Paraoxanase 1 Regulation of Cardiac Inflammation and Fibrosis in a Dahl Salt-Sensitive Rat Model of Chronic Kidney Disease

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Objective: Paraoxonase-1 (PON1) is a lactonase enzyme associated with high-density liproteins (HDL), contributing to its antioxidant, anti-inflammatory and anti-atherogenic properties. Deficiencies in PON1 result in oxidative stress and adverse clinical outcomes in chronic kidney disease (CKD), however the link to cardiovascular pathology in CKD is unknown. We investigated the hypothesis that PON1 is cardioprotective in a Dahl Salt-Sensitive model of hypertensive renal disease.

Methods: Age matched 10-week-old Dahl salt-sensitive (SS) and mutant PON1 knock-out (SS-PON-1 KO) male rats were maintained high salt diet (8% NaCl) for five weeks to induce hypertensive renal disease. Echocardiography was performed 1 week prior to euthanasia and hearts were processed for histopathologic and real-time (RT) PCR analysis of cardiac hypertrophy and fibrosis.

Results: RT PCR analysis of cardiac left ventricular tissue revealed an increase in the expression of natriuretic peptide A ($p< 0.0001$) and myosin heavy chain 7 ($p< 0.0001$), suggesting cardiac hypertrophy in SS-PON-1 KO male rats compared to controls (SS). A decrease in sarcoplasmic/endoplasmic reticulum Ca2+ ATPase ($p< 0.0001$) expression was observed. CD68 staining showed an increase in macrophage infiltration in both perivascular ($p< 0.0277$) and interstitial ($p< 0.005$) regions within the heart sections of SS-PON-1 KO male rats. Furthermore, upregulation of tissue inhibitor of metalloproteases 1 ($p< 0.0001$) expression was seen.

Results are consistent with the echocardiography analysis and trichrome analysis indicating increased cardiac fibrosis in SS-PON-1 KO vs SS rats.

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Conclusion: Our findings indicate that loss of PON1 in salt-sensitive hypertensive rats results in compromised left ventricular function and hypertrophy, increased cardiac fibrosis and macrophage infiltration.

