DYNAMIC VIEWS OF STRUCTURE AND FUNCTION DURING HEART MORPHOGENESIS

Thesis by

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The front office: Mory Gharib (*Donald Sterling*), Scott Fraser (*John Wooden*), Mary Dickinson (*Shaquille O'Neal*), Jay Hove (*Antoine Walker*), and Michael Dickinson (*Rick Fox*).

The starting lineup: Michael Liebling (*Steve Nash*), Julien Vermot (*Manu Ginobili*), John Dabiri (*LeBron James*), Reinhard Koster (*Scottie Pippen*), and Aaron Hawkey (*Tim Duncan*).

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Dedication

My Dad.

Abstract

Congenital heart defects remain the most common birth defect in humans, occurring in over 1% of live births. The high prevalence of cardiac malformations can be partially attributed to limited knowledge regarding the embryonic roots of the disease. A variety of congenital heart defects are thought to arise from combinations of genetic and epigenetic factors. In an effort to better understand this dynamic relationship, our study explores the structure and function of the developing heart and valves and examines hemodynamic factors influencing valvulogenesis. In order to study cardiac mechanics, we employed novel high-speed confocal microscopy and four-dimensional visualization techniques. A dynamic four-dimensional dataset describing heart and valve development along with blood flow patterns throughout cardiac morphogenesis is presented. Utilizing newly developed tools, we propose a novel pumping mechanism in the valveless embryonic heart tube via elastic wave propagation and reflection. We show that this form of pumping leads to oscillatory shear stresses in the developing atrio-ventricular canal, a phenomenon that had not previously been documented. An *in vivo* method to modulate trans-valvular oscillatory flows is described and used to test our hypothesis that oscillatory shear stress across the primitive valve cushions stimulates heart valve leaflet formation. Our results suggest hemodynamic forces contribute to valvulogenesis and enhance our understanding of normal and abnormal heart valve development.

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