Remote ischemic preconditioning ameliorates anthracycline-induced cardiotoxicity and preserves mitochondrial integrity: results from a randomized preclinical trial in pigs

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Introduction: Anthracycline-induced cardiotoxicity (AIC) is a serious adverse effect occurring in a significant proportion of patients. Irreversible mitochondrial damage is a central mechanism of AIC. Despite many efforts, there is a lack of therapies able to prevent AIC. Remote ischemic preconditioning (RIPC) could be a promising therapy to prevent AIC due to the scheduled application of chemotherapy in cancer patients.

Purpose: To evaluate the cardioprotective efficacy of RIPC in large animal model of AIC.

Methods: Large-White pigs (n=20) underwent a validated protocol of AIC consisting on five intracoronary doxorubicin injections (0.45 mg/kg), on weeks 0, 2, 4, 6, 8 of the study. Pigs were randomized before the initiation of the study to remote ischemic pre-conditioning (RIPC, 3 cycles of 5 min lower limb ischemia followed by 5 min reperfusion) or sham procedure immediately before doxorubicin injections. An additional group of 10 pigs without any exposure to doxorubicin was carried out as controls. Pigs underwent a comprehensive serial cardiac magnetic resonance (CMR) exam baseline, and on weeks 6, 8, 12, and 16. After 16-week CMR, pigs were sacrificed and tissue samples collected. A second group of 10 pigs (randomized 1:1 for RIPC) underwent the same protocol but were sacrificed 2 weeks after the third doxorubicin dose for early evaluation of tissue changes. Primary endpoint of the study was CMR-based left ventricular ejection fraction on week 16.

Results: Until week 6 (time of fourth doxorubicin injection), LVEF remained unchanged in both groups. From there on, a progressive decline in LVEF was observed. LVEF depression trajectory was blunted in RIPC animals. Compared to controls, pigs undergoing RIPC before each doxorubicin dose had a significantly higher LVEF at week 16: median (IQR) 45% (27–50%) vs 33% (19–47%) in RIPC and controls respectively, p=0.04. Improvement in LVEF was mainly due to a more preserved contractile function, as evidence by smaller LVESV, and better regional contractile function. After 3 doxorubicin doses, a time where global (LVEF) and regional contractile function was still unchanged, transmission electron microscopy (TEM) showed fragmented mitochondria with remodeled cristae only in control pigs. At the end of the 16 weeks, TEM evaluation in control pigs (as compared to RIPC pigs) showed overt cardiomyocyte's mitochondrial fragmentation with overt structural derangement. At this time, RIPC pigs had significantly less interstitial fibrosis on histology.

Conclusions: In a translatable large animal model of AIC, RIPC applied immediately before each doxorubicin cycle resulted in a preservation of cardiac contractility with significantly higher long-term LVEF and less cardiac fibrosis. RIPC prevented the deleterious effects of doxorubicin on mitochondria since early stages of AIC. RIPC is a promising intervention to be tested in clinical trials to prevent cardiotoxicity.