Lifelines of life

Summary

The cardiovascular system, responsible for distributing oxygen throughout the body to meet metabolic demands among its functions, plays a vital role in sustaining overall health and well-being. It is rightfully acknowledged as the *Lifeline of life*. The tightly interconnected components of this system create a complex and multifaceted system, in which any unaddressed disruption can result in cardiovascular disease. Computational models are invaluable in enhancing our understanding of this disease from a mechanistic standpoint. These models are particularly useful in situations where data is limited, such as in the fetal circulation (Part I), or where traditional methods are inadequate, as in the assessment of coronary microvascular function in the adult heart (Part II).

Part I: Lifeline of perinatal life

Birth is characterized by swift and complex transitions in hemodynamic and respiratory variables. Some of the necessary adjustments for the smooth fetal-to-neonatal transition include, but are not limited to, the initiation of continuous breathing, switch from placental to pulmonary gas exchange, and a major re-organization of the circulatory system. Most of our knowledge of the fetal circulation and its transition at birth is based on animal studies, due to the relative inaccessibility of the fetus and the high invasiveness of certain measurements. In this part of the thesis, we focus on developing a computational model to elucidate the hemodynamics of the complex fetal circulation and fetal-to-neonatal transition under physiological and pathological conditions, with the ultimate goal of improving perinatal care.

In **Chapter 2**, we developed a model of the term fetal cardiovascular circulation to simulate cardiovascular mechanics and hemodynamics of the healthy term fetus and its transition to neonate. We implemented three fetal shunts (ductus arteriosus, ductus venosus, foramen ovale), as well as the placental bed and other systemic elements to accurately represent the term fetal cardiovascular circulation. The transition model was controlled by a time- and event-based script of changes occurring at birth, such as lung aeration, pulmonary venous oxygenation, umbilical cord clamping and the transitory phase up to 24 hours after birth. Extensive validation of the model with human and animal data demonstrated that the model could provide realistic simulations of fetal and 24-hours old neonatal physiology in terms of pressure, flow (velocity), and oxygen saturation levels.

In **Chapter 3**, we assessed changes in hemodynamics and oxygen saturation levels caused by (supra)cardiac total anomalous pulmonary venous return (TAPVR), a

congenital heart defect in which the pulmonary veins are connected to the right atrium instead of the left atrium. We specifically focused on reversed differential cyanosis (RDC), a phenomenon in which the oxygen saturation levels in the right arm are lower than in the foot. Our model findings suggested that the often-present pulmonary over-circulation in neonates with TAPVR could significantly contribute to the anomaly's frequent omission during pulse-oximetry screening beyond the first 24 hours after birth. Moreover, our findings demonstrated the diagnostic value of RDC in an early screening in achieving a prompt diagnosis of (supra)cardiac TAPVR and in differentiating (supra)cardiac TAPVR from persistent pulmonary hypertension of the newborn.

Part II: Lifeline of cardiac life

The heart is responsible for providing its own blood supply through the coronary circulation. This system heavily relies on adjusting blood supply to meet metabolic demands, resulting in continuous regulation of coronary blood flow. While this tight coupling has been recognized for many years, our understanding of the underlying mechanisms remains rather limited. Additionally, the mechanisms through which the contracting myocardium exerts extravascular forces (known as intramyocardial pressure) on coronary vessels, impeding its blood flow, remain incompletely understood. Progress in understanding the mechanics of the coronary circulation has been hampered by a lack of insight into the events occurring in the intramyocardial small vessels. In this part of the thesis, we focus on developing a computational model for the coronary circulation to evaluate coronary function in both physiological and pathological contexts, with the ultimate goal of improving patient care.

In **Chapter 4**, we developed a computational modeling platform that couples a model of coronary mechanics to the closed-loop CircAdapt model of the human cardiovascular system. Coronary flow was made dependent on local myofiber mechanics and ventricular cavity pressure, which both determined intramyocardial pressure in the model. Validation of the model with reported human data confirmed that the phasic pattern of epicardial flow velocity as well as the transmural differences in flow and diameter were realistically represented. The versatility and validity of the model were demonstrated in a case study of aortic valve stenosis, where the model independently reproduced the effects of aortic valve stenosis and valve replacement on coronary flow velocity measured in patients before and after valve replacement.

In **Chapter 5**, we build upon the modeling framework for cardiac mechanics-to-perfusion coupling to improve our understanding of the coronary autoregulatory mechanism during asynchronous ventricular activation. By coupling myocardial oxygen demand to oxygen supply, the model hypothesized that septal hypoperfusion is most likely the result of physiological autoregulatory responses to reduced septal workload.

By coupling myocardial oxygen demand to myocardial growth, the model suggested that asymmetric hypertrophy, following chronic asynchronous ventricular activation, leads to homogenization of myocardial perfusion and flow reserve. These findings suggest that reported inconsistencies in myocardial perfusion and flow reserve responses with asynchronous ventricular activation between patients can primarily be explained by the degree of dyssynchrony and wall mass remodeling, which together determine the heterogeneity in regional oxygen demand and, hence, supply with autoregulation.

The clinical assessment of coronary microvascular function using intracoronary bolus thermodilution shows considerable inter- and intra-operator variability with manual bolus injections. In **Chapter 6**, we aimed to explore whether ECG-triggered bolus injections instead of manual bolus injections could help reduce this variability. Our *in silico* analysis in virtual patients exposed the inherent variability of bolus-derived indices of coronary microvascular function measured with manual bolus injections, revealing the potential for misinterpreting microvascular function. Furthermore, our simulations suggested that ECG-triggered bolus injections with fixed duration can significantly reduce this variability.

In summary, we have developed computational models to predict the hemodynamic behavior of the perinatal and coronary circulations under both healthy and diseased conditions. Additionally, we have revealed the underlying mechanisms of complex hemodynamics and proposed ways to potentially enhance the clinical diagnosis of specific cardiovascular diseases. **Chapter 7** discusses our most important findings and their clinical implications in a broader perspective. Moreover, we discuss the stages involved in model development, the challenges encountered during model development and validation, and possibilities to improve the modeling framework. In conclusion, the findings presented in this thesis illustrate that computational models of the perinatal and coronary circulations can serve as valuable tools in advancing our understanding of the **Lifelines of Life**.