A HOMOGENIZED CONSTRAINED MIXTURE MODEL FOR HEART VALVE GROWTH AND REMODELING

Elmer Middendorp (1,2), Fabian Bräu (3,4), Frank P.T. Baaijens (1,2), Jay D. Humphrey (5), Christian J. Cyron (6,7), Sandra Loerakker (1,2)

1.Department of Biomedical Engineering, Eindhoven University of Technology, The Netherlands; 2. Institute of Complex Molecular Systems, Eindhoven University of Technology, The Netherlands; 3. Singapore Eye Research Institute, Singapore National Eye Center, Singapore; 4. Singapore-MIT Alliance for Research and Technology, Singapore; 5. Department of Biomedical Engineering, Yale University USA; 6. Institute for Continuum and Material Mechanics, Hamburg University of Technology, Germany; 7. Institute for Material Systems Modeling, Helmholtz-Zentrum, Germany;

Introduction

In situ heart valve tissue engineering (HVTE)may provide superior valve replacements compared to the currently available valve protheses [1]. For in situ HVTE to be successful, a better understanding of the growth and remodeling (G&R) mechanisms is essential. G&R in engineered tissues is hypothesized to have similar mechano-regulated mechanisms as native G&R [2] Due to limited experimental data on in situ tissue engineered valves, we have investigated native G&R in this study using computational models. Specifically, we investigated if heart valve mechano-mediated G&R alone can explain the adaptation of pulmonary autografts after the Ross procedure. Since there is still uncertainty on the specific mechanisms of mechanically-regulated G&R, the potential consequences of both stress- and stretch-based mechanical homeostasis were evaluated.

Methods

To model heart valve G&R, a homogenized constrained mixture model [3] consisting of elastin, glycosaminoglycans (GAGs) and collagen was developed. In this model, turnover and production of collagen and GAGs were mediated by the stresses or strains experienced by these constituents. Changes in constituent mass due to deviations in either stress or strain could then result in changes in tissue composition, stiffness and/or volume. To simulate G&R after the Ross-procedure, the homeostatic collagen and GAG stretches (or stresses) were first determined by applying the diastolic pulmonary pressure to the outflow surface. Subsequently, this pressure was increased to its systemic diastolic level after which G&R was simulated until homeostasis was achieved.

Results

Both stretch- and stress homeostasis led to an increase in tissue mass and a change in morphology in our model (Fig 1a and b). This change is mainly characterized by a dilation of the leaflets, which was more extreme for stretch-homeostasis (Fig 1c and 1e). Despite this dilation, the average leaflet thickness increased by 27 and 43% in stretch- and stress-homeostasis, respectively. Upon achieving stress-homeostasis, the leaflets contained more collagen and less GAGs compared to achieving stretch-homeostasis (Fig 2d).

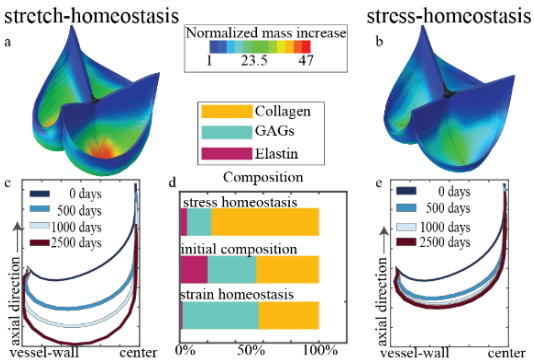

Figure 1: Valve morphology after G&R assuming stretch-(a) or stress-(b) homeostasis. Evolution of the midsection of a leaflet during stretch- (c) or stress-(e) homeostasis and homeostatic tissue composition (d).

Discussion

Leaflet thickening agreed well with the literature [4,5,6] for both stress- and strain homeostasis, and stress-homeostasis resulted in an increased collagen content as also observed in explants [4,5,6]. Altogether, this shows that mechano-mediated G&R is able to describe the adaptation of pulmonary autografts due to changes in hemodynamic loading.

References

1. Uiterwijk et al, PLoS One,16: e0258046,2021
2. Szafron et al, Ann Biomed Eng 46:1938-1950,2018.
3. Cyron et al, Biomech Model Mechanobiol 14:1389-1403,2016
4. Schoof et al, J. Thorac. Cardiovasc. Surg. 132:1426-1432,2006
5. Mookhoek et al, J. Thorac. Cardiovasc. Surg. 139:1416-1419,2010
6. Yacoub et al, Eur J Cardiothorac Surg, 57:977-985,2020

Acknowledgements

This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (Grant agreement No. [802967]).