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

Sophia Soehnlen1*, Prabhatchandra Dube1, Fatimah K. Khalaf1, Chrysan J. Mohammed1, Armelle DeRiso1, Dhanushya Battepati1, Tiana Sarsour1, Iman Tassavvor1, Andrew L. Kleinheng1, Steven T. Haller, PhD1, Eric E. Morgan1, David J. Kennedy, PhD1

1Division of Cardiology, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: Sophia.Soehnlen@rockets.utoledo.edu

Published: 05 May 2023

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.

https://dx.doi.org/10.46570/utjms.vol11-2023-645
Conclusion: Our findings suggest that loss of PON-1 in salt-sensitive hypertensive rats leads to a cardiac phenotype consistent with compensated heart failure.