Characterizing Embryonic Cardiac Hemodynamic Conditions and their Effect on Heart Formation

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ABSTRACT

Introduction: Cardiac development is a complex interplay of both genetic and environmental factors. Hemodynamics regulates cardiac morphogenesis by providing mechanical stimuli to which cardiac cells respond. Altered hemodynamics can lead to congenital heart diseases (CHD) by exposing cardiac walls to atypical fluid stresses, which affect cell proliferation, migration and transformation via mechanotransduction mechanisms. While altered blood flow induced by surgical interventions in developing animal models has been shown to cause a variety of cardiac developmental defects, the exact mechanisms by which altered hemodynamics leads to CHD are still unclear.

Methods: Our objective is to unravel how altered hemodynamic conditions affect cardiogenesis by using subject-specific 4D (3D + time) computational fluid dynamics (CFD) models as well as experimental biology techniques. Chicken embryos were used as animal models for investigating the effect of altered hemodynamics on cardiogenesis. Cardiac outflow tract (OFT) banding was performed at developmental stage HH18 to alter blood flow conditions. Structural images and flow velocities from the OFT were acquired using a custom-made Optical Coherence Tomography (OCT) system. The OFT region was chosen for investigation as it is the precursor of various cardiac structures such as semilunar valves and the interventricular septum. Subject-specific 4D geometries were reconstructed from OCT images using an in-house image segmentation algorithm. An inverse-method based optimization procedure was developed to replicate the subject-specific hemodynamic conditions within the OFT, measured by Doppler OCT. Representative computational models for a normal and a banded embryo were developed, and blood flow over the cardiac cycle was simulated.

Results: 4D geometries of normal and banded embryo OFTs were successfully reconstructed and segmented for performing CFD modeling. Results from the normal and banded embryo models were validated against independent blood flow velocities and blood pressure measurements. Blood flow velocities and wall shear rates in the OFT increased by > 30% for banded embryos compared to normal embryos. Moreover, the spatial distribution of the wall shear rates were non-uniform for both normal and banded embryos, indicating differential exposure of endothelial cells lining the OFT to hemodynamic stimuli.

Conclusion: CFD results show that OFT banding leads to increase flow velocities and heterogeneously distributed wall shear rates. Additionally, immunohistochemical analysis performed by our research group revealed an increased migration of cells from the endothelium into the OFT cushions in the banded samples. In addition, our results show different degrees of cardiac tissue remodelling following banding. Taken together, these results show that an abnormal hemodynamic environment in the developing heart causes early cardiac tissue adaptations and remodelling, which then lead to CHD. The models developed by our research group are currently being used to characterize early cardiac blood flow and to further develop predictive models of how altered hemodynamic conditions affect cardiogenesis.