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Coronary response in the doxorubicin-induced cardiomyopathy

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Background: Coronary reserve and reactivity traits regarding doxorubicin (Dx) cardiotoxicity are less known comparatively to myocardial contraction and inotropic capacities.

Aim: the in vitro evaluation of coronary response to natural vasotropic agent action in Dx-induced cardiomyopathy (Dx-CMP).

Material and methods. Dx-CMP has been reproduced in white rats by Dx administration during 2 weeks (4 i/p Dx injections of 4 mg/kg, cumulative dose 16 mg/kg). The izovolumic isolated heart was perfused by standard Krebs solution according to Langendorff method, and the coronary flow (CF) changes were determined during action of acetylcholine (Ach), adenosine (As), bradykinin (Bk), hydrogen peroxide (H2O2), epoxyeicosatriens 11,12 (EET-11,12) and endothelin 1 (ET-1) in a concentration range of 10-7-10-5 M.

Results: The basal CF in DxCMP did not differ from control index ($12,7 \pm 0,08$ vs $13,4 \pm 0,09$ ml/min). However, the endothelium dependent coronary functional reserve is impaired, manifested by significant lowered CF value during stimulation by Ach ($14,8 \pm 0,1$ vs $17,3 \pm 0,12$ ml/min), As ($13,9 \pm 0,09$ vs $15,5 \pm 0,11$ ml/min) and Bk ($13,8 \pm 0,08$ vs $15,3 \pm 0,12$ ml/min). Remarkably, the coronarodilation mediated by hyperpolarization was not compromised in Dx-CMP. The coronary reserve inherent to H2O2 action was as 15,7% in Dx-CMP (CF, $14,7 \pm 0,12$ ml/min) and 14,9% in control series (CF, $15,4 \pm 0,13$ ml/min). In a similar manner CF increased in response to EET-11,12 action: 14,3% in Dx-CMP (CF, $14,52 \pm 0,13$ ml/min) and 14,1% in control (CF, $15,29 \pm 0,14$ ml/min). Thus, the mediated by hyperpolarization coronary artery dilatation could be an alternative tool of coronary functional reserve control in Dx-CMP associated by endothelium dysfunction. Importantly, ET-1 in concentration of 10-7 M determined in Dx-CMP o reduction of CF equal to control pattern (11,3%), but in condition of isolated heart pretreatment by apamin (selective blocker of KCa channels) the coronaroconstriction in Dx-CMP has been more pronounced vs control (-17,1 vs -14,2%). In highest concentration (10-5 M) ET-1 led in Dx-CMP to a bigger decline of coronary flow FC (-16,8 vs -14,5%).

Conclusions: 1. The coronary functional endothelium dependent reserve is significantly reduced in Dx-CMP during Ach, As and Bk action averagely by 39-43,3% comparing to control, but the mediated by hyperpolarization coronarodilation proper to H2O2 and EET-11,12 action is not compromised.

2. In concentration of 10-5 M endoteline-1 induces a bigger fall of CF in Dx-CMP, but in concentration of 10-7 M the decline is similar to control, however CF decreases more if ET-1 action was preceded by KCa channels blocking.