Intracellular Free Zinc Ion Increase Triggers Hyperglycemia-Induced Cardiomyocyte Dysfunction through Endoplasmic Reticulum Stress

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As a result of more effective therapies, more patients recover from cancer. However, often they develop cardiotoxicity manifested, among others, as heart failure. Doxorubicin (Dox) is a widely used and high effective cancer chemotherapeutic agent, and radiation therapy (RT), when directed to the thorax, can affect cardiac function. Because intracellular Ca2+ fluxes underlie cardiac function, we investigated intracellular Ca2+ handling in mice treated with doxorubicin (Dox) or chest radiotherapy (RT). 12 weeks old, C57BL/6 male mice received 3 i.v. injections of 4 mg/Kg Dox each, reaching a cumulative dose of 12mg/kg of Dox. Data was obtained at 2, 6 and 15 weeks after last injection. RT-treated mice were locally irradiated with 2 and 16Gy localized to the heart, and experiments performed 20 and 50 weeks after irradiation. M-mode Echocardiography showed a significant reduction of the ejection fraction (EF) at 15w after last injection of Dox. Consistently, the amplitude of [Ca2+]i transients was decreased (F/F0: 4.10 ± 0.25, n=11 control cells, vs. 3.22 ± 0.14, n=15 Dox, p<0.01) and slowed (tau in ms: 138.98 ± 6.17, n=11 control vs 169.63 ± 11.91, n=15 Dox, p<0.05) at 15w with a significant increase in the frequency of Ca2+ sparks, but without changes on the SR Ca2+ content. RT induced a LV enlargement associated with a significant reduction of EF in low and high dose irradiated mice group at both time lapses. However, Ca2+ handling was minimally affected by RT. After 50w of 16Gy RT, we observed a faster decay of [Ca2+]i transients with unaltered amplitude and SR Ca2+ content. Our results indicate that the depressed cardiac function after Dox treatment involves [Ca2+]i transient reduction, while in RT-induced cardiotoxicity the Ca2+ alteration may not be involved likewise.

Mechanisms of Anthracycline-Induced Dysfunction of Calcium Handling Proteins in the Heart

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Anthracyclines are powerful chemotherapy agents, whose use is limited due to the onset of potentially fatal cardiotoxicity which includes arrhythmogenesis and heart failure. Several proteins important in intracellular Ca2+ signaling have been identified as drug binding targets, including the cardiac ryanodine receptor Ca2+-release channel (RyR2), the Ca2+-binding protein calseenetin (CSQ2) and the Sarco/Endoplasmic Reticulum Ca2+-ATPase (SERCA2a). The effects of the drug metabolites have been poorly characterized but are believed to be important in the devastating cardiac effects of these drugs.

The functional effect of doxorubicin and its metabolite, doxorubicinol on RyR2 was assessed by adding clinically relevant drug concentrations to single RyR2 channels in lipid bilayers. Both drugs caused biphasic modulation of RyR2 activity where there was an early increase in channel activity followed by a later, inhibitory phase. RyR2 channel activation, but not inhibition, could be reversed by drug washout, typical of a ligand binding effect. Conversely, the irreversible nature of the inhibitory effect suggested a non-ligand binding effect. Treatment with doxorubicin/doxorubicinol reduced the number of dihols on RyR2, indicative of drug-induced thiol oxidation. Additionally, doxorubicin abolished the response of RyR2 to changes in luminal Ca2+. Further experiments revealed that the loss of luminal Ca2+ sensing was due to an interaction between doxOL and CSQ2. Finally, we found that doxorubicin inhibits SERCA2a Ca2+ uptake into SR vesicles and that this was prevented by pretreatment with DTT. These results provide novel insight into the cellular mechanisms of anthracyclines. We suggest that, targeting multiple Ca2+ handling proteins in cardiac muscle, anthracyclines severely disturb cardiomyocyte Cas2+ homeostasis and that these effects have an important role in the onset of anthracycline-mediated arrhythmia and heart failure.