

ROLE OF HEMODYNAMIC SHEAR STRESS ABNORMALITIES IN CALCIFIC AORTIC VALVE DISEASE

Abstract

by

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The aortic valve (AV) ensures unidirectional flow between the left ventricle and the aorta. As compared to the normal tricuspid aortic valve (TAV) anatomy, which consists of three leaflets, the bicuspid aortic valve (BAV) is characterized by the presence of two leaflets, and is the most prevalent congenital cardiac anomaly. Regardless of the valve morphology, a common cause of valvular failure is calcific aortic valve disease (CAVD), a condition characterized by increased thickness and stiffness on the valve leaflets. Historically, CAVD has been considered a passive degenerative disease but is now recognized as an active pathology involving inflammation, remodeling and ossification and presumably triggered by atherogenic risk factors and hemodynamic cues. While TAV and BAV calcification seem to share common biological pathways, the calcification of the BAV is more rapid and severe than the TAV. The overall goal of this work is to characterize the role of FSS abnormalities on early progression of CAVD in both TAVs and BAVs. Specifically, this thesis will address the following research questions: 1) What are the mechanisms by which FSS alterations are transduced into valvular pathological responses? 2) Are there any potential target molecules for the pharmacological treatment of CAVD? and 3) What are the reasons for the early development and severity of BAV calcification? These questions will be addressed via three specific aims. 1) To elucidate the mechanisms of CAVD secondary to FSS magnitude & frequency abnormalities; 2) To investigate the role of BMP-4 and TGF- β 1 in FSS-induced valvular endothelial activation and ECM remodeling; and 3) To elucidate the

mechanisms of CAVD secondary to BAV hemodynamic abnormalities. The approach integrated the implementations of a novel *ex vivo* device to condition porcine AV leaflets under physiological and pathologically FSS environments, standard biological techniques to assess valvular biological response and pharmacological inhibition/promotion to elucidate the mechanisms of FSS signal transduction. The results reveal the contribution of FSS to the onset and early progression of CAVD has been demonstrated in this thesis work. The relationship between FSS magnitude/frequency and valvular responses can be used as input for prediction of CAVD progression. In addition, the findings from this dissertation can be used to further investigate the molecular signaling mechanisms in order to develop pharmacological treatments of CAVD.