DOXORUBICIN-INDUCED MYOCARDIAL INFLAMMATION, APOPTOSIS AND REMODELING ARE ATTENUATED BY CARDIAC-SPECIFIC TRANSGENIC INHIBITION OF NUCLEAR FACTOR-KAPPA

ACC Poster Contributions
Ernest N. Morial Convention Center, Hall F
Sunday, April 03, 2011, 3:30 p.m.-4:45 p.m.

Session Title: Cardiomyopathies/Myocarditis/Pericardial Disease
Abstract Category: 22. Cardiomyopathies/Myocarditis/Pericardial Disease
Session-Poster Board Number: 1053-38

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Background: Cardiac inflammation and apoptosis contribute to doxorubicin (DOX)-induced cardiomyopathy. Since NF-κB participates in inflammatory response and apoptosis, we investigated whether NF-κB is involved in DOX-induced cardiotoxicity.

Methods: A transgenic (Tg) mouse model of cardiac-specific inhibition of NF-κB was used. Age-matched wild-type (WT), nontransgenic littermates (NTg) and IκB-κ Tg mice received vehicle or DOX (7.5 mg/kg i.p. 2 times over 2 wks), and were divided into 6 groups: group I (WT, vehicle); group II (NTg, vehicle); group III (Tg, vehicle); group IV (WT, DOX); group V (NTg, DOX); and group VI (Tg, DOX). Cardiac function was assessed by echocardiography and hemodynamics. Mice were euthanized 2 wks after the first DOX. The LV tissue was harvested for myocardial protein expression of proinflammatory cytokines (TNF-α, IL6) and proapoptotic markers (Bax, p53).

Results: Compared with WT and NTg mice, survival was greater in Tg mice at 2 wks after DOX (43% and 43% vs. 73%, in groups IV-VI, respectively, p<0.05). After 2 wks, compared with group IV and group V, group VI exhibited improved LV EF, LV pressures, ±dP/dt, LV diameters, and LV end-diastolic volume. Hearts from Tg mice also showed a significant decrease in inflammation and apoptosis, as indicated by reduced protein expression for TNF-α, IL6, and Bax (Figure).

Conclusions: Inhibition of NF-κB protects against adverse consequences of DOX. This novel approach may be useful to prevent cardiomyopathy in DOX-treated cancer patients.