EDITORIAL

Can Exercise Training Prevent Doxorubicin-induced Cardiomyopathy?

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Editorial referring to the article: Physical Training Improves Cardiac Structure and Function of Rats After Doxorubicin-Induced Cardiomyopathy

Doxorubicin (DOX) is a cytotoxic antineoplastic agent of the anthracycline family. It has been used as the first-line chemotherapy drug for treating various types of cancer, such as breast, lung and bladder cancer, and lymphoblastic leukemia.[1] As any anthracycline, DOX is an effective chemotherapeutic drug. However, it holds a potentially lethal dose-dependent cardiovascular toxicity, which can manifest immediately or many years after chemotherapy, limiting its clinical application.[2]

After the discontinuation of DOX treatment, a seven-year follow-up of 1,807 patients reported 33% death from heart diseases. Similarly, a 7.5% incidence of some cardiomyopathies was reported in pediatric sarcoma patients within an average of 34 months post-DOX treatment.[3]

The pathophysiological mechanism involved in DOX-induced cardiotoxicity is likely multifactorial and complex. Multiple regulated cell death pathways and oxidative stress are involved in the loss of cardiomyocytes, playing a big role in heart injuries.[1,4] In addition, a lower regenerative capacity of cardiac muscle cells makes the heart more susceptible to long-term adverse effects. DOX simultaneously triggers or deregulates different cell death pathways in cardiomyocytes, including autophagy (degradation and recycling of cell components), ferroptosis (iron-dependent accumulation of lipid peroxides), necroptosis (regulated form of necrosis that involves the release of death-signaling cytokine); pyroptosis (highly inflammatory caspase-1 dependent cell death) and apoptosis, which have been recently reviewed.[4] The apoptosis induced by DOX is the most studied cell death pathway in cardiomyocytes, and it is totally linked to the excessive oxidative stress generated by the mitochondria. Reactive oxygen species (ROS) are generated when the electrons move through the complex I-IV in the mitochondrial electron transport chain (ETC), and some of them leak out to molecular oxygen (O_2) to form superoxide anion.[5] In normal conditions, the excessive superoxide is dismutated by mitochondrial superoxide dismutase (Mn-SOD) to hydrogen peroxide (H_2O_2) and may be fully reduced to water or partially reduced to hydroxyl radical.[6] However, experimental evidence has shown that DOX increases the leakage of electrons, interfering with the complex I activity, precisely the complex pointed as the major site of ROS generation in the ETC. Subsequently, increased levels of ROS inside mitochondria dysregulate mitochondrial transition permeability, causing the release of huge amounts of Ca^{2+} and proapoptotic proteins from mitochondria, leading to cell death.[7,8]

Given that most cardiotoxicity induced by anti-cancer therapy affects the functional or structural cardiac microcirculation network, it is not surprising that DOX also impairs endothelial function, which may contribute to the development or worsening of the cardiotoxic effects.[9,10] Functional capillary dysfunction refers to a temporary blood flow obstruction or reduced recruitment of non-perfused capillaries in the tissue. Structural capillary dysfunction, in turn, refers to a chronic functional capillary dysfunction characterized by capillary disappearance.[11] It has been proposed that a pro-oxidative profile generated by DOX treatment is an initial trigger of endothelial dysfunction and subsequent microvascular rarefaction. In endothelial smooth muscle, nitric oxide (NO), in a controlled diffusion reaction with superoxide anion, produces peroxynitrite. This reaction decreases the bioavailability of NO, affecting the capacity for endothelium-dependent vasodilation.[12] In addition, peroxynitrite plays a role in the systemic inflammatory response through increased signaling for platelet and leukocyte adhesion to the endothelium, increasing pro-inflammatory cytokine expression.[13] Complementarily,

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DOX showed a strong anti-angiogenic stimulus, inhibiting the vascular endothelial growth factor A (VEGF-A) expression and its cellular receptors in adult rat ventricular myocytes and cardiac microvascular endothelial cells.[14]

Limiting the cumulative dose of DOX, adjusting the DOX administration schedule, and using anthracycline analogs, liposomal formulations, or cardioprotective agents (e.g. dexrazoxane) are options available to clinicians to decrease the risk of cardiotoxicity from DOX.[15] However, since regular physical exercise is beneficial for cardiovascular health, especially in reducing the development of cardiovascular disease and cardiovascular mortality[16-18] – could it prevent DOX-induced cardiotoxicity? In fact, experimental evidence has demonstrated that regular or acute exercise can modulate different mechanisms to reverse/prevent DOX-induced cardiotoxicity.[16] Although several cardioprotective mechanisms activated by exercise are not entirely understood, previous studies have shown that exercise can prevent changes in the mitochondrial permeability transition pore. These changes could result in the rupture of the outer mitochondrial membrane and consequent release of cytochrome c and other proapoptotic proteins, which would potentially lead to cell death.[19] Exercise also plays a critical role in protecting the heart muscle against ROS-mediated damage observed during DOX treatment. In addition, exercise directly activates Mn-SOD and increases nicotinamide adenine dinucleotide phosphate (NADPH) oxidase levels, upregulating antioxidant defenses, and increases Sirtuin 3 (SIRT3) and p66shc, two essential proteins for mitochondrial function and modulation of ROS generation. It also prevented the inactivation of complexes I and IV in the ETC, reducing electrons' leakage and consequent excessive ROS generation.[20]

Another pathway induced by exercise to upregulate mitochondria function is related to the expression of heat shock protein 72 (HSP72), which has a cytoprotective function. This protein has been implicated in cellular functions by regulating protein folding and degradation, and in improving endurance running and increasing mitochondrial enzyme activity in human skeletal muscle.[21-23]

A recent study analyzed morphological adaptations in the cardiomyocyte of laboratory animals after DOX therapy and exercise. A significant increase in cardiac fibrosis was observed in DOX-treated animals after 12 weeks of treatment. In contrast, trained animals treated with DOX did not show a significant increase in fibrosis after the end of treatment. These data indicate that exercise suppressed acute cardiac damage and reduced late-onset cardiotoxicity from DOX. Furthermore, morphological adaptations in the cardiomyocyte induced by exercise improved cardiac function and diastolic blood flow, and reversed autophagy in the myocardium despite DOX

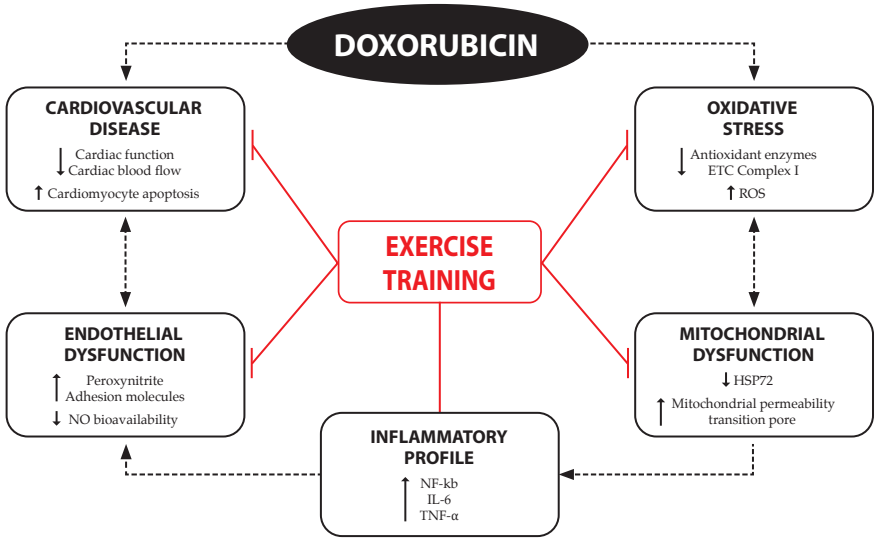

Figure 1 – Schematic representation of exercise-induced cardioprotection from deleterious effects of doxorubicin. Black line: Stimulus; Red line: Inhibition.
ETC: electron transport chain; ROS: reactive oxygen species; HSP72: heat shock protein 72; NF-kB: nuclear factor kappa B; IL-6: interleukin 6; TNF-α: tumor necrosis factor alpha; NO: nitric oxide.

therapy.[24,25] In addition, exercise improved myocardial vascular and preserved the vascular architecture of mice during and after DOX treatment, normalizing cardiac blood flow that was affected by DOX.[24-26] A brief overview of the mechanisms involved in exercise-induced cardioprotection is presented in Figure 1.

To conclude, physical exercise has been shown to exert cardioprotective effects during DOX treatment and could attenuate acute and late-onset cardiotoxicity associated with this therapy. Therefore, it may be beneficial to incorporate physical exercises to prevent cardiovascular diseases in chemotherapy patients. Further studies are warranted to investigate this therapeutic approach.

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