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Heart Failure

DOXORUBICIN-INDUCED CARDIOTOXICITY IN MICE IS BLUNTED BY LATE SODIUM CURRENT INHIBITION WITH RANOLAZINE, WITH IMPROVEMENT IN HEART FUNCTION, FIBROSIS AND APOPTOSIS

Poster Contributions
Poster Sessions, Expo North
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Authors: *Nicola Maurea, Carmela Coppola, Giovanna Piscopo, Clemente Cipresso, Domenica Rea, Aldo Giudice, Carlo Maurea, Claudio Arra, Claudia De Lorenzo, Carlo Gabriele Tocchetti, National Cancer Institute, Pascale Foundation, Naples, Italy*

Background: Doxorubicin (DOX) produces a cardiomyopathy through multiple mechanisms as Ca2+ overload. DOX generates Reactive Oxigen and Nitrogen Species, posing the heart at increased demand for oxygen, setting the stage for metabolic ischemia that activates late sodium current, target of ranolazine (RAN). We aim at assessing if RAN, diminishing intracellular Ca2+ through inhibition of late sodium current, prevents DOX cardiotoxicity at different levels.

Methods: We measured left ventricular (LV) fractional shortening (FS) with M-mode echocardiography, radial strain by speckle tracking in C57BL6 mice, 2-4 mo old, pretreated with RAN (370mg/kg/day, a dose comparable to the one used in humans) per os for 3 days. RAN was then administered for additional 7 days, alone and together with DOX (2.17mg/kg/day ip). Hearts were then excised, mRNA expression was analyzed by qRT-PCR, interstitial fibrosis with picrosirius red staining. By Western blotting, we measured the activation of the apoptotic pathway.

Results: After 7 days with DOX, FS decreased to 50±2%, p=.002 vs 60±1% (sham). RAN alone did not change FS (59±2%). Interestingly, in mice treated with RAN+DOX, the reduction in FS was milder: 57±1%, p=.01 vs DOX alone. DOX-cardiotoxicity was accompanied by significant elevations in ANP (1000 folds), BNP (500 folds), CTGF (26 folds) and MMP2 (81 folds) mRNAs, while co-treatment with RAN significantly lowered these same genes compared to DOX. The alterations in extracellular matrix remodeling were confirmed by an increase of interstitial collagen with DOX (3.66%), p=.004 vs 2.19% (sham), which was normal in hearts co-treated with RAN (2.02%, p=.0002 vs DOX). The levels of PARP and pro-Caspase 3 were significantly decreased with DOX, with a parallel increase in cleaved caspase 3, but not with RAN+DOX. Radial strain was already decreased after 2 days of DOX: 34±4%, p=.0003 vs sham (64±4%), but RAN+DOX-treated mice showed a higher value: 49±3%, p=.01 vs DOX alone.

Conclusions: In mice, DOX produces LV dysfunction which can be effectively predicted by early radial strain abnormalities. RAN is able to blunt such cardiotoxicity at different levels.