Diastolic dysfunction in doxorubicin cardiotoxicity: a new therapeutic target?

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Background: Doxorubicin (DOXO) is a highly effective anticancer drug but its clinical application is impeded by cardiotoxicity. Asymptomatic diastolic dysfunction can be the earliest manifestation of DOXO cardiotoxicity. Therefore, a search for therapeutic intervention that can interfere with early manifestations and possibly prevent late cardiotoxicity is warranted. Increased DOXO-dependent reactive oxygen species may explain, in part, Ca2+ and Na+ accumulation that contributes to diastolic dysfunction and development of heart failure.

Purpose: We tested whether the administration of ranolazine (RAN), an anti-anginal drug, immediately after completing DOXO therapy, can affect diastolic dysfunction and interfere with the progression of functional decline.

Methods: Fischer 344 rats received a DOXO cumulative dose of 15 mg•kg-1 over a period of 2 weeks. After the assessment of diastolic dysfunction, the animals were administered with RAN (80 mg•kg-1, daily) for the following 4 weeks.

Results: While diastolic and systolic function progressively deteriorated in DOXO-treated animals, treatment with RAN relieved diastolic dysfunction and prevented worsening of systolic function decreasing mortality. RAN lowered myocardial NADPH oxidase 2 expression and 3-nitrotyrosine content. A reduced NCX and Nav 1.5 expression and an increment of SERCA2 were also detected. In addition, RAN lowered DOXO-induced increased phosphorylation and oxidation of Ca2+/calmodulin-dependent protein kinase II and decreased fibrosis.

Conclusions: RAN, by modulating cardiac Ca2+ and Na+ handling proteins and oxidative stress, was effective in attenuating DOXO-induced diastolic dysfunction and prevented the progression of cardiomyopathy.