Reprinted Remote Ischemic Conditioning Protects Against Doxorubicin Cardiotoxicity
Never Too Much of a Good Thing*

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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, in-
 fammation, and mitochondrial dysfunction (3). The
 fact that many of these factors have also been impli-
cated 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 mitochon-
drial 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 noninva-
sive cardioprotective strategy for testing in patients
 undergoing anthracycline chemotherapy. In this re-
 gard, the ongoing ERIC-ONC study (Effect of Remote
 Ischemic Conditioning in Oncology Patients; NCT02471885)
 is currently investigating the car-
dioprotective 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 chemo-
 therapy, 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 exper-
 imental small animal models of AMI in terms of pre-
 venting adverse post-AMI LV remodeling via
 potential anti-apoptotic, anti-inflammatory, auto-
 phagic 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 car-
diotoxicity. 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 car-
dioprotective effect against DOX cardiotoxicity.
 However, a prolonged rRIC protocol would raise is-
 sues of patient compliance in future clinical studies.

Interestingly, the authors also demonstrated that
 rRIC had cytoprotective effects in other organs, such
 as the kidney, spleen, and liver, in terms of preserv-
ing organ weight and function (13). The multiorgan
 benefits of rRIC may be explained by the release into
 the systemic circulation of, so far unidentified, cyto-
 protective 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 stim-
 ulus 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 effi-
cacy 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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