MYOCARDIAL TRABECULAE IN ZEBRAFISH EMBRYOS IMPROVE TISSUE DEFORMABILITY AND REDUCE STRESSES

Adriana Gaia Cairelli[1], **Alex Gendernalik[2]**, **Julien Vermot[1,3]**, **Juhyun Lee[4]**, **David Bark Jr.[2]**, **Choon Hwai Yap[1]**

1.Dept of Bioengineering, Imperial College London, London, United Kingdom; 2.Department of Pediatrics, Washington University in St. Louis, St. Louis, United States of America; 3.Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC), Strasbourg, France; 4.Department of Bioengineering, University of Texas at Arlington, Arlington, United States of America

Introduction

During the development of the ventricle, the myocardium differentiates into two layers, a compact zone and a trabeculated zone. Cardiac trabeculae are uneven ventricular muscular structures important for proper cardiac function, as malformations in these structures can lead to embryonic death. Trabecular formation, which occurs only on the outer curvature of the ventricle, is a mechanosensitive process, but the biomechanics involved in it is not completely understood. Further, it remains unclear whether these structures confer biomechanical advantages to the heart's function, and how they might achieve this.

Methods

High-resolution, 4D imaging of zebrafish embryonic hearts at 2, 3, 4 and 5 days post fertilization (dpf) was performed with light-sheet microscopy using the *Tg(cmlc2:GFP)* line that expresses fluorescence in the myocardium. Motion tracking was performed with our validated algorithm [1], followed by image-based finite element (FE) simulations of tissue mechanics of zebrafish embryonic ventricles.

Results

At 3, 4, and 5 dpf, the trabeculated outer curvature (OC) region has higher contractile deformations compared to the non-trabeculated inner curvature (IC) (Fig 1A). This is likely due to trabeculations being standalone structures with reduced amount of surrounding tissue to constrain their deformations. However, before trabeculation occurs (2dpf) the opposite was true, suggesting that trabeculation has the function of conferring greater tissue deformability to the OC myocardium. We also discovered that between 2 and 3dpf, there is an increase in the curviness of the OC coupled with a reduction in thickness, which lead to higher tissue stresses. Comparing FE of normal trabeculated ventricles to FE of their artificially smoothed-out, non-trabeculated version (Fig 1B-C), trabeculations are found to be effective at reducing OC myocardial stresses, while retaining the same stroke volume and cardiac work. This is achieved by trabeculations providing bridging and bracing support at regions of high curviness and high stress. Results thus suggest that trabeculation also has the function of reducing overall stresses at the OC myocardium. The timing of trabeculation development also coincided with the time point when OC myocardium stresses increased due to geometric changes to the ventricle, corroborating this notion.

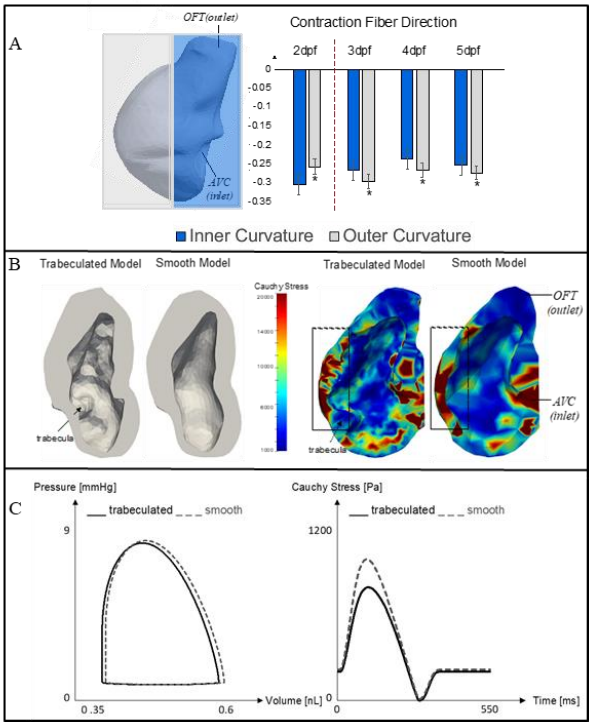

*Figure 1: (A) Left, 3D reconstruction of zebrafish ventricle; right, contractile strain in the fiber direction (n=6, * p<0.05). Red dashed line separates pre and post trabeculae. (B) Left, cross-section of the trabeculated ventricle and its artificially smoothed and non-trabeculated version; right, Cauchy stress magnitude in cross-section. The dashed rectangle focuses on the OC. (C) Left, pressure-volume relation for the two models; right, spatially-averaged Cauchy stress magnitude for the same models.*

Discussion

Here, we discovered that embryonic ventricular trabeculations have two biomechanically beneficial roles: first of all, they improve myocardial deformability to aid contraction motions, and secondly, they reduce stresses in the OC myocardium. This specifically occurs at the developmental time point where stresses elevate due to ventricular curviness and thickness changes. As such, we speculate that trabeculation formation is mechanobiologically cued by high myocardial stresses at the OC. Future work to verify this is warranted.

References

1. Wiputra et al,*Scientific Reports*, 10(1):1-4,2020