2018-2019 Lorne Phenix Graduate Award Recipient

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Sex differences in aortic valvular fibrosis are associated with perturbations in C-type natriuretic peptide signaling

Aortic valve disease is the most common heart valve disease in North America. Recent studies suggest that despite a similar clinical presentation, aortic valve disease develops differently in males and females: male valves harden and calcify like bone, whereas female valves scar in a process referred to as fibrosis. However, the underlying biological processes governing this are unknown. Our lab previously identified C-type natriuretic peptide (CNP) as an anti-fibrotic protein found in male aortic valves. Here, we tested the hypothesis that the predominance of aortic valve fibrosis in women is associated with deficiencies in the CNP signaling pathway. Diseased human aortic valves were collected from patients undergoing aortic valve replacement surgery and examined chemically. Female valves had more fibrosis compared with male valves, and this was significantly associated with a lower level of CNP and markers of its signaling pathway. We then cultured female and male aortic valve cells, and treated them with CNP to test if male and female cells respond differently to this protective stimulus. In male cells, CNP treatment suppressed the development of fibrosis, but female cells were largely non-responsive to the anti-fibrotic effects of CNP. These observations demonstrate, for the first time, a relationship between fibrosis and decreased CNP signaling in human aortic valve disease and suggest that the suppression of CNP in females makes them susceptible to fibrosis.