JACC: CARDIOONCOLOGY VOL. 2, NO. 1, 2020

EDITORIAL COMMENT

Repeated Remote Ischemic Conditioning Protects Against Doxorubicin Cardiotoxicity

Never Too Much of a Good Thing*

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The anthracycline chemotherapeutic, doxorubicin (DOX), is one of the most efficacious anticancer agents for treating a number of solid and hematological malignancies, but its use has been limited by its dose-dependent cardiotoxic effects, which can increase the risk of developing early or late-onset cardiomyopathy, and heart failure in cancer survivors. Postulated mechanisms underlying DOX cardiotoxicity include oxidative stress, iron overload, mitochondrial injury, topoisomerase IIb inhibition, and DNA intercalation (1). Therapeutic interventions to mitigate DOX cardiotoxicity, such as limiting the cumulative dose of DOX, use of liposomal DOX, dexrazoxane therapy, and cardioprotective therapies (such as beta-blockers and renin-angiotensin antagonists), have shown some benefit, but cardiovascular morbidity and mortality from cardiotoxicity in cancer survivors is still significant despite these measures (2). Therefore, new therapeutic strategies are needed to protect the myocardium against DOX cardiotoxicity to improve cardiac outcomes in oncology patients undergoing anthracycline chemotherapy. In this regard, the endogenous cardioprotective strategy, "remote ischemic conditioning" (RIC), has the therapeutic potential to protect the myocardium against DOX cardiotoxicity.

RIC refers to the phenomenon in which brief nonlethal cycles of ischemia and reperfusion to an organ or tissue remote from the heart confer cardioprotection against an episode of lethal acute myocardial ischemia/reperfusion injury (IRI) (3). Importantly, the RIC stimulus can be applied to the limb by simply inflating and deflating a pneumatic cuff placed on the upper arm or thigh (termed limb RIC) (4), making it a low-cost and noninvasive cardioprotective strategy that can be easily tested in the clinical setting. Although a single-limb RIC stimulus has been reported to reduce myocardial infarct size in patients with acute myocardial infarction (AMI) (5), a large multicenter study failed to demonstrate any beneficial effects on clinical outcomes (6). The mechanisms underlying the cardioprotective effect of

*Editorials published in *JACC: CardioOncology* reflect the views of the authors and do not necessarily represent the views of *JACC: CardioOncology* or the American College of Cardiology.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: CardioOncology* author instructions page.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2020.02.001

limb RIC remain unclear, but involve the release of cytoprotective factor(s) into the systemic circulation, and the activation of prosurvival signaling pathways in the heart, that target the detrimental effects of acute IRI, including oxidative stress, apoptosis, inflammation, and mitochondrial dysfunction (3). The fact that many of these factors have also been implicated as mediators of DOX cardiotoxicity, raised the possibility that limb RIC may be cardioprotective in patients undergoing anthracycline chemotherapy.

In this regard, Gertz et al. (7) recently reported the potential cardioprotective effects of limb RIC against DOX cardiotoxicity. Using a mouse model, they demonstrated that a single-limb RIC stimulus (three 5-min cycles of femoral artery ligation and reflow) reduced mortality, preserved left ventricular (LV) mass, decreased myocardial fibrosis and apoptosis, and upregulated autophagy signaling. However, no beneficial effects were observed on either mitochondrial or cardiac function, and so the mechanisms underlying the observed improvement in survival with RIC remain unclear. The findings from this study suggested that a single-limb RIC stimulus has the therapeutic potential to prevent or attenuate DOX cardiotoxicity, and provide a low-cost and noninvasive cardioprotective strategy for testing in patients undergoing anthracycline chemotherapy. In this regard, the ongoing ERIC-ONC study (Effect of Remote Ischemic Conditioning in Oncology Patients; NCT02471885) is currently investigating the cardioprotective effects of a single-limb RIC stimulus (four 5-min inflations and deflations of a pneumatic cuff placed on the upper arm) applied immediately before each chemotherapy cycle in adult oncology patients newly referred for anthracycline chemotherapy, with the primary endpoint being myocardial injury (measured by high-sensitive troponin T at 6 and 24 h) (8).

Interestingly, emerging data have suggested that repeated daily episodes of limb RIC for 28 days, termed repeated RIC (rRIC) or chronic remote ischemic conditioning (9), may have beneficial effects over and above a single-limb RIC stimulus in experimental small animal models of AMI in terms of preventing adverse post-AMI LV remodeling via potential anti-apoptotic, anti-inflammatory, autophagic effects, and exosome-mediated improvements in intercellular communication (10,11). Furthermore, in patients with intracranial arterial stenosis, rRIC administered for 365 days was shown to reduce the risk of stroke (12), and rRIC applied for 7 to 28 days has been shown to have vascular and cytoprotective effects that may benefit patients with endothelial dysfunction, hypertension, chronic heart failure, and post-AMI LV remodeling (9).

In this issue of *JACC: CardioOncology,* a study by He et al. (13) tested the cardioprotective efficacy of rRIC in a mouse model of doxorubicin-induced cardiotoxicity. They found that limb RIC (four 5-min cycles of limb ischemia and reperfusion using a tourniquet placed on the hindlimb), initiated 30 min before DOX administration and applied daily for 5 days, had the following beneficial effects: it reduced DOX-induced myocardial apoptosis, myocardial injury (measured by troponin release), myocardial inflammation, and interstitial fibrosis; it enhanced cellular autophagy and maintained cardiomyocyte size and heart weight; and it partially attenuated the DOX-induced depression in cardiac function, although the effect was modest (assessed by echo-determined LV ejection fraction [DOX 47.5% vs. DOX + rRIC 51.6%] and fractional shortening). As no sham limb RIC group was included in the study, the potential confounding effects of daily episodes of anesthesia over 5 days (which would be required to administer the limb RIC stimulus) on the observed effects of rRIC, cannot be excluded. Given that the salutary effects on cardiac function of rRIC were modest, perhaps a more prolonged course of rRIC (as used in the studies demonstrating less post-AMI adverse LV remodeling with rRIC applied for 28 days [10,11]) may have had a greater cardioprotective effect against DOX cardiotoxicity. However, a prolonged rRIC protocol would raise issues of patient compliance in future clinical studies.

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Interestingly, the authors also demonstrated that rRIC had cytoprotective effects in other organs, such as the kidney, spleen, and liver, in terms of preserving organ weight and function (13). The multiorgan benefits of rRIC may be explained by the release into the systemic circulation of, so far unidentified, cytoprotective factor(s) by the limb RIC stimulus (3). In future studies, it would be important to determine whether rRIC can protect mitochondrial respiratory function against the damaging effects of DOX in the heart and other organs, although a single RIC stimulus did not have any mitoprotective effects against DOX cardiotoxicity in a recent study (7). Furthermore, studies of rRIC in a tumor-bearing animal model are needed before clinical testing to ensure rRIC does not attenuate the cytotoxic potency and anticancer efficacy of DOX.

In summary, recent studies have demonstrated potential cardioprotective effects of limb rRIC against

DOX cardiotoxicity, providing a low-cost noninvasive treatment strategy for improving cardiac outcomes in oncology patients undergoing anthracycline chemotherapy. Further work is needed to determine the optimal rRIC protocol for cardioprotection in terms of the duration of the rRIC protocol (as this will have implications for patient compliance); the number of ischemia and reperfusion cycles that make up the optimum limb RIC stimulus (this has not been adequately defined); whether it is efficacious in patients with cardiovascular morbidities such as diabetes, hypertension, and obesity, factors that may confound RIC-induced cardioprotection; and its safety (in relation to whether it interferes with the cytotoxic actions of DOX). Identification of the circulating cytoprotective factor(s) released by limb RIC, and the elucidation of the molecular pathways underlying RIC-induced multiorgan protection, may result in the discovery of novel therapeutic targets and treatments for improving clinical outcomes in oncology patients at risk of DOX cardiotoxicity.

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KEY WORDS anthracycline cardiotoxicity, cardioprotection, chronic remote ischemic conditioning, repeat remote ischemic conditioning