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The Journal of the Heart Team
Volume 5, 2021 - Issue sup1: HVS 2021 Abstracts Supplement

On Demand

Late-stage Calcific Aortic Valve Disease Within an Aortic Valve-on-a-chip Model

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Pages 69-70 | Published online: 09 Apr 2021

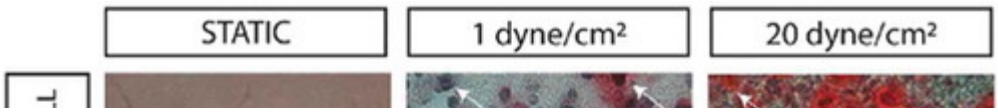
Download citation https://doi.org/10.1080/24748706.2021.1900702 Check for updates

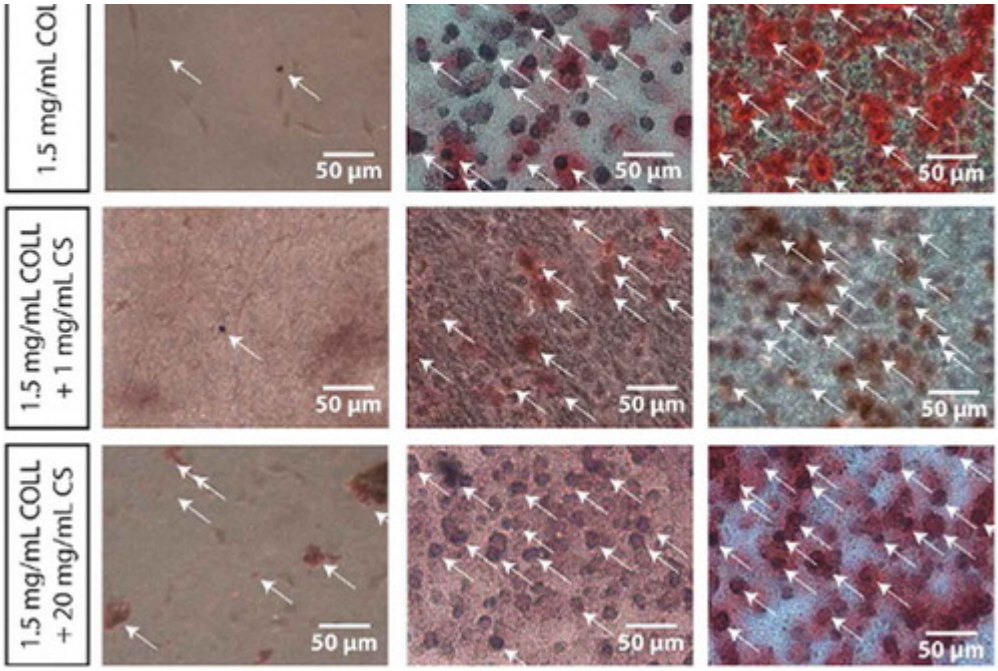
Abstract

Objective: Calcific aortic valve disease (CAVD) is a progressive disease ranging from aortic sclerosis to severe aortic stenosis. Current treatments include total valve replacement and drug interventions tailored to other cardiovascular diseases. In late-stage CAVD, glycosaminoglycans (GAGs), such as chondroitin sulfate (CS), deposit in the fibrosa layer. Here we utilize 3D microfluidic devices to study the effects of shear stress, CS, and endothelial cells on calcification in an aortic valve fibrosa model to understand CAVD progression.

Methods: Valve-on-a-chip devices were fabricated utilizing a wafer mold, soft lithography, and corona discharge. Devices have a flow channel and 3D matrix reservoir of collagen-only healthy controls or with 1mg/mL or 20mg/mL CS. Porcine aortic valve interstitial cells (PAVIC) are embedded within and endothelial cells (PAVEC) seeded onto the matrix. Steady shear stress at 1dyne/cm^2 and 20dyne/cm^2 was applied using a peristaltic pump at 37°C and 5%CO_2. Alizarin Red S (ARS) was used to assess calcific nodule formation after 14-day cultures.

Results: PAVIC/PAVEC co-cultures with increasing shear stress and GAGs exhibit increased calcification compared to static controls (Figure 1). Quantitatively, ARS increased as shear stress increased, regardless of GAGs. In the presence of CS, analysis of nodules indicated that nodule size decreased with shear stress, however it increased the total average percent area stained. Valve-on-a-chip models with PAVIC-only show decreased calcium deposition when compared to co-cultures.





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Conclusions: *In vitro* calcification increases in the presence of shear stress, PAVEC, and increased concentrations of GAGs. Further studies will identify the chemical composition of nodules and to understand early-CAVD pathophysiology. Given that CAVD has no targeted therapies, the creation of a physiologically-relevant test-bed of the aortic valve will lead to contributions in new therapeutics.

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Disclosure Statement

The authors do not declare any conflict of interest.

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Published online: 9 Apr 2021