioration and degradation of myofibrillar titin, which is a major protein and key component of the cardiac sarcomere. Inhibition, or perhaps more accurately, the prevention of calpain activity could help to maintain these structures as contractile and functioning[32].

Structural integrity of cardiomyocytes: An experimental study in mice developed by Campos et al. in 2012 described

the importance of structural proteins present in cardiomyocytes in the occurrence of heart failure after treatment with DOX[29]. Dystrophin is a key component of the dystrophin-glycoprotein complex that links the cytoskeleton and the extracellular matrix and is important for contraction and maintenance of sarcolema and myofiber integrity[36-38]. It is suggested as a common route for inducing cardiomyopathy and heart failure[39-41], and led the authors to investigate the hypothesis that DOX could affect dystrophin expression and its associated proteins in rat hearts. This study provides new data that assisted in clarifying the molecular events involved in the cardiotoxicity caused by DOX. The treatment caused a sharp reduction/loss of dystrophin and of β-dystroglycan in cardiomyocytes and left ventricular dysfunction, which may constitute in combination with the loss of actin and myosin proteins, the structural basis of heart failure induced by DOX. Moreover, increased sarcolemmal permeability demonstrated by an increase in intracellular albumin suggests functional impairment of dystrophin and glycoproteins in cardiomyocytes treated with DOX. Another important finding was the significant increase in calpain expression. Treatment with dantrolene (a sarcoplasmic reticulum ryanodine receptor blocker) significantly improved survival rates and preserved the dystrophin and left ventricular function[29].

Recently, mitochondrial connexin (mCx43) has been indicated as a new regulator of mitochondrial function[30]. MCx43 is the main protein forming the gap junction in adult cardiomyocytes and appears to prevent mitochondrial calcium increase induced by DOX, preventing the formation of transitional pores, decreasing depolarization time and the release of apoptogenic mitochondrial content[30].

Changes in sarcomeric structure: Cardiotoxicity induced by anthracyclines also occurs at the level of sarcomeric structures, primarily characterized by the breakdown and loss of myofilaments and sarcomere anchoring proteins. A study by Rochette et al. demonstrated that the anthracyclines are capable of modifying the structure of the contractile apparatus by direct mechanisms, or even from the cytotoxic effects mediated by ROS[25]. The rapid degradation of titin through proteolytic pathways plays an important role in the pathophysiology of dilated cardiomyopathy, with consequent functional impairment of the cardiac cell. In vitro and in vivo studies have shown that this effect is also related to the loss of structural integrity and disorder, and even myocyte necrosis of a calpain-dependent substance[26,29,42]. Another study described the role of cardiac ankyrin repeat protein (CARP or ANKRD1, a regulatory protein of transcription that acts as a nuclear transcription factor that negatively regulates the expression of cardiac genes) in the pathophysiology of cardiomyopathy induced by anthracyclines. CARP is sensitive to DOX, leading to depletion of its levels by inhibiting its transcription, with consequent sarcomeric disorder[43].

Changes in the set of high energy phosphates: Mitochondrial damage impairs the ability to generate ATP; this depletion decreases the affinity of Hsp90 (90kDa heat shock protein, which appears to have a central role in the pathology of many types of cancer) for ErbB2 (Tyrosine kinase 2 receptor - oncogene), a cardioprotective protein that is upregulated in the myocardium. In conditions where ATPs can be depleted, ErbB2 levels fall as Hsp90 cannot maintain its affinity[44]. Decreased levels of ATP can also originate from the activation of apoptotic pathways and of calcium-dependent proteases. Energy costs to replace damaged proteins can be considerable, especially if these proteins have high molecular weight such as in titin and dystrophin, which is degraded by indiscriminately activated calpain[32].

Iron Metabolism (Fe): It has been considered that anthracyclines are able to alter iron homeostasis by creating iron-anthracycline complexes and subsequent production of ROS[19.31]. At the same time, iron is capable of catalyzing several molecular reactions, which create ROS regardless of iron-anthracycline complexes, thus generating hydroxyl radicals. Recently, studies in humans have confirmed that even cumulative DOX doses at "safe intervals" are capable of inducing high levels of iron in the heart tissue, leading to the possibility of cardiotoxicity related to iron deposits as a new pathophysiological mechanism and raising the question of whether an actual ''safe'' dose exists in terms of preventing cardiomyopathy long-term[45].

Current strategies for minimizing cardiotoxic effects

Clinical strategies have been proposed in order to mitigate the cardiotoxicity of anthracyclines. Currently, there is no

treatment based on specific evidence for this cardiotoxicity. For each type of anthracycline, total recommended doses must not be exceeded or should only be exceeded with cardiac monitoring and/or pharmacological cardioprotection, but unfortunately, they do not completely eliminate the risk of cardiotoxicity[32,46].

The use of pharmacological cardioprotective agents: Dexrazoxane is an iron chelating agent which reduces the formation of iron-anthracycline complex. ROS generation is limited without these complexes, thus restricting toxicity. Dexrazoxane also interferes with Topoisomerase IIB, thereby antagonizing the DNA damage induced by DOX. The use of carvedilol (a beta-blocking agent) provides cardioprotection by inhibiting ROS, thus preventing lipid peroxidation and increased concentrations of vitamin E in rats, but this study should continue to be developed in humans[48]. Coenzyme Q (an antioxidant) is an important part of the mitochondrial respiratory chain, and it has been reported that its supplementation prevented the cardiotoxicity induced by anthracyclines. Glutathione (a thiol tripeptide) is another antioxidant which eliminates free radicals, and its supplementation can protect the heart from the effects of anthracyclines, as observed in vitro and in animals[33].

The role of physical exercise: Physical exercise has been suggested as an effective and low-cost non-pharmacological strategy to minimize or prevent myocardial damage associated with the treatment of DOX. Several mechanisms are activated during and after physical exercise in order to maintain or restore cellular homeostasis. Changes in intracellular concentrations of ATP with increased ADP and AMP levels, reduced glycogen reserves, temperature and pH changes, and loss of calcium homeostasis can be, among others, important stimuli to the increased formation of RONS (reactive oxygen and nitrogen species) in the myocardium during and after prolonged exercise. If this situation persists, there may be a modulatory effect on cardiac cell defense systems, in contrast to the previous idea that RONS mainly serve as a trigger for oxidative damage due to their role as a signaling molecule[51].

Despite the lack of direct evidence of increased production of oxidants after acute exercise, changes in antioxidant systems in addition to oxidative myocardial injury markers after acute exercise are strong indirect signs of redox disorders. It seems clear that when the myocardium is stimulated by acute exercise, it has increased cell signaling due to oxidative stress. On the other hand, the potential adaptability of the myocardium to exercise leads to careful analysis of the training effect, especially resistance training, on the modulation of the redox-oxidative system in the heart. The significant decrease in antioxidant capacity of the heart after exhausting all reserves following an extensive period of swimming in rats of both genders can also be an indication of additional RONS production[51].

In a study by Scott et al.[52], the cardioprotective properties of increased NRG1 (neuroregulin 1 - cardiac and nervous system development pathway)/ErbB signaling are well described. Increased NRG1/ErbB signaling induced by drugs in the myocardium significantly improved cardiac function and survival in rodents who had left ventricular failure, inducing differentiated cardiomyocytes to proliferate. In vitro studies with isolated heart endothelial cells (the major source of NRG1 in the heart) have shown that mechanical stress increases the synthesis and release of endothelial NRG1, while NRG1 release is directly inhibited by angiotensin II and adrenergic agonists. Thus, increased synthesis of NRG1 in the ventricle in response to exercise-induced mechanical stress will induce suppression of neurohormonal factors, leading to cardioprotection[52].

Aerobic exercise can also modulate a number of myocardial intracellular processes. One study indicated that exercise increases Akt (protein kinase B) of the myocardium, with subsequent attenuation of left ventricle pathological remodeling, fibrosis and protein degradation. Physical training increases PI3K activity (Phosphatidylinositol-3-kinase) of the myocardium with an effective decrease in the extent of myocardial and cardiomyocyte apoptosis in rats with myocardial ischemic reperfusion injury and improves survival in rats with dilated cardiomyopathy. These studies provide evidence for the protective effects of Pi3K/Akt cell signaling. Endurance training prior to administration of DOX can protect the heart and skeletal muscles against toxicity induced by doxorubicin[53].

Physical training alone is effective in reducing mortality from heart failure induced by DOX. The results of the study by Chicco et al. (2006) demonstrate for the first time that physical training before DOX treatment protects against

cardiac dysfunction induced by DOX, while preserving the intrinsic cardiac function before treatment[54]. The benefits of physical exercise may be due, at least in part, to restoring vascular smooth muscle relaxation properties, which in turn decrease peripheral vascular resistance and pressure on the heart[5]. Evidence has demonstrated that aerobic exercise prevents lipid peroxidation induced by DOX in the myocardium and reduces mortality. There is also an indication that physical exercise can protect the skeletal muscles against exacerbation of autophagy induced by doxorubicin[56].

It has been demonstrated that 10 weeks of preconditioning with exercise resulted in preserving cardiac function and reducing DOX accumulation in cardiac tissue. These results suggest that regular physical activity can be valuable complementary therapy to minimize cardiotoxicity that often occurs in patients who receive DOX treatment. In addition, patients who participate in exercise programs may be able to better tolerate exposure to the drug, resulting in increased survival and improved quality of life[57].

DISCUSSION

It is possible that more than one mechanism of cardiotoxicity may occur in the same individual, and many of them have not yet been fully clarified, in addition to possible cardioprotective strategies. Most studies are still performed in experimental animals and each one of those only studies one mechanism related to changes and loss of heart function. Moreover, simultaneous administration of other cardiotoxic drugs and radiotherapy can be correlated to an increased risk of cardiomyopathy and heart failure. In addition, other chronic diseases such as hypertension, diabetes mellitus, liver disease and prior heart disease[35] can also contribute to an increased risk of cardiotoxicity[32].

Most studies describe oxidative stress, generation of free radicals and alterations in membrane structure and contractile apparatus of cardiomyocytes as the mechanisms which are mainly involved in cardiotoxicity from doxorubicin. Octavia et al.[32] reported that the mechanism for this oxidative stress and ROS generation are also related to mitochondrial alterations present in cardiomyocytes. It is plausible that these events disrupt the mitochondrial metabolism and thus of the whole cell, since mitochondria produce more than 90% of the ATP (adenosine triphosphate) used by cardiomyocytes. This functional disorder leads to pathological ultrastructural abnormalities such as mitochondrial swelling and forming of myelin figures, a loss of energy production capacity and difficulties in maintaining metabolic demands[44].

Compromised membrane integrity results in the hypothesis of increased ion influx into the cell. Intracellular calcium overload can trigger the indiscriminate activation of calcium-dependent proteases, especially calpain, resulting in the degradation of the main intracellular proteins which make up the cytoskeleton (especially dystrophin and associated proteins, and sarcomeric structure), activating proteases such as calpain, resulting in cardiomyopathy with consequent loss of contractile function[29, 32, 42,46].

Despite the toxicity (with an emphasis on cardiotoxicity), anthracycline treatment efficiency explains its widespread use as a highlighted drug in the arsenal of anti-cancer medications[58]. It is therefore essential to search for a solution, or solutions for the prevention and/or reduction of the cardiotoxic effects caused by using anthracyclines for cancer patients undergoing chemotherapy. The use of pharmacological agents such as Dexrazoxane[47], Carvedilol[48], Coenzyme Q[49], and Glutathione[33], in addition to physical activity have been demonstrated as cardioprotective strategies.

With regard to physical exercise and its possible protective role in the occurrence of cardiotoxicity, only animal studies have shown its effect on reducing structural and functional cardiac alterations caused by doxorubicin. One of the mechanisms involved in cardioprotection may be related to its antioxidant effects due to myocardial ability to adapt to the effects of aerobic exercise training[51]. Other mechanisms that could be involved in reducing cardiotoxic effects both through aerobic exercise and endurance training are related to cell signaling by NRG1/ErbB[52] and the Pi3K/Akt[50] pathways, thereby reducing myocardium pathologic remodeling, protein degradation and apoptosis. Thus, in situations in which myocardial damage is significant and results in heart failure, physical training can reduce the risk of cardiotoxic manifestations after DOX treatment[55,56].

Consequently, it is suggested that physical exercise positively modulates physiological mechanisms and raises some important cardiac defense systems to antagonize the

toxic effects caused by DOX treatment. Increased antioxidant capacity seems to be the consensus mechanism observed for cardiac protection with exercise. Additional beneficial adaptations that induce a heart phenotype which renders the heart more resistant to the deleterious effects of DOX administration may include increased expression of heat shock proteins (HSP), and anti-apoptotic proteins. A central role in this process should be attributed to mitochondrial adaptations resulting from exercise that can be beneficial to the myocardium in DOX-induced cardiomyopathy, a condition in which acute and chronic exercise would act as protectors[16].

In the surveyed literature, studies on the cardiotoxicity mechanism attributed to anthracyclines, particularly doxorubicin, are not unified or definitive, and there still is not consensus about the best explanation for this occurrence. However, pharmacological and non-pharmacological cardioprotection measures are extremely important for these patients. Scientific evidence verifying the real effectiveness of physical exercise as a cardioprotective agent should be further explored/studied, taking into account issues such as at what point does exercise becomes cardioprotective (before or concomitantly to treatment); and which exercise would be more effective in promoting this cardioprotective action in terms of type, intensity, frequency and duration?

The authors declare that no competing interests exist and they all contributed equally to this work.

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