BASIC SCIENCE - ANIMAL EXPERIMENTATION

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Inflammation inhibition effects in diabetes induced heart failure

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Background: Inflammation is appreciated as a leading factor regarding cardiovascular disorders triggering and exacerbation. Nevertheless a promising antinflammatory treatment concerning cardiac mismatch improvement is not yet consolidated.

Aim: The in vitro evaluation of cardiac effects of the TNF-alpha antagonist administration during diabetes-induced heart failure (DHF).

Material and methods: DHF was classically reproduced in rats by i/p administration of streprozotocin (50 mg/kg, 5 days) – series 1 (of reference). TNF-alpha antagonist, TNF-McAb (TNF monoclonal antibody, analog of infliximab) has been administered i/p during DHF modeling and 5 days after – series 2. After 10 days animals of both series have been euthanized, and isolated heart was perfused in isovolumic regimen (Langendorff model) or exterior working (Neely-Rovetto model). Cardiac reactivity was assayed in: (1) hemodynamic effort due to pre- and afterload

increase; (2) neuroendocrine activation modulated by action in diverse concentrations of norepinephrine, angiotensin II and endothelin-1 (ET-1); (3) in ischemia (30 min) followed by reperfusion (45 min) syndrome.

Results: TNF-alpha inhibition led to significant increase of cardiac output (CO) in effort with volume and resistance respectively by 23,7 and 26,2% comparatively to reference indices. Systolic pressure of left ventricle (LV) was in series 1 higher in all induced hemodynamic stress levels, but on aortic pressure of 100 and 120 cm H20 the increment was significant and averagely represented 18-19%. DHF was characterized by LV lusitropic function impairment, whose principal parameters, telediastolic pressure (LVTDP) and index of diastolic myocardial rigidity significantly decreased during TNF-alpha inhibition by 26-28%. The norepinephrine action led in DHF to inotrop-chronotropic effect dissociation, but endothelin-1 (ET-1) induced a negative inotropic effect, associated by CO reducing by 10,3%. TNF-alpha inhibition led to appearance of positive inotropic effect to ET-1 action and cardiac output increase by 11%. Myocardial ischemic contracture assayed after 30 min of ischemia thereby of LVTDP is doubly more in DHF vs control pattern (56,3 ± 3,6 vs 28,4 ± 1,9 mm Hg) and remains above on 45th min of reperfusion (39,2 ± 2,5 vs 18,8 ± 1,2 mm Hg). TNF-McAb notably attenuated consequences of ischemia-reperfusion syndrome, leading to LVTDP drop by 29,3% at finish of ischemia and by 26,8% at finish of reperfusion.

Conclusions: 1. TNF-alpha inhibition during diabetes-induced heart failure improved cardiac functionality, confirming the pathogenical role of inflammation and, on the other hand, the therapeutic relevance of TNF-McAb regarding outworn heart functioning in hemodynamic and neuroendocrine efforts.

2. Most conspicuous TNF-McAb benefit has referred to appearance of positive inotropic effect to ET-1 action and significant decrease of LV telediastolic pressure by around 29% in ischemia-reperfusion syndrome.