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Recent advances in quantifying the mechanobiology of cardiac development via computational modeling

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Abstract

Mechanical forces are essential for coordinating cardiac morphogenesis, but much remains to be discovered about the interactions between mechanical forces and the mechanotransduction pathways they activate. Due to the elaborate and fundamentally multi-physics and multi-scale nature of cardiac mechanobiology, a complete understanding requires multiple experimental and analytical techniques. We identify three fundamental tools used in the field to probe these interactions: high resolution imaging, genetic and molecular analysis, and computational modeling. In this review, we focus on computational modeling and present recent studies employing this tool to investigate the mechanobiological pathways involved with cardiac development. These works demonstrate that understanding the detailed spatial and temporal patterns of biomechanical forces is crucial to building a comprehensive understanding of mechanobiology during cardiac development, and that computational modeling is an effective and efficient tool for obtaining such detail. In this context, multidisciplinary studies combining all three tools present the most compelling results.

Keywords

hemodynamics; cardiac development; mechanotransduction; mechanobiology; CFD

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

1 Introduction

The development of the heart and its substructures, including chambers, trabeculae, and valves, is a complex and multifaceted process. While genetics is certainly central to development, it is now understood that biomechanical forces provide essential epigenetic cues for the proper development of cardiac tissues and structure. Moreover, early alterations in the biomechanical environment are involved in the etiology of a host of congenital heart diseases. We conceptualize this interplay among mechanics, cell biology, and cardiac structure and performance as a "mechanobiology feedback loop" (see Figure 1). The mechanobiology loop is inherently multi-scale and involves multiple physical processes; thus no single technique can investigate it in its entirety. Instead, three classes of tools are often used to probe different sections of the loop. Genetic and molecular analyses are essential to understand how cells sense mechanical stimuli and how these stimuli are communicated within and between cells to promote tissue-scale remodeling. Computational modeling has emerged as a powerful tool to quantify biomechanical forcing with high spatial and temporal precision, combining information at multiple scales to potentially yield a complete mechanical description of the heart. Finally, high-resolution *in vivo* imaging is often used in concert with the previous two tools. With genetic and molecular analyses, imaging can identify if and where a particular genetic marker is expressed. With computational modeling, imaging is necessary to obtain tissue-scale properties and organ-scale dynamics, which are often essential inputs to physiological computational models of the heart. Imaging techniques such as 4D flow MRI, Ultrasound Doppler, and particle image velocimetry (PIV) are also used to validate numerical methods for simulating cardiac blood flow [1, 2, 3].

Perturbations to the mechanobiology loop, typically in the context of animal experiments, reveal important details obscured in normal development. Zebrafish and chicken embryos are popular animal models; zebrafish for their optical transparency and easy genetic manipulation, and chicken for their accessibility to imaging and surgery, and their four-chamber heart morphology. Mechanical interventions, such as left atrial ligation (LAL), in which the developing left atrium is tied to disrupt left heart blood flow [4], alter the biomechanical environment. Right atrial ligration (RAL) [5] and conotruncal banding (CTB) [6] are also common procedures to modulate blood flow. Genetic or pharmacological treatments, such as *NICD* mRNA injection, which upregulates the Notch signaling pathway [7], alter cell signaling or function. In particular, CRISPR-Cas9 gene-editing technology is emerging as a powerful method to replicate human cardiovascular diseases in animal models [8]. These perturbations are used to help identify which mechanical stimuli and which genetic pathways are responsible for particular aspects of cardiac (mal)development.

In this review, we present recent works that use computational modeling to investigate mechanobiology in cardiac morphogenesis. The power of computational modeling lies in its ability to reproduce physiological behavior and quantify mechanical forces with a high degree of precision (see e.g. [9]). In cardiac mechanics, simulations are performed by solving the governing equations of fluid and/or structural mechanics, and may also account for active contraction, growth and remodeling (G&R) [10], and other physical

processes. The methods described in this review come with varying degrees of accuracy and complexity: 2D vs. 3D simulations, fixed domain vs. moving-boundary, idealized vs. image-based geometries. Of course, with increased accuracy comes increased computational cost. Quantities of interest may be extracted from such simulations. For example, from computational fluid dynamics (CFD) analysis, a key quantity is wall shear stress (WSS), defined as the tangential force exerted by blood on the tissue. Decades of research have established the critical role of WSS in mechanobiology. While there exist experimental methods of flow characterization, such as particle image velocimetry (PIV) and 4D MRI, the resulting velocity fields typically have limited spatial resolution, hampering the accuracy of estimates of WSS [11]. Moreover, in small animal models, these experimental techniques are often difficult or impractical to apply.

While this review concerns computational studies, we place particular emphasis on studies that combine computation with biochemical analysis and *in vivo* imaging. In our opinion, the relatively few studies that take this multidisciplinary approach are the most comprehensive and enlightening. We note that this review is concerned in part with the *causes* of congenital heart defects. The use of computational tools to study the phenomenology and treatment of such defects is well established [12, 13, 14, 15].

The remainder of the paper is organized as follows. Topics are organized according to components of the heart. Section 2 focuses on recent studies related to cardiac morphology (chambers and outflow tract shape), while Section 3 discusses research on trabecular development. Section 4 presents studies on valve development. Finally, in Section 5, we summarize our review and discuss future directions and challenges in the field.

2 Cardiac chambers and outflow tract morphology

The heart begins development as a linear tube. The heart tube bends in the looping stage, and subsequently the two parts expand to form the developing atrium and ventricle. The foundation of the progression into a functional heart is the change in cellular morphology. Typically, cells in the inner curvature remain cube-shaped, while cells in the outer curvature are elongated and flattened [16]. It is hypothesized that mechanical flow forces guide this process, but little is known about the changes in tissue composition caused by abnormal hemodynamics. A recent study showed that cell remodeling can lead to spontaneous looping in a buckling-like process [17].

Salman *et al.* (2021) [4] investigated disturbed hemodynamics and deteriorated cardiac growth following a left atrial ligation (LAL) procedure on chicken embryos with the goal of exploring possible mechanobiological mechanisms for the development of hypoplastic left heart syndrome (HLHS). Combining techniques including echocardiography, histology, micro-CT scan and CFD, they observed that LAL caused flow redirection to the right side of the heart, increasing WSS on the R-AV canal, decreasing on L-AV canal and altering normal shear stress balance. They also found a correlation between the reduced size of superior (or ventral) AV cushions of LAL hearts and lowered WSS level on the superior side. Similar results have been showed in [18] on human HLHS fetal hearts at later stage in the gestational phase.

Wiputra *et al.* (2018) [19] applied ultrasound-based moving-boundary CFD methods developed previously to compare the fluid dynamics of normal human fetal hearts and fetal hearts with Tetralogy of Fallot (ToF). They found that compared to normal hearts, ToF hearts experience higher ventricular pressure, as well as greater WSS in the RV and at the wall of the ventricular septal defect. This study was one of the first to analyze the blood flow in fetal ToF hearts in detail, laying the groundwork for future studies to elucidate the mechanotransduction mechanisms at play in congenital heart diseases. Building on their prior work, Wiputra *et al.* (2021) [20] then analyzed fetal LV hemodynamics from approximately 7 weeks to 20 weeks of gestational age. Using moving-boundary CFD simulations, they identified a cut-off point in the Reynolds number (*Re*) of LV flow, which they hypothesize to be relevant to proper fetal heart growth due to a positive feedback relationship between WSS and growth above the cut-off.

Examining the outflow tract, Lindsey *et al.* (2019) [21] investigated the role of hemodynamics on development of the pharyngeal arch arteries (PAAs) during development of the chicken embryo. In a subsequent work [22], the same authors investigated the correlation between primitive PAAs morphogenesis and hemodynamics. They combined varying degrees of occlusion experiments, which they performed on the 4th right arch artery of chicken embryos, with 3D CFD on anatomical geometries. They observed that abnormal hemodynamic flow patterns led to adaptive morphogenetic responses. Additionally, they discovered that WSS drives defect propagation, which can result in enlarged OFT diameters, irregular regression patterns, and abnormal rotation of the OFT.

In a complementary study, Ho *et al.* (2019) [23] investigated OFT flow using image-based moving-boundary CFD, coupled with Doppler measurements to determine the inlet velocities for chicken embryos. While previous studies focused on earlier embryonic stage, noninvasive 4D high-frequency ultrasound with B-mode gain used here enabled the acquisition of images employed in hemodynamics simulations at later developmental stages. They suggest the possibility that elevated oscillatory flow near the cushions and helical flow structures guide valvulogenesis and septation in the OFT.

3 Cardiac trabeculation

Trabeculae are protrusions of the myocardium into the luminal space, most prominently in the ventricles. They begin as ridges and grooves on the endocardial surface and eventually develop into a sponge-like morphology. Later, during the compaction phase, the trabeculae fuse together to form a smoother, but still corrugated, endocardial surface in normal adult hearts [24, 25]. In the embryonic stage, trabeculae are thought to enhance nutrient and oxygen transport to the myocardium before the development of the coronary vasculature. Trabeculae also play a role in the heart's conduction system [24] and mechanical performance [26, 27]. While genetic factors certainly play a role, numerous experiments have demonstrated a critical role for mechanical forcing in trabecular development (see e.g. [28]). Several signaling pathways are implicated in the regulation of cardiac trabeculation, including Notch, Neuregulin, Hippo, Ephrin, Semaphorins, and Extracellular Matrix components (ECM) [24, 29]. The studies reviewed below have used

computational modeling to investigate the specific mechanobiologic pathways regulating trabecular development.

Building from earlier works establishing CFD as a quantitative tool to study mechanotransduction [30] and applying 4D light-sheet imaging to study Zebrafish cardiac development [11, 28] Lee *et al.* (2018) [31] investigated the relationship between WSS and trabeculae in developing zebrafish. They found that high oscillatory shear index (OSI) in trabecular grooves was spatially correlated with high Notch activation. In a separate *in vitro* flow experiment, they also demonstrated that oscillatory shear stress, more so than steady or pulsatile shear stress, activates Notch signaling. Together, these findings build a picture in which *spatiotemporal variations* in hemodynamics, particularly wall shear stress, coordinate cardiac trabeculation via the Notch signaling pathway, and likely via other mechanotransduction pathways.

Battista *et al.* (2018/2019) [32, 33] described biologically-relevant vortices that underlie the spatiotemporal variations in wall shear stress examined previously. Simulating blood flow in fixed-boundary 2D image-derived and idealized trabeculated zebrafish ventricles, they found that chamber-scale vortices emerge in pulsatile flow, while intertrabecular vortices are generated in both pulsatile and steady flow. By varying shape parameters of their idealized trabeculated ventricle and the Reynolds number of their simulations, they also demonstrated that flow patterns and hemodynamic forces are highly sensitive to morphology as well as blood rheology. Their findings underscore the need for precise imaging and model building techniques and rheological measurements, and imply that flow and thus hemodynamic-mediated mechanotransduction likely vary significantly during development, between individuals, and across species.

Using 3D moving-boundary CFD, Cairelli *et al.* (2022) [34] further investigated the fluid dynamics associated with trabeculae in embryonic zebrafish hearts. They described an intertrabecular “squeezing flow“ induced by contraction of intertrabecular spaces (grooves) and showed that this squeezing flow, rather than the main chamber flow, is the primary driver of WSS in trabecular grooves. This finding implies that the intertrabecular vortices described by Battista *et al.* [32] may not be relevant when considering trabeculae motion, although this requires further investigation. They also described cells attached to the endocardium residing in trabecular grooves, hypothesizing that these are embryonic hemogenic cells. They showed that the presence of these cells significantly affects the WSS in grooves. Additionally, we note that they used a fish line that fluoresces at the endocardial cell membrane and reported higher WSS values than previous studies, which used myocardial markers. Overall, their study highlights the complexity of fluid flow associated with cardiac trabeculae.

4 Heart valves

Heart valve malformations are a very common form of congenital heart defects, yet their etiology remains unclear. Genetics alone explains only a minority of cases and mechanical forces are well known to regulate heart valve formation. Vermot *et al.* (2009) [35] focused on the role of oscillatory flows during valvulogenesis and showed how relatively

modest perturbations of normal hemodynamics can lead to both valve dysgenesis and gene alterations. Bassen *et al.* (2021) [36] investigated the effect of compressive and tensile stresses, discovering that compression drives cushion growth, while tension induces shape maturation. Additionally, deformation and cyclic tension have a notable impact on heart valve function and tissue adaptive remodeling. We refer to [37] for a review on recent discoveries of mechanosensitive mechanisms and [38] for a study on the effect of pressure compared to shear on valve development. Regarding the mechanosensitive pathways linked to valve formation, the most studied are, for instance, Nfatc, Notch and TGF-β/BMP. Recently, [39] placed Piezo mechanosensitive ion channels as central modulators of OFT valve morphogenesis in zebrafish.

Fukui *et al.* (2021) [40] investigated cell differentiation in response to mechanical forces in valvulogenesis using zebrafish embryos. Identifying two mechanosensitive pathways linked to valve formation (transient receptor potential (TRP)-mediated *klf2a* activation and adenosine triphosphate (ATP)-mediated Ca^{2+}), they demonstrated that mechanical forces are converted into bioelectric signals (Nfatc1) to generate positional information and control over valve formation. Strikingly, they observed ectopic valve-like cluster formation near a magnetic bead inserted in the cardiac lumen, asserting that shear stress, quantified using image-based 3D CFD analysis, is necessary and sufficient to promote valvulogenesis.

Boselli *et al.* (2017) [41] analyzed the spatial patterns of wall shear stress in the zebrafish embryonic heart tube using 2D moving-boundary CFD. Integrating *in vivo* experiments, they showed that endocardial cells migrate opposite the direction of the time-averaged WSS, and toward regions of higher amplitude oscillatory shear stress.

Hsu *et al.* (2019) [7] combined a 4D light-sheet imaging technique with moving-domain 2D CFD, to assess changes in Notch-mediated OFT valve development of transgenic zebrafish models. They sought to evaluate the separate impacts of contractility and wall shear stress on the ventriculobulbar valve development, using different treatments (e.g. Isoproterenol, Metoprolol, BDM and *Gata1a* MO). Based on their results, they propose that contractility is mainly responsible for initial valve formation, while WSS promotes leaflet growth at later embryonic stages.

Salman *et al.* (2021) [42] performed 2D left heart hemodynamic simulations at different gestational stages for healthy fetal hearts in human geometries derived from ultrasound images. They focused mainly on the mitral valve regions of the left side of the heart, and they observed an unbalanced distribution of WSS on the two sides of the mitral valve. Together with a reduction in vorticity and average WSS, the mitral valve is subjected to a more regular WSS distribution throughout the development. In accordance with previous studies [19, 43], they suggested that high levels of WSS and vorticity influence the growth of the left heart and the development of the leaflets, until they reach a stable WSS level at late gestational stages.

5 Conclusions and future directions

We have reviewed recent works in the field that use computational modeling to investigate mechanobiologic pathways in cardiac development, often in concert with genetic and molecular analysis and *in vivo* imaging. These studies have revealed that the complex spatial and temporal patterns of mechanical forces found in the developing heart are important drivers in cardiac mechanobiology.We show in Figure 2 a summary of the widely investigated biomechanical pathways and forces sensed by cells, organized by cardiac substructure. We do not claim the list to be exhaustive, but we simply illustrate the relationships that, at the moment, are generally accepted. To end, we discuss recent advances and future directions relevant to this field.

Many computational methods obtain the geometries and motions of the relevant cardiac structures from image data. This can be a time-consuming and imprecise process, depending on the quality of the image and the segmentation technique. Accurate geometries are essential for accurate results. In light of these challenges, we expect recent advances in imaging and segmentation technology to benefit the field (see e.g. [45, 46, 47, 48, 49]).

So far, most of the studies reviewed have focused on the mechanotransduction associated with blood flow, using CFD to quantify WSS and related quantities derived from the velocity field. However, stress and stretch in the heart wall are also important epigenetic cues for myocardial development. *In vitro* experiments have demonstrated that electromechanical stimulation of cardiomyocytes is critical to cell maturation, and that the frequency of stimulation influences the maturation process [50]. How myocytes sense mechanical stretch is not yet fully understood, but Piezo mechanosensitive ion channels have received special attention lately [39, 51, 52, 53]. Some studies have already applied computational tools to elucidate the mechanobiological processes in cardiac tissues [54, 55, 56, 57], but many open questions remain.

Finally, we believe those multidisciplinary studies combining computation and experiments present the most compelling results and build the most detailed and comprehensive picture of the mechanobiology loop for a given cardiac substructure. Thus, we encourage more collaborations between experimentalists and computational modelers in the field.

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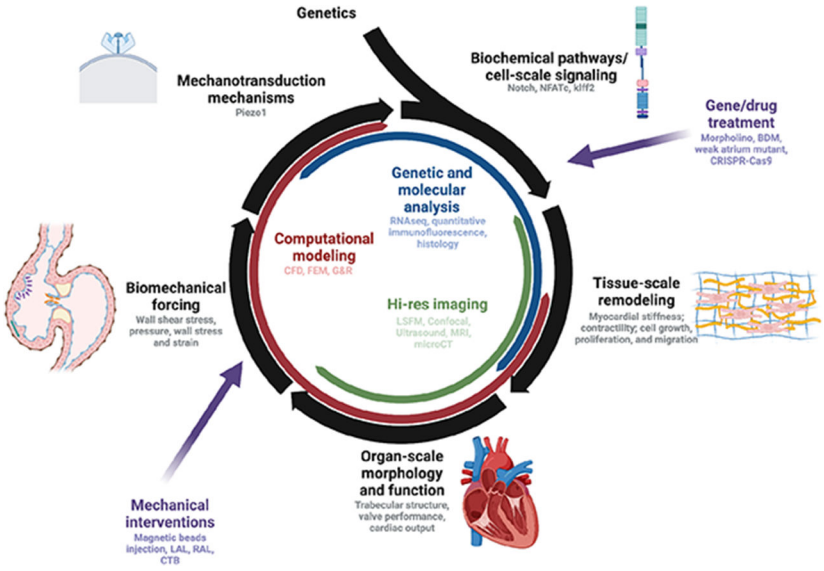

Fig 1.

Mechanobiology conceptualized as a feedback loop. Cells sense biomechanical stimuli through mechanotransducers and respond by engaging specific biochemical pathways and cell-scale signaling. This leads to tissue remodeling, which modulates cardiac function and morphology, which in turn determine the biomechanical environment, completing the loop. Mechanical interventions and genetic/pharmacological treatments are used to perturb the loop. Three tools (computational modeling, genetic and molecular analysis, and high-resolution imaging) are used to investigate different sections of the loop. This review focuses on computational modeling. Created with BioRender.com.

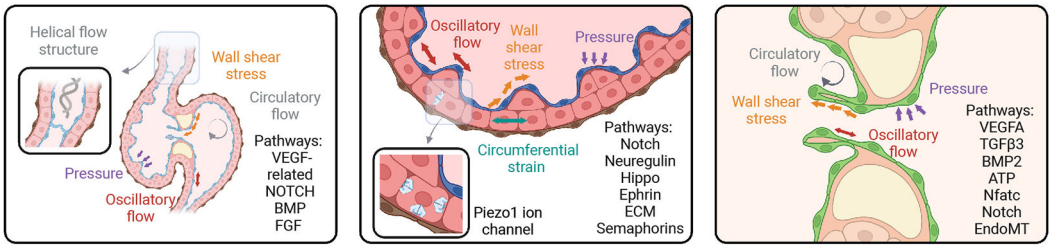

Fig 2.

Summary of the main investigated biomechanical forces, genetic pathways and mechanotransduction mechanisms involved in cardiac morphogenesis in animal and human models, separated by area [24, 44]. Zebrafish heart geometry shown as an example with cardiac chambers and OFT (left), trabeculation (center), and heart valves (right). Created with BioRender.com