

DOXORUBICIN CARDIOTOXICITY AND APOPTOSIS: VARIATION OF EXPOSURE TIMES TO THE SAME CUMULATIVE DOSE

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Cardiac apoptosis (CA) is involved in doxorubicin (DOX) induced cardiomyopathy. Aim of this study was to assess the influence on CA of different exposure times to the same DOX cumulative dose (20 mg/kg) in rats. Wistar rats were randomly assigned to either controls (CTL) (n=10) or to each DOX-treated (TRT) groups (n=20). DOX was administered intraperitoneally four times per week at the following doses: a) 5 mg/kg/day for one week; b) 2.5 mg/kg/day for two weeks; c) 1.25 mg/kg/day for four weeks. 48 h after first DOX administration and at the end of treatments hearts were used for western blotting analysis.

48 h after first DOX administration, 5 mg/kg/day DOX significantly ($p<0.05$) increased expression levels of: a) procaspase 3 (TRT 1.81 ± 0.1 vs CTL 1.30 ± 0.08) and its cleaved form (TRT 7.41 ± 1.33 vs CTL 0.6 ± 0.2); b) procaspase 9 (TRT 0.94 ± 0.12 vs CTL 0.18 ± 0.06) and its cleaved form (TRT 0.61 ± 0.09 vs CTL 0.10 ± 0.02); c) Bax/Bcl₂ (TRT 0.46 ± 0.03 vs CTL 0.22 ± 0.02). On the contrary, 2.5 mg/kg/day DOX and 1.25 mg/kg/day DOX did not affect expression levels of pro- and antiapoptotic proteins.

At the end of treatments: 1) 5 mg/kg/day DOX significantly ($p<0.05$) increased expression levels of: a) procaspase 3 (TRT 3.9 ± 0.2 vs CTL 2.8 ± 0.13) and its cleaved form (TRT 2.5 ± 0.1 vs CTL 1.6 ± 0.07); b) Bax/Bcl₂ (TRT 0.2 ± 0.01 vs CTL 0.08 ± 0.02); c) procaspase 8 (TRT 3.3 ± 0.1 vs CTL 2.6 ± 0.2); d) procaspase 12 (TRT 6.83 ± 0.3 vs CTL 4.31 ± 0.4) and its cleaved form (TRT 8.82 ± 1.15 vs CTL 0.23 ± 0.11); e) calpain I (TRT $1.22\pm 0,16$ vs CTL $0,43\pm 0,13$). Furthermore, 5 mg/kg/day DOX significantly ($p<0.05$) decreased expression levels of: a) troponin I (TRT 0.71 ± 0.07 vs CTL 2.17 ± 0.32); b) Myosin Heavy Chain (MHC) (TRT $0,83 \pm 0,11$ vs CTL $1,56 \pm 0,13$). 2) 2.5 mg/kg/day DOX significantly ($p<0.05$) increased expression levels of: a) procaspase 12 (TRT 7.95 ± 0.1 vs CTL 4.83 ± 0.53). 3) 1.25 mg/kg/day DOX did not affect expression levels of pro- and antiapoptotic proteins.

Therefore, 20 mg/kg DOX for four weeks induced minor apoptotic effects respect to the administration of the same cumulative dose in shorter period. This could be useful to establish a treatment scheme with best efficacy and less toxicity.