

the D263E desmin, as well as the other ID proteins, retained at high level their proper localization in the myocardium of D263E MHCsTNF mice.

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Keywords: Desmin; TNF- α ; Aggregates

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Abstract No. 116

Regulation of Calreticulin, a SR chaperone, in human heart failure

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Background: Calreticulin (CRT) is a calcium binding chaperone in the endoplasmic reticulum. Previously, high expression of CRT in transgenic animals resulted in a cardiomyopathic phenotype including decreased systolic function, chamber dilation, and sudden death. The role of CRT in human heart failure has not been characterized yet.

Methods and results: Left ventricular myocardial tissue from explanted non-failing hearts (NF; $n=17$), from terminally failing hearts due to dilated cardiomyopathy (FAIL; $n=18$; EF: $27.4\pm 2.2\%$), and myocardial biopsies from compensated hypertrophic hearts due to aortic stenosis (AS; $n=18$; EF: $51.6\pm 3.3\%$) were subjected to quantitative Western-blot analysis (data expressed as percent change of NF-levels). Calreticulin expression was significantly increased in both, failing hearts (FAIL: $155.6\pm 8.9\%*$) and aortic stenosis hearts (AS: $141.4\pm 7.8\%*$), compared to non-failing myocardium (NF: $100\pm 11.1\%$; $*p<0.05$). Calcineurin, a putative downstream effector of calreticulin, was found to be upregulated in a parallel fashion (NF: $100\pm 10.2\%$; AS: $142.9\pm 6.6\%*$, FAIL: $180.3\pm 6.6\%*$). Interestingly, like in CRT-overexpressing mice, the gap junctional protein connexin 43 was already significantly down-regulated in myocardium from patients suffering from aortic stenosis (NF: $100\pm 7.1\%$; AS: $56.7\pm 15.8\%*$, FAIL: $57.5\pm 8.6\%*$), which may contribute to the AV-conduction delay found in Calreticulin-overexpression mice as well as in patients suffering from aortic stenosis or heart failure. Since CRT may serve as a SR luminal Ca^{2+} sensor and might be induced by low SR Ca^{2+} load, we co-incubated adult rabbit cardiomyocytes with the SR Ca^{2+} ATPase inhibitor Thapsigargin (10^{-8} M), which resulted in depletion of SR Ca^{2+} and a marked increase of CRT protein expression after 24 h.

Conclusion: This is the first study showing upregulated Calreticulin protein levels in human heart failure. Our observations support the role of Calreticulin as a SR calcium sensor.

Keywords: Heart failure; SR calcium regulation

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Abstract No. 117

Myocardial protection: Efficacy of RS-C (Aqix®), a novel magnesium-cardioplegia, compared to St Thomas' hospital solution

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Objective: The current gold standard for myocardial protection is hyperkalemia; however, depolarization can cause myocardial Ca-overload and dysfunction. Alternative cardioplegic solutions, such as the novel Mg-cardioplegia (RS-C) based on RS-I solution (Aqix®; a new perfusion solution formulated to exclude free inorganic phosphate ions and prevent potential deleterious effects), may be beneficial. We compared the efficacy of RS-C to St Thomas' solution No 2: STH2 (16 mM Mg).

Methods: Isolated Langendorff-perfused rat hearts were used, and function measured. In Study 1, the optimal Mg concentration (16, 25, 35 or 50 mM) in RS-C was established after 50 min global 37 °C ischemia compared to STH2. Study 2 compares single-dose RS-C (25 mM Mg) to STH2 at different ischemic durations (20, 30, 40 or 50 min). Study 3 investigated multiple infusions (every 20 min) of RS-C compared to STH2 during 60 min global ischemia. All hearts were reperfused for 60 min and recovery (%) of function determined.

Results: In Study 1, LVDP recovery in RS-C (16, 25, 35 or 50 mM Mg) was 48 ± 3 , 50 ± 2 , 50 ± 3 and $30\pm 3\%$ compared to $51\pm 2\%$ for STH2. Contracture related parameters (time to onset and peak) in 25 mM Mg was 32 ± 1 min (longest) and 35 ± 1 mm Hg (lowest) ($p<0.05$) vs. STH2 (26 ± 1 min and 43 ± 2 mm Hg). Optimal Mg for RS-C was 25 mM. In Study 2, recovery in RS-C (25) was significantly ($p<0.05$) higher after 20 min ischemia than with STH2 ($81\pm 1\%$ vs. $74\pm 1\%$); however, there were no differences at 30, 40 or 50 min of global ischemia. In Study 3, RS-C (25) significantly improved recovery compared to STH2 (LVDP: 73 ± 2 vs. $44\pm 1\%$; LVEDP: 9 ± 2 vs. 45 ± 2 mm Hg; $p<0.001$).

Conclusion: Mg-based cardioplegia, at an optimal Mg concentration of 25 mM, improved protection compared to the hyperkalemic STH2 at a short (20 min) ischemic duration or after 60 min ischemia with multiple infusions. Mg-based cardioplegia may be a beneficial alternative to hyperkalemia under certain specific ischemic conditions.

Keywords: Myocardial protection; Cardioplegia; Magnesium

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