Bioengineering Approach to Study Biomechanical Drivers of Calcific Aortic Valve Disease

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Calcific aortic valve disease (CAVD) is an inflammatory condition that progressively narrows the aortic valve, hindering cardiac output. Despite its significance, there is no effective treatment beyond surgical or transcatheter valve replacement to prevent or reverse valvular calcification.

As CAVD progresses, the biomechanics of the aortic valve are altered due to stiffening and calcification of the valve leaflets, leading to reduced valve movement and increased blood velocity, which ultimately results in left ventricular hypertrophy and heart failure.

Mechanotransduction—the process by which mechanical stress is converted into biochemical signals—may serve as the link through which altered valve biomechanics lead to chronic valvular inflammation in CAVD.

To investigate the impact of changes in valve biomechanics as it calcifies and undergoes ECM remodelling, my lab has pioneered bioengineered models to systematically study the effects of ECM remodelling, changes in blood velocity, and tensile force on endothelial and inflammatory cells. Furthermore, these models, combined with blood samples and valve tissues surgically removed from patients with CAVD, enable us to gain a better understanding of the molecular drivers of CAVD.

Our findings show that high shear stress[1,2] or stretch[3] activates inflammatory cells, increases the expression of inflammatory markers, and affects their metabolic activity, differentiation, and ability to form foam cells once recruited to the calcified valve environment. Additionally, we have found that reduced stretch forces on the valve and glycation of the extracellular matrix induce the endothelial-to-mesenchymal transition of valvular endothelial cells.

Our research highlights the critical role of altered biomechanics in driving chronic inflammation and disease progression in CAVD. These findings pave the way for the identification of novel therapeutic targets aimed at mitigating inflammation and preventing disease progression.

References:

[1.] S. Baratchi, M.T.K. Zaldivia, M. Wallert, J. Loseff-Silver, S. Al-Aryahi, J. Zamani, P. Thurgood, A. Salim, N. M. Htun, D. Stub, P. Vahidi, S. J. Duffy, A. Walton, T. H. Nguyen, A. Jaworowski, K. Khoshmanesh, K. Peter, Transcatheter aortic valve implantation represents an anti-inflammatory therapy via reduction of shear stress–induced, piezo-1–mediated monocyte activation, 142, 11 (2020)

[2.] S. Baratchi, H. Danish, C. Chheang, Y. Zhou, A. Huang, A. Lai, M. Khanmohammadi, K. M Quinn, K. Khoshmanesh, K. Peter, Piezo1 expression in neutrophils regulates shear-induced NETosis, *Nature Communications*, 15, 7023 (2024)

[3.] M. Khanmohammadi, H. Danish, N. Chandra Sekar, S. Aguilera Suarez, C. Chheang, K. Peter, K. Khoshmanesh, S. Baratchi, Cyclic stretch enhances neutrophil extracellular trap formation, *BMC Biology,* V22, 209, (2024)