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Influence of blood flow on cardiac development

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A R T I C L E I N F O

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A B S T R A C T

The role of hemodynamics in cardiovascular development is not well understood. Indeed, it would be remarkable if it were, given the dauntingly complex array of intricately synchronized genetic, molecular, mechanical, and environmental factors at play. However, with congenital heart defects affecting around 1 in 100 human births, and numerous studies pointing to hemodynamics as a factor in cardiovascular morphogenesis, this is not an area in which we can afford to remain in the dark. This review seeks to present the case for the importance of research into the biomechanics of the developing cardiovascular system. This is accomplished by i) illustrating the basics of some of the highly complex processes involved in heart development, and discussing the known influence of hemodynamics on those processes; ii) demonstrating how altered hemodynamic environments have the potential to bring about morphological anomalies, citing studies in multiple animal models with a variety of perturbation methods; iii) providing examples of widely used technological innovations which allow for accurate measurement of hemodynamic parameters in embryos; iv) detailing the results of studies in avian embryos which point to exciting correlations between various hemodynamic manipulations in early development and phenotypic defect incidence in mature hearts; and finally, v) stressing the relevance of uncovering specific biomechanical pathways involved in cardiovascular formation and remodeling under adverse conditions, to the potential treatment of human patients. The time is ripe to unravel the contributions of hemodynamics to cardiac development, and to recognize their frequently neglected role in the occurrence of heart malformation phenotypes.

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Abbreviations

Cardiac defect phenotypes

VSD	ventricular septal defect
TOF	Tetralogy of Fallot
DORV	double outlet right ventricle
AVV	atrioventricular valve malformation
PAA	pharyngeal arch artery malformation

Techniques to measure and quantify cardiac flow and form

OCT	optical coherence tomography
PIV	particle image velocimetry
UBM	ultrasound biomicroscopy
microCT	micro computed tomography
CFD	computational fluid dynamics

Interventions to alter flow in chicken embryos

OTB	outflow tract (conotruncal) banding
VVL	vitelline vein ligation
LAL	left atrial ligation

Miscellaneous

OFT	outflow tract (conotruncus)
AVC	atrio-ventricular canal
HH	Hamburger-Hamilton stage
EMT	endocardial-to-mesenchymal transition
ECM	extracellular matrix

1. Introduction

Cardiac formation and the dynamics of blood flow, or hemodynamics, are intrinsically linked. The heart's main function is to pump blood to the lungs for oxygenation and to the systemic circulation for oxygen and nutrient exchange. Looking at the heart from this 'mechanical' perspective, cardiac development must end with a fully functional pump. Heart development has to be exquisitely sensitive to the mechanics of pumping and blood circulation to ensure optimal cardiac performance; and to maximize the chances of the embryo surviving under different environments, it has to be adaptable to changes. This is accomplished in part by signaling pathways that sense and respond to mechanical stimuli from blood flow during heart formation and, in so doing, modulate developmental processes.

Extensive research has been directed at understanding the mechanisms that drive the various stages of cardiac development. As a result, a wealth of information is now available on regulatory pathways and processes that act during heart development. Furthermore, the consequences of genetic anomalies and disruptions in normal processes via teratogen exposure are being actively investigated. Efforts have also been directed at understanding both how blood flow dynamics regulates cardiovascular development and how perturbing normal blood flow conditions impacts cardiac formation. Ultimately, the goal of these investigations is to fully comprehend the processes governing cardiac formation and how human babies develop congenital heart defects. Because blood flow is an integral part of heart development, it influences heart formation under normal and anomalous conditions. The effects of blood flow on cardiovascular development therefore cannot be neglected.

The ways in which hemodynamic conditions modulate cardiac development remain unclear. Several pathways and molecular mechanisms affected by hemodynamics are beginning to be examined and understood, but much research is still needed. The inherent complexity of the response of cardiac tissue to blood flow, with its diverse, interconnected and potentially redundant array of mechanosensors and mechanotransducers, can initially be overwhelming. Looking at heart development from a more macroscopic perspective, however, it is certainly possible to observe outcomes and infer general 'rules' (whether biomechanical, biophysical and/or biochemical) by which the heart responds to disruptions. For example, by determining cardiac anomalies after different exposures, it is possible to formulate a general theory about when malformation phenotypes appear and in response to what. In turn, this knowledge can point to developmental pathways of interest and inform future investigations.

Overall, about 1% of newborns have some form of congenital heart disease (Mozaffarian et al., 2015), a malformation of the heart that is present at birth. The most severe cases undergo cardiac surgery as soon as hours after birth. Nowadays, and thanks to many advances, more children with congenital heart disease are surviving into adulthood, but better strategies for treatment and follow up are needed. This can only be achieved by continuing to enhance our understanding of heart formation and the role of different factors on cardiac development and cardiovascular adaptation before and after birth.

In this review, we will first briefly summarize heart development, highlighting the role of hemodynamics. Next, we will discuss the different methods used to perturb blood flow in animal models with the goal of understanding the role of hemodynamics on cardiac formation, and review the common techniques used to measure and quantify cardiac blood flow parameters during embryonic development. Finally, and as an example, we will analyze the immediate and delayed hemodynamic and morphological effects of perturbing blood flow in an avian model during a specific developmental window.

2. Heart development

Cardiac development starts during the early embryonic stages and consists of a complex progression of events that ultimately mold the mature heart (see Fig. 1 and Table 1). In the pre-somite embryo, the splanchnic mesoderm differentiates into a layer of myocardial progenitors with a plexus of elongated endothelial precursors beneath them (DeRuiter et al., 1992). Left and right populations of the differentiated mesoderm migrate and align themselves into bilaterally-paired fields, the cardiogenic cords

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