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Early, combined heart failure therapy attenuates doxorubicin cardiomyopathy in rats

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Background: Doxorubicin (DOX) is a widely used chemotheraputic agent with well known cardiotoxic side effects. High doses of DOX are commonly used to induce cardiomyopathy in experimental animal models of heart failure (HF). However, less data are available regarding the cardiotoxicity of therapeutic DOX doses, analogous with human oncotherapy.

Purpose: Our aim was to establish a rodent model of cardiomyopathy demonstrating early myocardial injury induced by repeated iv. DOX injections, with concentrations (ccs) extrapolated from consecutive cycles of human oncotherapy. In addition, we tested prophylactic (PRE) and delayed (POST) combined HF therapies in order to prevent DOX induced adverse myocardial changes.

Methods: We used 12-week-old male Wistar rats and divided them into 4 subgroups. Blood pressures (BP) and heart rate (HR) were monitored during the study by the tail-cuff method. DOX ccs were calculated from human doses of existing chemotherapy protocols and were corrected to the body surface of rats. After baseline echocardiography (echo), animals in the PRE group received a daily combination of bisoprolol (2.5 mg/kg), perindopril (2 mg/kg) and eplerenone (6.25 mg/kg) before, while those in the POST group 1 month after DOX treatment. Drugs were applied in a mucous vehicle by oral gavage. Positive controls received both DOX treatment and a drug-free vehicle (D-CON), while negative controls received drug-free vehicle only (CON). DOX exposure was carried out by injecting 1.5 mg/kg DOX into the tail veins of the animals on 6 occasions. Follow-up echo was carried out 1 and 2 months after DOX treatment. DOX induced ultrastructural changes were validated by in vitro electron microscopic (EM) measurements.

Results: Systolic and diastolic BP, as well as HR were significantly lower in the PRE group, compared to all other groups. Follow-up echo revealed a gradually reducing ejection fraction (EF) in the D-CON and POST animals over the 2-month-period compared to CON (64.3±3.5 and 67.4±4.7% vs. 72.4±3.2%, p=0.0001), while no significant drop in the EF was observed in the PRE group

(79.2±6.4%). At 2 months, a restrictive filling pattern was observed in the D-CON and POST groups but not in the CON and PRE animals. DOX induced a significant increase in the isovolumetric relaxation time, which could not be attenuated by either the PRE or POST treatment. EM measurements revealed pronounced myocardial damage in the D-CON group, which was partially attenuated in the PRE and POST groups.

Conclusions: We successfully established a rodent model to examine the cardiotoxicity of DOX chemotherapy. Prophylactic, but not post-exposure supportive treatment was capable of attenuating the DOX induced systolic and diastolic dysfunction. Our model seems eligible for future investigations to further elucidate cardiotoxic side effects of DOX, as well as for the development of early drug intervention protocols to eliminate myocardial injury induced by DOX chemotherapy.