Valvular Heart Disease

ACTIVATION OF OXIDIZED SOLUBLE GUANYLATE CYCLASE SLOWS PROGRESSION OF AORTIC VALVE STENOSIS

Moderated Poster Contributions
Valvular Heart Disease Moderated Poster Theater, Poster Hall B1
Sunday, March 15, 2015, 3:45 p.m.-3:55 p.m.

Session Title: Novel Observations of Aortic Valve Disease
Abstract Category: 42. Valvular Heart Disease: Therapy
Presentation Number: 1239M-03

Authors: Bin Zhang, Carolyn M. Roos, Female, Grace Verzosa, Heyu Zhang, Male, Maurice Sarano, Jordan D. Miller, Male, Mayo Clinic, Rochester, MN, USA

Background: While nitric oxide (NO) signaling is reduced in valves from patients with aortic valve stenosis (AVS), restoring NO signaling to slow progression of valve calcification is challenging due to oxidation of soluble guanylate cyclase (sGC), the key target of NO. We hypothesized that Ataciguat (ATA), an anthrallic acid derivative that activates oxidized sGC, attenuates osteogenic signaling in valve interstitial cells and slows progression of aortic valve calcification.

Methods: To determine whether Ataciguat attenuates bone morphogenetic protein signaling in vitro, we treated valve interstitial cells with BMP2 (200 ng/ml) or BMP2 + ATA (10 nm) and measured canonical BMP signaling and BMP target gene expression. To determine whether Ataciguat slows progression of AVS in mice, 100 ldlr-/-/apoB100/100 mice were assigned to one of two groups: 1) 9 months of western diet feeding (WD), 2) 9 months of western diet feeding + ATA (5mg/kg ATA). Blood pressure, blood glucose levels, body composition, and aortic valve function (cusp separation distance by echocardiography) were measured following 9 months of treatment.

Results: In vitro, treatment of valve interstitial cells with ATA reduced BMP2-dependent Smad1/5/8 phosphorylation and osteogenic gene induction by more than 50% (p < 0.01). In vivo, ATA-treated mice did not have significant alterations in blood pressure, blood glucose, or body composition compared to mice fed WD. While aortic valve function was not altered in male mice receiving ATA for 9 months (WD = 0.81±0.02mm, ATA = 0.80±0.02mm). In contrast, aortic valve function was significantly improved in female mice receiving ATA compared to the WD group (WD = 0.76±0.02mm, ATA = 0.82±0.02mm; p < 0.05) at the 9 month time point.

Conclusion: In conclusion, our data support a working model in which activation of oxidized sGC is a novel therapeutic strategy to slow progression of aortic valve calcification and stenosis. Importantly, restoration of sGC signaling does not appear to alter the systemic hemodynamic or metabolic milieu, but instead exerts its protective effect through attenuation of local, BMP-dependent osteogenic signaling in aortic valve interstitial cells.

NIH Grant TR000954