Paraoxanase 1 Deletion Leads to Increased Cardiac Remodeling and Cardiac Fibrosis in a Dahl Salt-Sensitive Rat Model of Chronic Kidney Disease

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Introduction: Paraoxanase 1 (Pon-1) synthesis occurs in liver and circulates bound to high-density lipoproteins (HDL), contributing to HDL's antioxidant, anti-inflammatory and anti-atherogenic properties. Decreased circulating Pon-1 activity is associated with increased oxidant stress and adverse clinical outcomes in the setting of chronic kidney disease (CKD). Whether decreased Pon-1 is mechanistically linked to adverse cardiovascular outcomes in CKD, however, remains unclear. We tested the hypothesis that Pon-1 is cardioprotective in a Dahl salt-sensitive model of hypertensive renal disease.

Methods: Ten-week-old, age-matched male and female control Dahl salt-sensitive rats (SS) and Pon1 mutant rats (SS-Pon1 KO) were maintained on high salt diet (8% NaCl) for up to 12 weeks to initiate salt-sensitive hypertensive renal disease. Left ventricular geometry and function were assessed in male SS and SS-Pon1 KO rats at the end of week four of high salt diet via echocardiography and animals were euthanized and hearts processed for histology.

Results: SS-Pon1 KO male rats demonstrated a significantly increased relative cardiac wall thickness (0.77+/-0.05 vs. 0.58+/-0.02) and fractional shortening (0.62+/-0.02 vs. 0.53+/-0.01), as well as significantly increased mean velocity of circumferential fiber shortening (circ/s, 6.37+/-0.33 vs. 5.52+/-0.17) and cardiac index (ml/min/kg, 184+/-18 vs. 136+/-11) vs age matched SS rats. No difference in heart rates was observed. Upon histological examination, heart sections of SS-Pon1 KO male rats showed a significant increase in fibrosis and heart-weight-to-body-weight ratio compared to the age matched SS rats.

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Conclusion: Our findings suggest that loss of PON-1 in salt-sensitive hypertensive rats leads to a cardiac phenotype consistent with compensated heart failure.

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