Smooth muscle cell specific activity of SGK-1 alters pulse propagation velocity as a major indicator of wall stiffness in AAA

Mario Figueroa MD, Ryan Gedney MD, Victoria Mattia, Ying Xiong, Rupak Mukherjee PhD, Jeffery A. Jones PhD, Jean Marie Ruddy MD

Introduction: Progressive wall stiffness in abdominal aortic aneurysms (AAA) contributes to rupture, but we are currently unable to apply vascular mechanics to patient-care decision-making. As a potential pharmacotherapeutic target to reduce growth of small AAA, our laboratory has been studying the mechanosensitive kinase, serum and glucocorticoid inducible kinase-1 (SGK-1). It promotes tension-induced production of pro-inflammatory cytokines in aortic vascular smooth muscle cells (VSMCs) and blocking SGK-1 activity has reduced murine AAA growth. We hypothesize that inhibiting SGK-1 to abrogate AAA growth will correlate to a reduction in ultrasound-derived aortic stiffness parameters to allow for non-invasive monitoring of AAA mechanics.

Methods: C57Bl/6, Myh11^{Cre+}, and SGK-1$^{flox+/+}$ mice (n=4 for each) were treated with periadventitial $CaCl_2$ for AAA induction with or without infusion of EMD638683, a specific SGK-1 inhibitor (2.5mg/kg/day x 21 days). The VeVo3100 ultrasound system was used to capture images of the abdominal aorta on Day 0 and Day 21. Ultrasound imaging was performed with a high-frequency linear array probe (MX 400, frequency 20–46 MHz) and the validated VevoVasc software quantified the stiffness parameters: pulse propagation velocity (PPV), distensibility, and global radial strain. Aortic diameter (AoD) was obtained by ultrasound and digital microscopy. By crossing the Myh11^{Cre+} and SGK-1$^{flox+/+}$ mice (both on C57Bl/6 background), a novel smooth muscle specific SGK-1 knockout mouse (SMC-SGK-1KO$^{+/-}$) was created and these underwent parallel experimentation (n=4).

Results: Our laboratory has previously demonstrated AAA development in C57Bl/6 mice with average increased diameter of 76+/-3% and significant reduction when treating with EMD638683 (26+/-3%, $p<0.05$ vs C57Bl/6+AAA). Similar AAA growth was observed in Myh11Cre+AAA (61+/-9%) and SGK-1flox+AAA (66+/-10%), and again infusion of EMD638683 significantly reduced aortic dilation (25+/-3% for Myh11Cre+AAA+EMD and 27+/-5% for SGK-1flox+AAA+EMD). Likewise, SMC-SGK-1KO$^{+/-}$+AAA mice only dilated to 33+/-5%, indicating that SGK-1 activity specifically within the aortic VSMC promoted degenerative remodeling. As expected, AAA growth correlated with increased aortic wall stiffness, particularly decreased distensibility and global radial strain among all animals that underwent peri-adventitial $CaCl_2$ application. Treatment with EMD638683 did not alter these parameters. PPV, on the other hand, was preserved in animals treated with EMD638683 and in the SMC-SGK-1KO$^{+/-}$ mice, perhaps indicating variability in how SGK-1 impacts matrix versus VSMC contribution to aortic wall stiffness.

Conclusion: The vital role of SGK-1 in tension-induced aortic degenerative remodeling and AAA development has been demonstrated utilizing pharmacotherapeutic blockade and a novel genetic knockout. Altering this mechanosensitive cascade in aortic VSMCs specifically reduced PPV, a clinically relevant indicator of aortic stiffness. Further investigation is indicated to define how targeting SGK-1 in patients with small AAA may represent an opportunity to reduce growth and preserve vascular function.