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UNIVERSITY OF CALIFORNIA, SAN DIEGO

Growth Modeling of the Normal Human Fetal Left Ventricle and a Patient-
Specific Case Study of Hypoplastic Left Heart Syndrome

A Thesis submitted in partial satisfaction of the requirements for the
degree Master of Science

in

Bioengineering

by

Devleena Kole

Committee in Charge:

Jeffrey Omens, Chair
Andrew McCulloch, Co-Chair
Sukriti Dewan
Adam Engler

2016

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Co-Chair

Chair

University of California, San Diego

2016

EPIGRAPH

The little space within the heart is as great as the vast universe. The heavens and the earth are there, and the sun and the moon and the stars. Fire and lightning and winds are there, and all that now is and all that is not.

Swami Prabhavananda

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ABSTRACT OF THE THESIS

Growth Modeling of the Normal Human Fetal Left Ventricle and a Patient-Specific Case
Study of Hypoplastic Left Heart Syndrome

by

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Master of Science in Bioengineering

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Congenital heart defects such as hypoplastic left heart syndrome (HLHS) develop during gestation due to altered biomechanical stimuli during fetal growth. Currently, predicting growth behavior in hypoplastic hearts using mid gestational fetal echocardiography is a clinical challenge. In order to more accurately predict and optimize the outcomes of congenital heart defects on individual patients, first a comprehensive understanding of normal fetal growth and its sensitivity to various biomechanical stimuli is necessary. Computational models based on realistic in-vivo geometry contribute

significantly to the understanding of cardiac physiology and mechanics. Though structural and functional development of the human heart is well understood, there are limited computational models of this process, specifically at the fetal stage. Therefore, there is a growing need for a robust computational model of the normal human fetal heart based on clinical measurements that can predict organ-level growth and can be used as a benchmark to compare against disease models. A novel three-dimensional (3D) finite element (FE) model of the human fetal left ventricle (LV) was developed using human fetal geometry at 22 weeks gestation. The model, in which cardiac myocyte growth rates as a function of end-diastolic strain, which correlates with ventricular filling, can predict organ-level growth. Predictions from the model were validated with LV echocardiographic dimensions from 22 to 40 weeks. An extreme sensitivity analysis was conducted to study the effects of size, shape, preload, ventricular filling, and material properties on fetal LV growth. The model provides insight into the parameters that growth is most sensitive to, in which growth is quantified as changes in LV cavity volume, wall volume, cavity shape, and wall thickness from mid gestation to birth. This is extremely useful when prioritizing patient-specific model parameters and improving the predictive capability of the model. In addition, a retrospective case study for a severe HLHS patient was conducted using mid gestation echocardiographic data. The model predicted a severely hypoplastic LV consistent with the patient's diagnosis and replicated LV short-axis and long-axis dimensions from late-gestation data. The work presented in this study is a step towards the development of a clinical tool that may be used to predict LV size and shape at birth based on mid gestation data.

CHAPTER 1

BACKGROUND

1.1 Significance

In 2012 there were 19.15 births per 1,000 of the total world population on average [1]. In the United States alone, every year there are 13 live births per 1,000 of the population [2]. In 2014, this translated to a total of 3,988,076 births, of which approximately 3% are affected by birth defects accounting for 20% of all infant deaths (3,4). Congenital heart defects (CHDs) are the most common type of birth defects, affecting nearly 1% of all births (roughly 40,000) per year in the United States. CHDs are a leading cause of birth defect-associated infant mortality, specifically contributing to 4.2% of all neonatal deaths, which occur when the baby is less than 28 days old [5]. Although approximately half of the cases of CHD have minor consequences or can be corrected with surgical intervention, 1 in 3 newborns with a potentially severe CHD-derived cardiac malformation may leave the hospital undiagnosed, and it is recognized that delayed diagnosis of CHD impairs the outcome of surgery in neonates [6, 7].

Screening for disturbances in fetal growth, particularly structural abnormalities of the

heart, becomes imperative to prenatal detection of CHDs. Ultrasound examination during the first trimester of pregnancy can successfully be used to detect fetuses at high risk of major CHD even in cases of a normal karyotype, based on nuchal translucency thickness measurements [8]. During the second and third trimesters, routine ultrasound examination, which includes visualization and interpretation of the fetal heart's four-chamber view along with outflow tract views at mid gestation (16 to 24 weeks' gestational age), has been well established as an efficient and accurate diagnostic tool for prenatal detection of a majority of cardiac anomalies and malformations [7]. Diagnosis of CHD via fetal echocardiography allows for a smooth transition between the pre- and post-natal phases, appropriate counseling for the parents, and the opportunity to provide immediate care at birth [11].

Despite the recent advancements in ultrasound technology and the widespread use of ultrasound, prenatal detection rates have varied widely for CHD. A recent study found significant geographic variation in rates of prenatal detection of CHD in the United States (range 11.8%-53.4%, $P < .0001$) and significant variability in detection identified on four-chamber view as opposed to outflow track visualization (57% vs. 32%, $P < .0001$) [12]. This can be attributed in part to sonographer experience, transducer frequency, maternal obesity, abdominal scars, gestational age, amniotic fluid volume, and fetal position [9]. Another major contributing factor is the lack of suitable national and international standards for prenatal screening similar to those used for monitoring infant growth. Without uniform standards and guidelines, there is a significant variation in clinical decision-making regarding fetal growth patterns, which leads to diagnostic uncertainty, difficulties comparing outcomes across populations, and compromised health for affected

newborns [10].

Recent efforts have been made to compile data for fetal hearts during healthy pregnancies to characterize growth patterns of normal fetal cardiac growth. In cases of suspected cardiac structural anomalies, previously compiled databases with measurements of cardiac structures via fetal echocardiography help to confirm and define abnormalities, especially when values can be compared to an accepted range of standard measurements derived from normal healthy fetuses over a range of gestational ages [13]. This is especially imperative because fetal cardiac physiology differs from the adult, mature cardiovascular system, which has been vastly explored and characterized, so clinicians must rely on echocardiography to gain insight into fetal growth patterns. Although ultrasound technology has made it possible to take measurements of cardiac structures in a non-invasive manner, these studies can be limited due to the technical difficulties of obtaining measurements from the fetal heart via an indirect method, subjective assumptions that are made to compensate for poor image resolution, and lack of specialized expertise of the sonographer [13]. Despite these challenges, technological advances and increasing experience have improved the evaluation and assessment of fetal heart structures, in conjunction with the generation of normative dimensional and flow data that can be used to facilitate diagnosis of CHDs and contribute significantly to our understanding of the normal development of fetal cardiac structures and function, which is critical for improving prenatal care and for development of timely and effective post-natal intervention [14].

1.2 Cardiac Developmental Physiology

The heart is the first organ to fully form and function in human development. Much of our understanding of early cardiac development in the human embryo and its underlying mechanisms is extrapolated from development research in model organisms, such as the chick, mouse, and frog [15, 16]. With advances in medical imaging, researchers have been able to overcome technical challenges that arise when gathering information from histological sections of human embryos, and instead reconstruct sectioned images in 3D to then facilitate comprehensive understanding of the complex morphological changes that occur in the developing heart, specifically in the early first trimester [15].

1.2.1 Embryonic

The cells fated to become the heart are among the first cell lineages formed in the human embryo. By day 15 of human development, the primitive streak forms, which initiates formation of the three germ layers: ectoderm, endoderm, and mesoderm. The first mesodermal germ layer cells that migrate through the primitive streak give rise to the heart.

Embryonic development of the heart begins with the formation of two lateral endocardial tubes that grow and by the third week of human development converge towards each other to merge and form a single endocardial tube, the tubular heart. The tubular heart quickly divides into five distinct region within the tubes: truncus arteriosus, bulbus

cordis, primitive ventricle, primitive atrium, and sinus venosus. Initially, all blood flows into the sinus venosus and contractions drive the blood from tail to head, or from the sinus venosus to the truncus arteriosus. Eventually, the truncus arteriosus divides to form the ascending aorta and pulmonary artery; the bulbus cordis develops into the right ventricle; the primitive ventricle forms the LV; the primitive atrium becomes the front parts of the left and right atria and their appendages, and the sinus venous connects to the fetal circulation [15, 16].

As the heart begins to beat, a cascade of signals initiates the process of heart tube looping. From days 22 to 28 of human development, the heart tube elongates on the right side, looping and exhibiting the first signs of left-right asymmetry of the body. During this process, the heart tube increases significantly in length, which is an important step for the proper alignment of the inflow (venous) and outflow (atrial) tracts. At this stage of development, the chambers of the heart are in position and demarcated while primitive vasculature is extensively remodeled. Septa form within the atria and ventricles to separate the left and right sides of the heart during which time the valves also develop. Cardiac activity is visible beginning at approximately 5 weeks of clinical gestation [15, 16].

1.2.2 Fetal

The primitive vasculature of the heart is bilaterally symmetric initially, but undergoes extensive remodeling during weeks 4 to 8 of development. Although the heart is, at this stage, able to generate coordinated contractions, the fetal myocardium still differs from the adult, fully mature myocardium. 60% of fetal myocardium is composed

of non-contractile elements compared to 30% in the adult myocardium, which significantly affects cellular replication. Cardiomyocytes contain the contractile elements of the heart and receive signals to exit the cell cycle at the time of birth. While fetal cardiomyocytes are able to divide and increase in number (hyperplasia), adult cardiomyocytes can only grow in size (hypertrophy). Fetal myocardium also demonstrates a difference in the process of rapid removal of calcium from troponin C, the mechanism responsible for myocardial relaxation [17].

These impaired relaxation and stiffness properties in fetal myocardium may account for limitations in stroke volume augmentation unique to the fetal heart. The adult myocardium follows the Frank-Starling law, which predicts that with increasing preload there is an increase in stroke volume. The fetal myocardium operates at the upper limit of this law where there is a plateau (Figure 1.1).

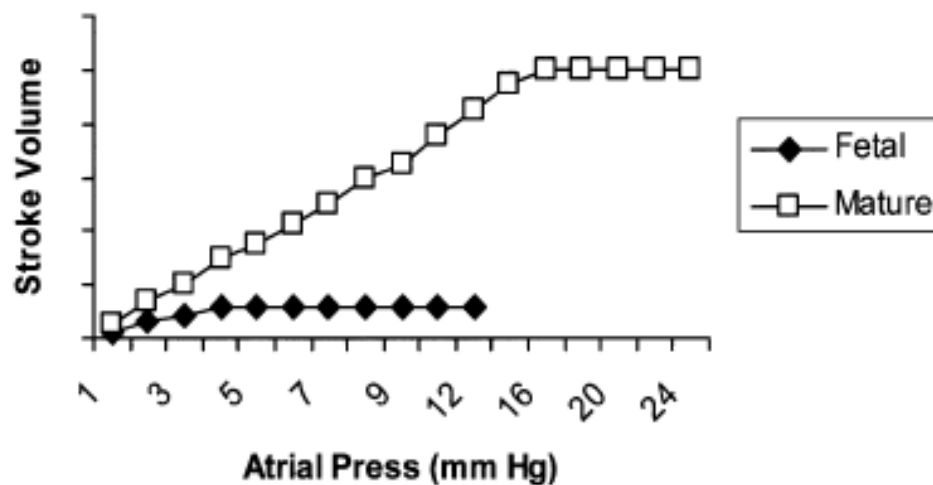


Figure 1.1: Atrial pressure and stroke volume relationship in the fetal and mature heart.

Reprinted with permission from "Fetal Cardiovascular Physiology" by J. Rychik, 2004, Pediatric Cardiology [17].

Alternative theories suggest that fetal stroke volume may be limited by ventricular constraints that arise from the surrounding tissues including the chest wall and the lungs,

which limit fetal ventricular preload and cardiac function. These constraints are relieved at birth, which accounts for the significant increase in LV preload and stroke volume in newborns. Hence, fetal myocardium due to its immature myocardial architecture and ventricular constraints can only increase stroke volume to a small degree in response to increase in preload [17].

Unlike the adult heart, fetal ventricles work in parallel rather than in series. Due to the presence of the ductus arteriosus and foramen ovale, there are almost identical pressures in the aorta and pulmonary artery, and atria respectively. Hence, the left and right ventricles are also subjected to the same filling pressure and their combined ventricular output perfuses the fetal system. The LV primarily perfuses the coronary and cerebral circulations through the ascending aorta and the RV perfuses the lower body and placental circulation through ductus arteriosus and descending aorta [17, 18].

1.2.3 Neonatal

At birth, there are transitional events in the cardiovascular system to ensure that the newborn has adequate systemic blood flow and pressures. The ventricles begin to work in series, rather than in parallel, and the fetal extracardiac and intracardiac shunts close. Epinephrine levels increase during labor and at birth to mediate increased cardiac output and myocardial contractility, which are critical during changes in myocardial function and the associated stresses of transition. Oxygen availability increases due to the shifting of oxygenation from the placenta to the lungs. Oxygen delivery in the neonate at rest is estimated to be 75% higher than in the adult. This also leads to an increase in blood volume in the arterial system since blood that no longer needs to return to the

placenta instead is accommodated in the systemic circulation and, as a result, systemic blood pressure increases over the first hours to days after birth. The ductus venosus is closed within minutes of birth due to cessation of placental blood flow. Pressure changes within the chambers, specifically the left atrial pressure rising and exceeding that of the right atrium, causes the foramen ovale to close and functionally separate the atria by 30 months of age. At birth, the ductus arteriosus begins to constrict but does not fully close for a few days in a healthy, full term infant. This leaves a small shunt of blood from the aorta to the left pulmonary artery, which eventually decreases as a result of pulmonary arterial pressure falling below the systemic level due to reduced pulmonary vascular resistance. The ductus arteriosus achieves functional closure by 96 hours in nearly all infants. Due to these changes in the cardiovascular system at birth, the nonfunctional vessels form ligaments and fetal structures such as the foramen ovale remain as vestiges of the fetal circulatory system [19].

The neonatal myocardium undergoes structural and functional changes that contribute to a functional cardiovascular system for the newborn. The newborn myocardium contains less non-contractile tissue than the fetal myocardium and the myocytes become more cylindrical. The myocardium is able to generate increased force and influenced by ventricular preload, myocardial contractility, heart rate, and ventricular afterload. Myofibrils increase in number, become more organized, and have an improved ability to shorten. This leads to an increase in cross-bridge formations and therefore greater force generation. The LV increases in mass more than the right while the latter becomes more compliant. There is a significant increase in the combined ventricular output after birth but the neonatal myocardium still operates at the upper limit of the

Frank-Starling law discussed above and must fully undergo a maturation process into adult myocardium [19].

1.3 Cardiac Mechanics

The fully mature, adult myocardium along with the atrioventricular and semilunar valves contribute to the primary function of the heart, which is fundamentally mechanical—to pump blood throughout the body’s circulation system. The heart contracts approximately 2.5 billion times during the average human life span, adapting to the constantly changing demands of the system. The heart is a highly complex organ whose geometry, structure, and boundary conditions are three-dimensional and often irregular, heterogeneous, and time varying. In addition, the constitutive properties of the myocardium are nonlinear, anisotropic, and heterogeneous. Over the past several decades, enormous efforts have been made to formulate and validate mathematical descriptions, or constitutive laws, of the complex nature of the ventricular myocardium for passive and active mechanics. This section discusses cardiac function within the context of mechanical properties of the myocardium. While the focus is on the normal heart, it is important to consider that these properties may be altered as a result of abnormal development and growth, which has an impact on cardiac mechanics and function [20].

1.3.1 Anatomy and Ventricular Function

The heart is a muscular organ that consists of four pumping chambers, the right and left atria and ventricles. The atria receive blood that returns to the heart: the right

atrium receives deoxygenated blood via the superior and inferior vena cava, whereas the left atrium receives oxygenated blood from the lungs via the pulmonary veins. The atria and ventricles are bridged via the atrioventricular valves: the tricuspid in the right side and the mitral in the left side of the heart. These valves are connected to the papillary muscles that extend from the ventricular cavities via collagenous fibers called chordae tendineae. The ventricles pump blood from the heart: the right ventricle pumps blood to the lungs through the pulmonary valve and pulmonary arteries, and the LV through the aorta to the rest of the body. The cardiac wall itself is perfused via the coronary arteries and is divided into three distinct layers: an inner layer called the endocardium, a middle layer called the myocardium, and an outer layer called the epicardium. The endocardium is a thin layer composed of collagen and elastin as well as a layer of endothelial cells that act as a direct interface between the blood and the wall. The myocardium, as discussed previously, consists of myocytes that are arranged into locally parallel muscle fibers and endow the heart with its ability to pump blood. The epicardium is also a thin layer consisting of collagen and elastic fibers. In addition to these three layers, the heart is surrounded by the pericardium, a thicker layer of collagen and elastin that serves to limit the gross motion of the heart [20].

The ventricles are three-dimensional pressure chambers with walls that vary in thickness regionally and temporally during the cardiac cycle. The ventricular walls in the normal heart vary in thickness from the base to apex. The ventricles consist of complex three-dimensional muscle fiber architecture. The primary mechanical parameters of the cardiac pump are blood pressure and volume flow rate, with ventricular pressure being the most important boundary condition [20]. The cyclic mechanical function of the heart

can be illustrated by the left ventricular pressure-volume relation, where the LV pressure at each instant during the cardiac cycle is described as a function of the volume. The phases of the cardiac cycle are divided into systole and diastole, which can be further separated into ventricular filling, isovolumic contraction, ejection, and isovolumic relaxation. These sub-phases are defined by the opening and closure of aortic and mitral valves.

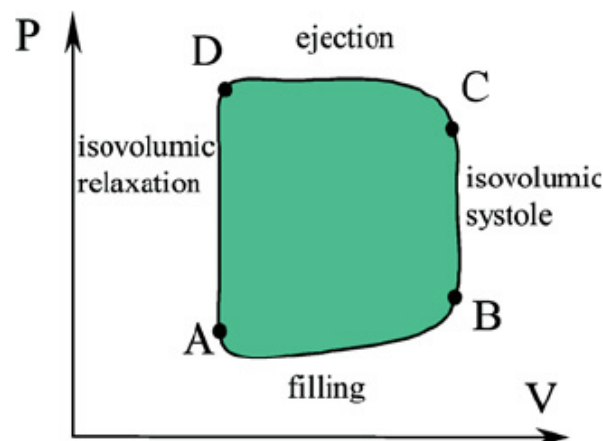


Figure 1.2: Pressure-Volume diagram of the cardiac cycle.

Reprinted with permission from “Fluid-Structure Coupled CFD Simulation of the Left Ventricular Flow During Filling Phase” by Y. Cheng, 2005, *Annals of Biomedical Engineering* [20]

Systole, which is considered to be the active phase of the cardiac cycle, begins when the mitral valve closes and the LV begins to contract, initially via isovolumic contraction. During isovolumic contraction, the LV pressure rises rapidly while the volume remains constant and when the ventricular pressure exceeds that of the aorta, the aortic valve opens leading to ejection of blood. During the ejection phase, the LV volume decreases while the pressure increases to its peak value, known as peak systolic pressure, and then decreases as the ventricle relaxes. Deceleration of the ejecting blood causes the aortic valve to close after ventricular pressure falls below the aortic pressure. Closure of

the aortic valve marks the beginning of diastole.

Diastole is the period of left ventricular relaxation and filling, which begins with the aortic valve closing and ends with the mitral valve closing. Closure of the aortic valve leads to isovolumic relaxation in the LV, in which the LV pressure decreases while maintaining constant volume. When the LV pressure falls below the left atrial pressure, the mitral valve opens and ventricular filling occurs, and the cycle continues.

As the ventricle fills with blood and the volume increases, the pressure within the chamber passively increases. This relationship is not linear and is limited by the compliance of the ventricular wall, where a more compliant ventricle will allow for a larger change in filling volume for a given change in pressure. LV compliance curves describe this inflation by plotting the change in pressure versus change in volume. At low pressures, the LV compliance curve is almost linear, but begins to curve more steeply at higher volumes and pressures. The slope of this relationship is the reciprocal of compliance, or ventricular stiffness. LV compliance is determined by structural properties of the cardiac muscle, such as the fiber orientation, and the state of ventricular contraction and relaxation. For instance, in ventricular hypertrophy, the compliance is lower because the ventricular wall thickness is increased; hence, end-diastolic pressure (EDP) is higher at any given change in end-diastolic volume (EDV) [21, 22].

The net volume ejected by the LV per unit time is defined as the cardiac output and is determined by a number of factors, defined in Table 1.1 along with other terms related to cardiac performance relevant to this study.

Table 1.1 Terms describing cardiac performance.

Term	Definition
Preload	The ventricular wall tension just prior to contraction, clinically approximated by the EDP
Ventricular filling	Volume of blood that fill the ventricles during diastole ($= EDV - V_o$)
Stroke Volume	Volume of blood ejected from the ventricle in systole ($= EDV - ESV$)
Ejection Fraction	The fraction of EDV ejected from the ventricle per beat ($= SV/EDV$)
Cardiac Output	Volume of blood ejected from the ventricle per minute ($= SV \times HR$)

1.3.2 Myocardial Mechanical Properties

Constitutive laws used to describe the mechanical behavior of the ventricular myocardium are formulated with material parameters obtained from mechanical testing, such as uniaxial and biaxial tests. Uniaxial are useful for identifying general characteristics of the tissue behavior, but are not adequate for determining the three-dimensional constitutive behavior of the myocardium. Biaxial tests are valuable tools that enable estimation of myocardial constitutive parameters as they can measure the force and displacement (stress and strain) along orthogonal fiber and cross-fiber axes.

Mechanical behavior of the heart and global cardiac function requires a mathematical description not only for the passive properties, but also the mechanics of the active cardiac muscle fibers. Cardiac myocytes exhibit a specific activation profile based on location within the myocardium. Active stresses generated by cardiac muscle fibers are dependent on parameters, such as activation time, shortening velocity,

sarcomere length, and intracellular calcium concentration. The active mechanical properties are also patient-specific parameters that may vary between individuals. Therefore, parameters such as the twitch duration scaling factor, the active stress-scaling parameter, and the relationship between time-to-peak tension and sarcomere length need to be estimated in a patient-specific manner [23].

1.4 Computational Modeling

Computational models based on realistic geometry contribute significantly to the quantitative and qualitative understanding of cardiac physiology and mechanics. Previously, computational models have been utilized to provide insight into the morphogenetic process of cardiac looping in the embryonic chick heart, cardiac growth in the post-natal rat, and the complex mechanisms regulating cardiac signaling networks in human hearts [24-26]. The following section will briefly introduce common computational approaches to model three-dimensional cardiac structures and review selected models of cardiac physiology and mechanics.

1.4.1 Introduction

Anatomical computational models of the heart with realistic fiber orientation that represent cardiac anatomy have been developed based on histo-anatomical slices, from measurements taken on explanted hearts, or by segmenting pictures of histo-anatomical slices. With the evolution of computer-aided design and improvement in medical imaging technology, 3D cardiac models can be constructed from in-vivo or ex-vivo images. The

rising trend and need for personalized medicine has also enabled the development of patient-specific cardiac computational models that are based on in-vivo images that can be taken via MRI, CT, or ultrasound for in-utero patients. There are many challenges associated with computational modeling of a dynamic organ such as the heart; however, 3D cardiac models are becoming increasingly complex and starting to be used in clinical settings [27].

Computational cardiac mechanics is at the intersection of continuum mechanics, materials science and numerical methods. Continuum mechanics is based on the hypothesis that matter is continuous, which is not exactly true but provides an adequate description of the deformation of matter based on the equilibrium equations. These equilibrium equations are derived from conservation laws of mass, momentum, and energy, and apply to all materials and living tissues. For any given material or tissue, the constitutive stress-strain relationship describes how much force is developed under stretch or strain, or vice versa. Hence, the constitutive stress-strain relationship describes the mechanical behavior of the material. While there are many formulations of stress-strain relationships for cardiac tissue, they all share the key features of having a nonlinear and anisotropic relationship, and the ability to contract in the muscle fiber direction once stimulated. The equations from continuum mechanics and constitutive stress-strain are combined to yield a set of coupled partial differential equations, which when solved can describe the displacement, stress, and strain at every material point within the heart wall. However, these equations cannot be solved analytically for realistic geometries and boundary conditions, so numerical approaches must be utilized. Numerical methods are often used to approximate systems of differential equations in cardiac mechanics with the

most widely used method being the finite element (FE) method due to its versatility and solid theoretical foundation. The FE method operates by discretizing the original continuous problem, splitting the structure into subparts called elements whose vertices are called nodes [28].

The FE model developed in this study was numerically solved using *Continuity* 6.4, a problem-solving environment for multi-scale modeling of cardiac biomechanics, biotransport, and electrophysiology. It is distributed free for academic research by the National Biomedical Computation Resource and can be downloaded at <http://www.continuity.ucsd.edu/Continuity>.

1.4.2 Modeling of Cardiac Structures

Previously, several computational models of cardiac structures and the whole heart have been developed that contribute to the understanding of cardiac physiology in animal models as well as humans. In addition, several FE models of cardiac mechanics have been developed to study pump function in relation to the 3D geometrical, passive, active, and anisotropic properties of the myocardium [29-35]. This section will provide a brief overview of past efforts in modeling cardiac structures.

Established whole heart models of the heart are FE biventricular models based on structural information obtained by a combination of mechanical and histological measurements, built largely using data from animal anatomies, such as rabbit or dog [36-38]. The models were generated by fitting the nodal parameters of piecewise polynomials in a prolate coordinate system using least squares. Smooth estimates of the geometry and fiber structure of the ventricles were obtained using Hermite interpolation. These models

provide a coarse representation of the overall cardiac structure and lack details such as the endocardial trabeculations and papillary muscles, which are important for functional cardiac electrophysiology and mechanics. Whole heart models with such detail have been developed recently [39, 40]. Plotkowiak et al reconstructed models from high-resolution MR images of rabbit hearts with detailed geometric features. However, fiber orientations were not incorporated and the ventricles were not separated from the surrounding tissue.

Human ventricular models have been constructed, in addition to animal models, that are used to study propagation and dynamics of fibrillation [41, 42]. The geometry in the model from Tusscher's group was obtained from histological slices of a human heart, but fiber orientation data was not acquired. The group mapped the fiber architecture of a canine heart onto the model to account for anisotropic behavior. Similarly, Potse et al constructed a model using CT data that generated a mesh with 45 million nodes with calculated fiber orientations that mimicked structural data [43]. Human atrial 3D models have also been generated for studies of normal conduction along atrial structures. The model geometry was based on surface meshes with muscle bundles represented as anisotropic structures and the rest of the atrial tissue as isotropic. The most structurally detailed atrial model to date was presented by Reumann et al, who generated a model based on cryosection images to study atrial fibrillation [44].

While the focus of computational cardiac modeling has largely been on adult hearts, there have been efforts to model and understand the changes in morphology that occur during cardiac development. Shi et al developed a FE model for the early heart tube that explores the mechanics of the first phase of cardiac looping, c-looping. The model features realistic 3-D geometry reconstructed from images of an embryonic chick heart

acquired via optical coherence tomography. The model captures the morphology of the looping heart under controlled and mechanically perturbed conditions, laying the foundation for future patient-specific models for cardiac morphogenesis [24]. Similarly, Ramasubramanian et al developed FE models for the embryonic chick heart that can simulate a number of morphogenetic mechanisms, including cytoskeletal contraction, and was used to understand the mechanical stimuli that drives c-looping (45).

Recently, there have been efforts to construct computational models of the electrophysiology of the human fetal heart as early as 60 days gestational age to full term. The geometry for the models is derived from fast low-angle shot and diffusion tensor magnetic resonance images of aborted fetal hearts. However, prior to imaging, these hearts are stored in formalin for days to weeks, which may lead to systemic changes in the myocardial structure and gap-junction connections [46]. In addition, there is a limited availability of fetal human hearts for structural or functional studies as they are only available, with informed maternal consent, after abortion. Most abortions occur before the fetus is 10 weeks gestational age, which greatly limits the data that can be acquired during the fetal stage of cardiac development. The developing fetal heart, which is already limiting in terms of its size, can only be studied and imaged in utero via ultrasound and, in the case of developmental abnormalities, clinical MRI, posing a challenge for the computational cardiac modeling field.

1.4.3 Growth Modeling

While the previously discussed models of cardiac mechanics take into account the complex geometry and passive, active, and anisotropic properties of the myocardium, it is

important to consider that tissue properties are not constant over time as the tissue undergoes growth and remodeling in response to changes in mechanical loading [47-51]. Clinically, this is most evident in left ventricular hypo- or hypertrophy in response to hemodynamic under- or overloading, respectively. Furthermore, regional changes in loading, as induced by asynchronous contraction, result in asymmetric wall thickening [52]. Hence, it becomes important to incorporate features of growth and remodeling into models of cardiac mechanics and eventually more precisely estimate or predict long-term outcome of clinical interventions that cause changes in load.

3D FE models have been developed that enable computation of volumetric growth in patient specific geometries [53-56, 84]. In these models, volumetric growth is defined as a deformation that can potentially change the initial, unloaded shape, volume, and state of stress of the tissue [57-59]. Growth is dependent on the initial tissue configuration as the stresses are constitutively related to growth deformation and the initial stress-free configuration remains fixed throughout the entire growth process. An alternative approach considers the tissue as a mixture of constituents, each of which exhibits continuous turnover [60]. Hence, this disregards the initial configuration and constitutive laws relating internal stresses to growth deformation are not related to a fixed reference configuration, but rather to an evolving configuration throughout growth [61].

Based on these approaches, Kroon et al were able to simulate load induced inhomogeneous volumetric growth in a FE model of the LV consisting of 252, 27-noded hexahedral elements [62]. Kerckhoffs applied a novel strain-based growth law to a passively loaded FE model of a newborn residually stressed rat LV. This model was able to qualitatively reproduce physiological postnatal growth in the rat LV on both the

chamber and cellular level, which included increase in cavity and wall dimensions [25]. Furthermore, Kerckhoffs applied the growth law to a nonlinear FE model of the beating canine ventricles with realistic fiber anatomy coupled to a lumped-parameter model of circulation that included the heart valves. The model was allowed to adapt in shape in response to mechanical stimuli and grow to a final state with new geometry and hemodynamics. The model was able to reproduce most physiological responses, including both acute and chronic changes in structure and function, even when integrated with models of pressure-overloaded (by aortic stenosis) and volume-overloaded (by mitral regurgitation) canine whole hearts. The strain-based growth law was able to drive wall thickening during pressure-overload as opposed to the more commonly stress-based stimuli [63]. Therefore, this serves as a framework for future work in improving validated patient-specific growth models of the heart including single ventricle models that aim to understand the mechanics of cardiac development.

1.5. Clinical Relevance

Recent efforts have been able to combine experimental findings and computational models to reduce the complexity and accelerate insight into cardiac mechanics, mechanisms of disease, and signaling networks that mediate cardiac development in both normal and diseased states. Models are often validated with experimental data and they also integrate well with experimental studies to explain observations and test new hypotheses. As evident, computational models including patient-specific models of the adult human heart are growing in number and complexity, improving with increasing

demand for personalized medicine, advancement in medical imaging technology, and evolution of well-annotated cardiac atlases.

Compared to established models of adult cardiac structures and whole heart, computational models of the human fetal heart, which can contribute significantly to the knowledge base of cardiac development, are vastly limited. Although structural and functional development of the human heart is well understood, there are limited computational models of this process, specifically at the fetal stage. Unlike the embryonic stage, which deals with cell proliferation and the morphological development of cardiac structures, the fetal stage focuses on the development of the mechanics of the heart, specifically as the heart starts to beat at 4 weeks gestation. The majority of significant cardiovascular lesions in the fetus develops within the first trimester and is presumed to be present at the time of second trimester ultrasound examinations [64]. Moreover, pathophysiological conditions of the heart that impair the proper mechanical function of the heart such as hypoplastic left heart syndrome (HLHS), which is a CHD leading to an under-developed LV that provides inadequate blood flow post-natally, endocardial fibroelastosis (EFE), which is a thickening of the ventricular endocardium causing myocardial dysfunction, and aortic and mitral valve stenosis can all be detected during the fetal stage. Currently, there are chick models of HLHS and EFE that quantify myocardial performance and study the abnormal hemodynamics and flow patterns in these diseases [65, 66], stem cell models of HLHS that are used to explore the genetic abnormalities and functional differences [67], and human genetic studies that aim to identify mutations in genes important for early heart formation that may lead to HLHS [68]. Due to the nature of animal model and ex-vivo experiments, the primary limitation

with all of these studies is that they cannot adequately represent the pathophysiological behavior of HLHS in a human fetus in-utero. Computational cardiac models of HLHS based on realistic fetal geometry and patient-specific data can faithfully elucidate the mechanical behavior of the disease and be used as a clinical tool to predict the growth of the fetus, allowing adequate preparation for post-natal intervention.

In order to contextualize the findings of these disease models and identify the functional differences from a normally developing heart, it is critical to first understand and characterize the growth behavior and mechanical properties of a normal human fetal heart under different physiological conditions. Therefore, there is a growing need for a robust computational model of the normal human fetal heart based on clinical measurements that can predict organ-level growth and can be used as a benchmark to compare against disease models.

1.6 Specific Aims

Computational growth modeling of the average, normal human fetal heart is improved by data acquisition that can accurately reproduce physiological behavior of the heart. This data provides unique information specific to the fetal heart including the 3D geometry, mechanical parameters, and clinical measures of function. To build an accurate model, reliable clinical and experimental measurements as well as robust methods for optimizing the developed model are necessary. Hence, the goal of this study was to develop a robust single ventricle model of an average human fetal heart and to characterize normal growth behavior in order to serve as a reference model for future

studies. A goal for these types of computational methodologies is to develop patient-specific models of cardiac developmental pathophysiology to predict outcomes and serve as a clinical tool for anticipating treatment options.

The current study is divided into four aims, as follows:

1. To statistically analyze 23 model geometries of the left ventricle of the human fetal heart at mid gestational age to identify the best fit geometry satisfying ex-vivo unloaded geometry, end diastolic geometry and clinical measures of function at end diastole (pressure and volume).
2. To use the normal fetal LV model to assess the sensitivity of the growth model and quantify how changes in individual growth model parameters affect volumetric and shape behavior.
3. To test the ability of the model in predicting reverse growth from 22 weeks gestation to an *in vivo* unloaded state at the onset of fetal growth.
4. To develop a patient-specific model of HLHS based on data at mid gestation and test the predictive capability of the model in a case study

CHAPTER 2

Model Selection for Normal Human Fetal LV Growth

2.1 Methods

Developing a reliable and predictive growth model of a normal fetal LV requires several criteria to be considered in estimating model parameters from available clinical and experimental data. An initial requirement is to define the unloaded ventricular geometry that, when loaded at normal preload, results in the end diastolic geometry. A second requirement is to simultaneously adjust the resting material properties of the myocardium so that the end diastolic pressure-volume relation matches human measurements, as reported in literature. A third requirement is to validate the geometry by allowing it to grow to term and ensuring that the dimensions found at birth match those reported in literature [69].

With the above requirements met, the resulting geometry will serve as the reference, unloaded state for the normal fetal LV growth model. To develop such a geometry, however, is an iterative process as it becomes necessary to mathematically optimize the geometry based on the results of the previous iteration and adjust the

geometry, preload, and resting material properties to reach the optimal combination of results. Therefore, it is just as necessary to conduct a statistical analysis of all of the developed geometries to determine the best-fit geometry suitable for model development.

2.1.1 Study Design

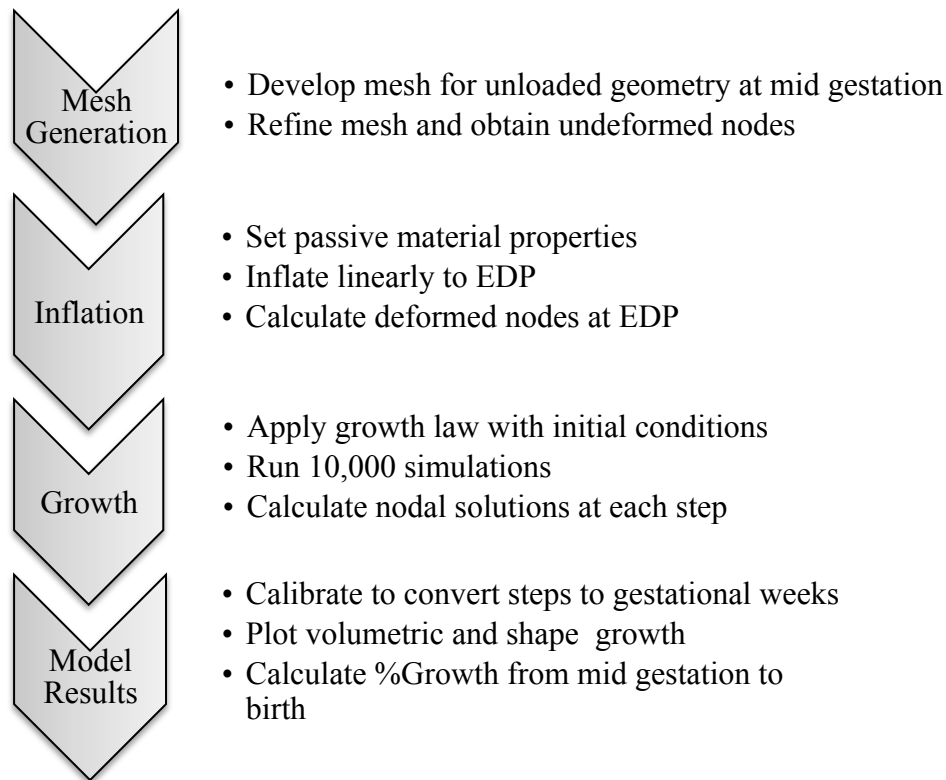


Figure 2.1: Workflow for developing a clinically relevant normal human fetal LV growth model.

The study design for this aim is outlined above in Figure 2.1. The end goal is to develop a computational model describing normal growth of a human fetal left ventricle from mid gestation to birth. The first step is to generate a mesh representing the unloaded geometry of the fetal LV at mid gestation (22 weeks). This requires accurate data from a large sample size of healthy fetuses regarding the geometry of the fetal LV in terms of short- and long-axis dimensions, as well as wall thickness measurements from different

sections of the ventricle. The resulting mesh is refined to generate the working unloaded mesh. The second step in the workflow is to incorporate the passive myocardial properties and inflate the mesh in incremental load steps from unloaded to a selected end-diastolic cavity pressure, uniformly imposed on the endocardium, resulting in the end-diastolic geometry at mid gestation. The third step is to apply a strain-based growth law to the inflated mesh, while keeping pressure constant, and allowing the simulation to run for a number of growth steps that correspond to growth from mid gestation to birth (40 weeks), calculating nodal solutions and strain distribution at each step size. The final step is to calibrate for time and plot the resulting growth from mid gestation to birth. Numerically, normal growth is quantified by calculating percent change from 22 weeks to 40 weeks gestation in LV cavity volume, shape, wall volume, and thickness.

2.1.2 Mesh Generation

Previously, 24 geometries were iteratively developed to match (a) ex-vivo unloaded geometry, (b) end diastolic geometry as measured from echocardiography, and (c) clinical measures of end-diastolic function (EDP and EDV) as measured by *in utero* catheterization and echocardiography at mid gestation. In order to generate a clinically relevant mesh, the normal ranges for these data were compiled from literature.

Since obtaining data for unloaded geometry is not yet clinically feasible in-vivo, measurements from isolated, fixed human organ donor hearts were extrapolated. Arteaga-Martinez et al reported measurements of LV anteroposterior and lateral diameters, inflow and outflow tract lengths, and thickness of walls at different levels of 103 total hearts from 13 to 20 weeks' gestation [70]. End-diastolic LV short- and long-axis dimensions

from mid gestation to term were extracted from Z-score equations relative to estimated gestational age reported by McElhinney et al. The Z-scores were calculated based on unpublished fetal norms that were derived from data collected at Children's Hospital Boston between 2005 and 2007 on 232 normal fetuses [71]. End-diastolic LV pressures were extracted at mid gestation from a study by Johnson et al that directly measured pressures in 39 normal fetuses [72]. To obtain end-diastolic LV volumes from mid gestation to term, first LV stroke volumes were extracted from mid gestation to term from a study conducted by Kenny et al, in which Doppler echocardiography was used to quantify stroke volume in 52 normal fetuses [73]. Then, the EDVs were calculated at each gestational week as 30% more than the stroke volume.

The left ventricular measurements obtained were used to generate a FE mesh in a prolate spheroidal coordinate system as it is an ideal coordinate system for describing the ellipsoidal nature of the heart: a thick-walled truncated ellipsoidal shell bounded by inner and outer surfaces (Figure 2.2). The relationship between the rectangular Cartesian coordinate system and the prolate spheroidal coordinate system is given by:

$$Y1 = d \cosh \Lambda \cos M$$

$$Y2 = d \sinh \Lambda \sin M \cos \Theta$$

$$Y3 = d \sinh \Lambda \sin M \sin \Theta$$

where the focal length d is a parameter used for dimensional scaling of the mesh and is determined by:

$$d^2 = b^2 - a^2$$

where the major radius b is the distance between the origin and the apex along the x-axis and the minor radius a is the radius at the origin.

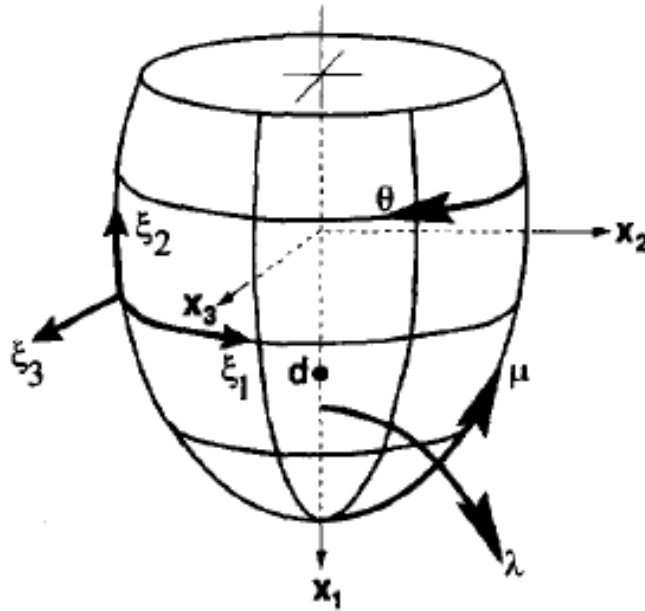


Figure 2.2: An ellipsoidal mesh in prolate spheroidal coordinate system (λ, μ, θ) and its relationship to rectangular Cartesian coordinate system (X_1, X_2, X_3).

Reprinted with permission from “Three-dimensional analysis of regional cardiac function: a model of rabbit ventricular anatomy” by F. J. Vetter and A. D. McCulloch, 1998, Progress in Biophysics and Molecular Biology [36].

The initial FE mesh developed in Continuity consists of 8 nodes and 3 elements.

The nodal coordinate parameters of bicubic Hermite FE meshes for LV were fitted to a corresponding set of data points using the linear least-squares method. The resulting surface mesh was refined by Hermite interpolation of coordinates to generate a mesh of 30 nodes and 20 elements representing the end-diastolic geometry at 22 weeks gestation. The 24 generated meshes were then put through the pipeline described earlier in Chapter 2.1.1.

2.1.3 Material Properties

Prior to inflating the meshes to the EDP, the material properties of the LV myocardium were determined. The material properties for the model consisted of passive

properties only and described by a strain energy law W , assumed to be transversely isotropic and slightly compressible [74, 75]:

$$W = \frac{1}{2} C_{pas} * (e^Q - 1) + C_{comp} (\det(\mathbf{F}) - 1) \ln(\det(\mathbf{F})) / 2$$

where $\mathbf{F}$ is the deformation gradient tensor and

$$Q = b_f E_{ff}^2 + b_c (E_{cc}^2 + E_{rr}^2 + 2E_{cr}^2) + b_{fr} (2E_{fc}^2 + 2E_{fr}^2)$$

E_{ff} is the strain in the fiber direction, E_{rr} is transmural radial strain transverse to the fiber, E_{cc} is cross-fiber strain perpendicular to the former two, and the remaining are associated shear strains. C_{pas} , C_{comp} , b_f , b_c , and b_{fr} are material parameters, which were obtained from Omens et al [76]. With these material parameters set, the meshes were inflated from an unloaded state to a deformed state.

Table 2.1: Passive material properties of the LV growth model

Coefficient	Description	Value
C_{pas} [kPa]	Passive stress scaling constant	0.33
b_f	Fiber strain coefficient	9.2
b_c	Cross-fiber strain coefficient	2.0
b_{fr}	Shear-strain coefficient	3.7
C_{comp}	Bulk modulus	350

2.1.4 Growth Law

The inflated mesh was then set to grow from mid gestation to birth at a constant EDP with the parameters listed in Table 2.2. Our group previously developed a strain-based volumetric growth model that deforms the stress-free tissue configuration B_0 to a

grown configuration B_g , which may not be stress-free; the methods are detailed in [63]. Briefly, the growth model is based on a multiplicative decomposition of the deformation gradient F :

$$F = F_e \cdot F_g$$

The growth deformation gradient F_g applies between B_0 and an intermediate configuration B'_g . The latter is a stress-free growth state where local kinematic compatibility conditions do not apply. The deformation gradient F_e describes the elastic deformation between B'_g and B_g and the Cauchy stress in the tissue is only dependent on this. F_g , on the other hand, describes plastic deformation. Volumetric growth is linearly related to biomechanical stimuli, which are derived from a difference in fiber and cross-fiber strain with fixed values. The deformation gradient tensors are defined with respect to the local fiber orientation (with component F_{ff} in the fiber direction, F_{cc} in cross-fiber direction parallel to the wall, and F_{rr} the radial component perpendicular to the two former). This allows for the definition of a transversely isotropic growth tensor. The cumulative growth deformation gradient tensor $F_{(n)g}$ is updated each growth step with the incremental deformation gradient tensor $F_{g,i}$. $F_{g,i,ff}$ describes incremental growth in the fiber direction due to addition of sarcomeres in series whereas $F_{g,i,cc}$ and $F_{g,i,rr}$ describe growth due to sarcomere addition in parallel. β_l and β_t are growth rate constants in fiber and cross-fiber direction respectively and Δt is the time step. The homeostatic set points for fiber and cross-fiber strains ($E_{ff,set}$, $E_{cc,set}$) are chosen to be 0 with the assumption that hemodynamic load is low in the fetal heart, which would lead to approximately zero average strains with respect to the unloaded reference state [63].

Table 2.2: Growth parameters of the LV model

Coefficient	Description	Value
$E_{ff,set}$	Homeostatic set point for fiber strains	0.0
$E_{cc,set}$	Homeostatic set point for cross-fiber strains	0.0
β_l	Growth rate constant in fiber direction	0.0008
β_t	Growth rate constant in cross fiber direction	0.00026667

2.1.5 Statistical Analysis using Z-scores

With the 24 models developed, a statistical analysis was conducted in order to determine the best-fit geometry satisfying all of the aforementioned criteria. The previously described experimental and clinical data was used to calculate mean values and standard deviation for normal fetal LV dimensions (short axis; long axis; and, when applicable, an average of wall thickness at the base, mid, and apex level) and EDV from mid gestation to term. EDP mean value and standard deviation were calculated at mid gestation and assumed to remain constant throughout gestation. The same dimensions and measures of function were extracted for each of the 24 developed LV geometries referred henceforth as Models 1-24. For geometries developed prior to Model 19, the inner diameter was obtained from the base level. For Model 19 and consequent geometries, the inner diameter was extracted from the more clinically relevant level corresponding to our geometry: the level between the base and mid, referred here as “next to base”. The length was derived from the base to apex level. Wall thickness was computed as an average of the thickness at the base, next to base, mid and apex levels for all unloaded geometries.

End diastolic volume was a direct output from Continuity based on the origin of the mesh.

For the 24 geometries, Z-scores were computed comparing LV dimensions and measures of end diastolic function for the unloaded and loaded state at mid gestation to determine the magnitude of deviation from the measured mean. A Z-score is defined as

$$Zscore = \frac{x - \mu}{\sigma}$$

where x is the observed measurement, μ is the expected measurement (experimental mean) and σ is the standard deviation of the population [77]. Z-scores above the population mean have a positive value and those below the population mean have a negative value. While the sign indicates direction of deviation from the mean, the Z-score value conveys magnitude of deviation, which is of more interest for the statistical analyses in this study. Hence, absolute Z-scores were used in calculations whereas plots were based on the raw Z-score values.

With all criteria weighted equally, the LV geometries of the fetal heart with the cumulative minimum Z-score that best fit the described data for geometric and functional measures at mid gestation were identified as the starting reference models for normal human fetal growth. Finally, LV short- and long-axis dimension data were extracted for each of the reference models from mid gestation to birth. Of these, the reference model that best predicted shape for the entire gestational period, as scored using least Z-scores, was identified as the working reference model for normal human fetal growth for the remainder of this study.

2.2 Results

2.2.1 Z-score Analysis for Model Selection

Unloaded (mid gestation)

The normal reference ranges for fetal LV dimensions at mid gestation, as extracted from ex-vivo experimental data is shown in Table 2.3.

Table 2.3: Mid gestational fetal LV dimensions at an unloaded state, as reported in literature [70]

Dimension	Experimental Mean [mm]	Std Deviation	Lower Limit [mm]	Upper Limit [mm]
Inner Diameter	6.184	0.681	5.503	6.866
Length	15.560	1.510	14.051	17.07
Wall Thickness	2.519	0.129	2.39	2.648

The Z-score distribution of LV dimensions extracted from each of the 24 geometries in an unloaded state at mid gestation are shown in Figures 2.3-2.5. For all plots, red squares represent the experimental mean derived from literature and white diamonds represent the geometries, for which larger size of diamonds represent multiple geometries that overlap in their dimensions.

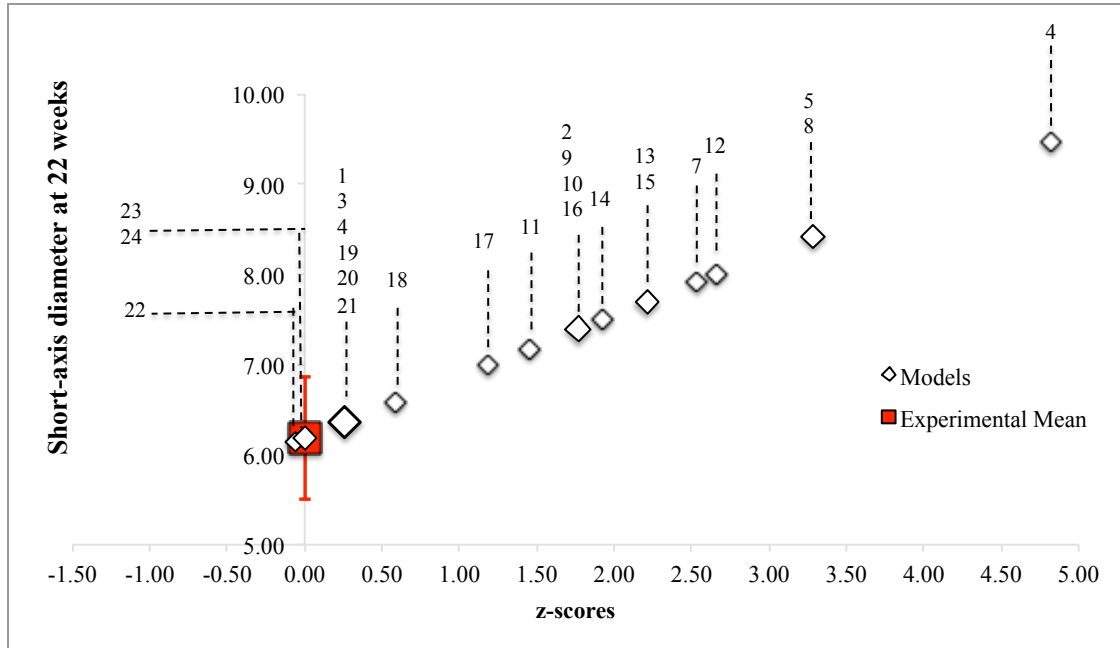


Figure 2.3: Z-score distribution of fetal LV inner diameter at an unloaded state.

The 24 model geometries are presented by white diamonds and compared to the experimental mean, represented by the red square, which has a normalized Z-score of 0.

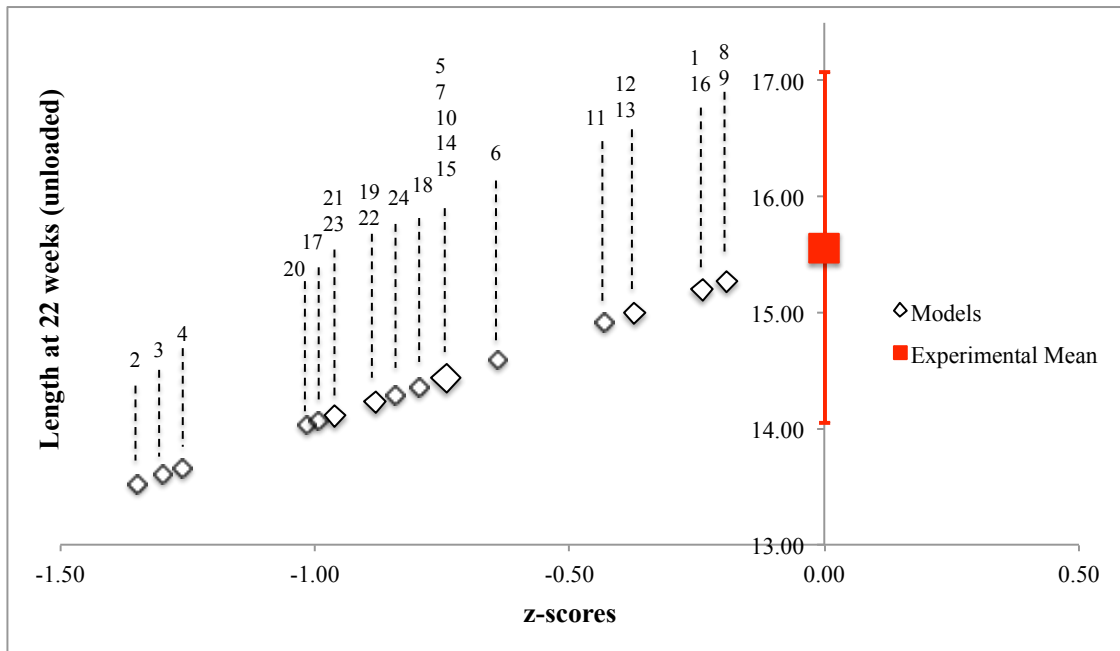


Figure 2.4: Z-score distribution of fetal LV inner length at an unloaded state.

The 24 model geometries are presented by white diamonds and compared to the experimental mean, represented by the red square, which has a normalized Z-score of 0.

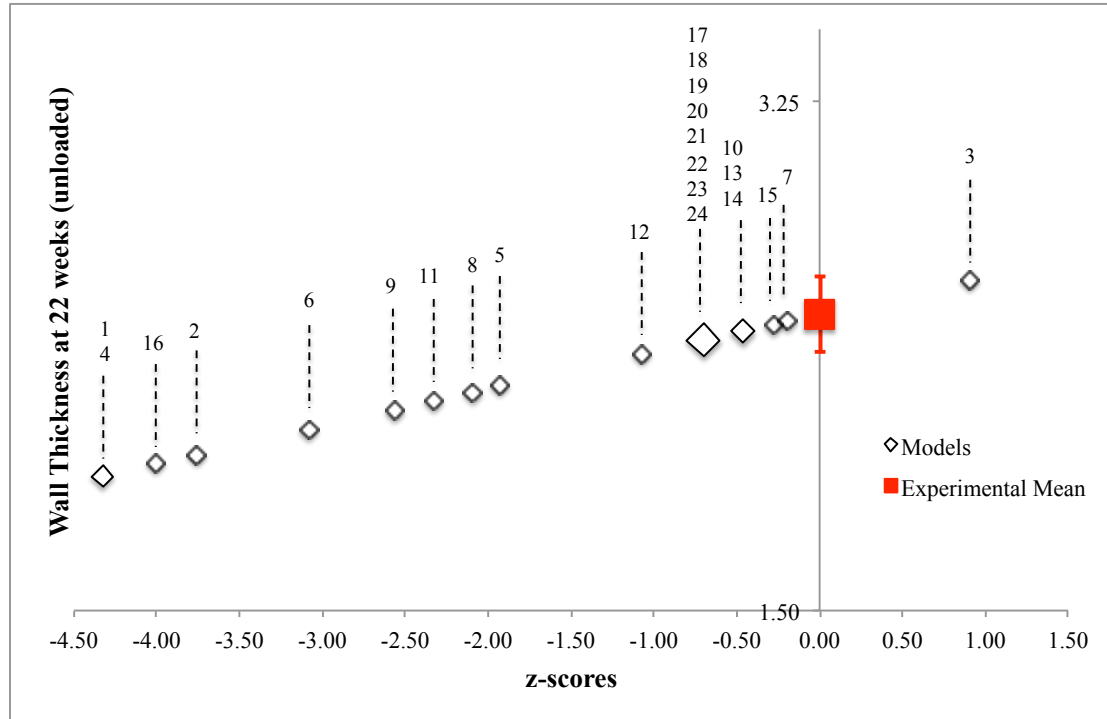


Figure 2.5: Z-score distribution of fetal LV average wall thickness at an unloaded state.

The 24 model geometries are presented by white diamonds and compared to the experimental mean, represented by the red square, which has a normalized Z-score of 0.

Loaded (mid gestation)

The normal reference ranges for fetal LV dimensions at mid gestation in a loaded state, as reported in literature, are listed in Table 2.4. The Z-score distribution of the dimensions extracted from each model are shown in Figures 2.6-2.7.

Table 2.4 Mid gestational fetal LV echocardiographic dimensions at a loaded state, as reported in literature [71]

Dimension	Experimental Mean [mm]	Std Deviation	Lower Limit [mm]	Upper Limit [mm]
Inner Diameter	7.959	1.095	6.864	9.053
Length	15.460	1.840	13.620	17.300

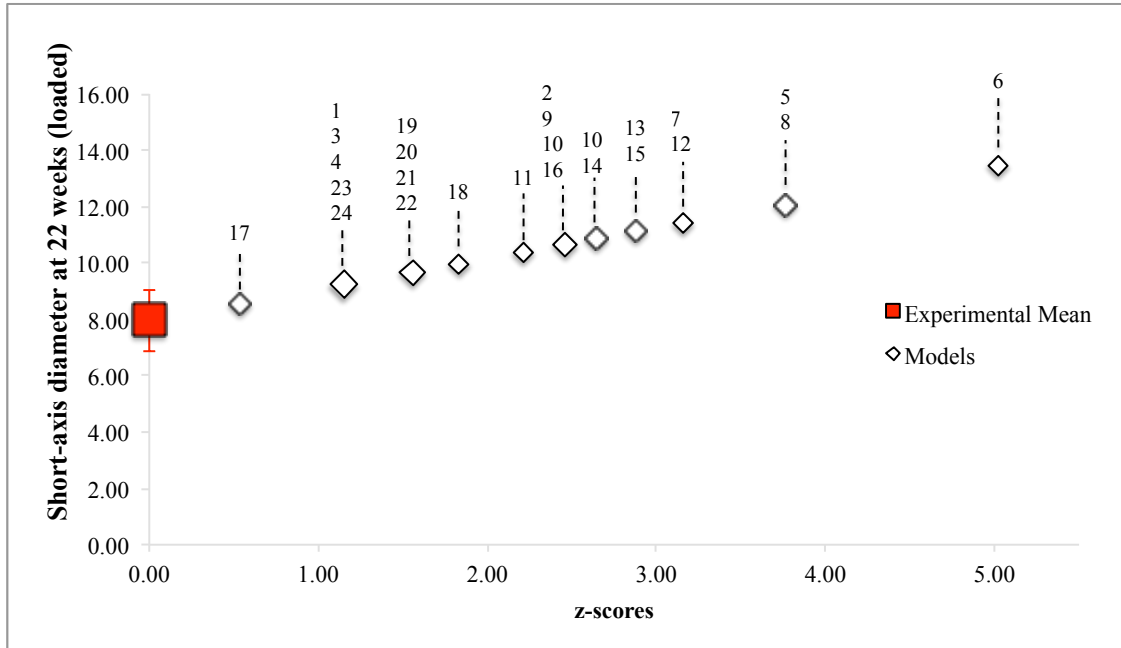


Figure 2.6: Z-score distribution of fetal LV inner diameter at a loaded state.

The 24 model geometries are presented by white diamonds and compared to the experimental mean, represented by the red square, which has a normalized Z-score of 0.

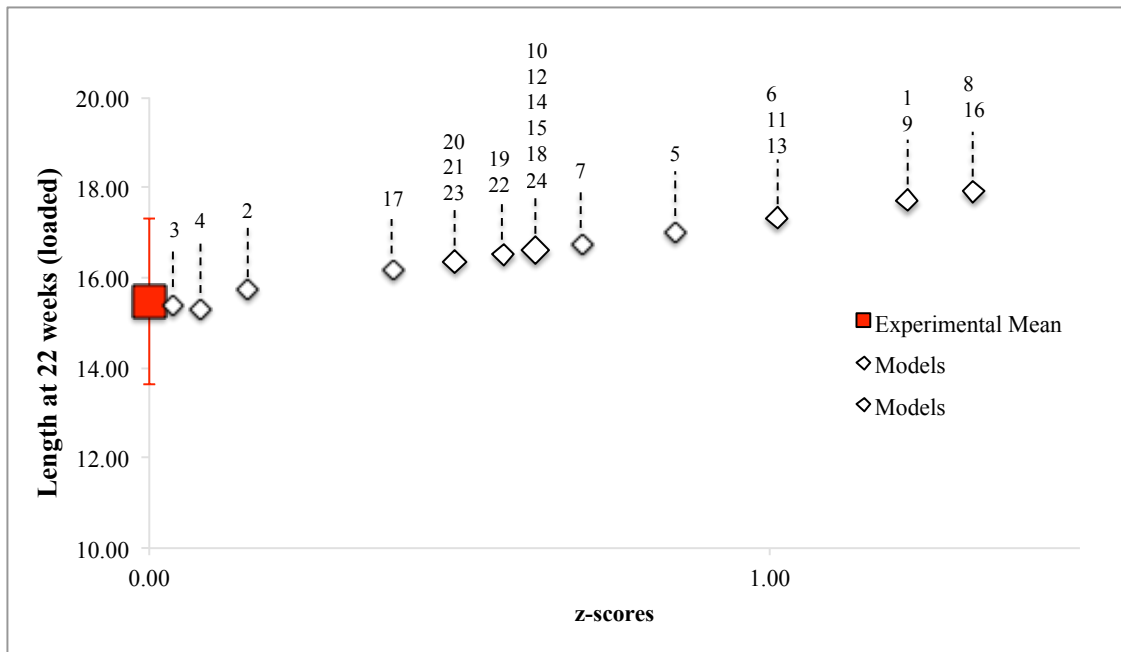


Figure 2.7: Z-score distribution of fetal LV inner length at a loaded state.

The 24 model geometries are presented by white diamonds and compared to the experimental mean, represented by the red square, which has a normalized Z-score of 0.

Growth (mid gestation to term)

Table 2.5 lists the Z-scores for LV dimensions (SA: short-axis; LA: long-axis, WT: wall thickness) and measures of end-diastolic function (EDV, EDP) at 22 weeks prior to applying the growth law, as well as Z-scores for LV dimensions from 22 to 40 weeks post-growth. The cumulative Z-scores of the models for combined pre- and post growth criteria are listed in Table 2.6.

Table 2.5: Compiled Z-score distribution of model geometries pre- and post-growth

	Pre-Growth (22 weeks)							Post-Growth (22-40 wks)	
Model	Unloaded Dims			Loaded Dims		EDV	EDP	Dimensions	
	SA	LA	WT	SA	LA			SA	LA
1	0.26	0.24	4.08	1.15	1.13	1.62	1.09	5.55	5.88
2	1.77	1.35	3.55	2.46	0.16	0.75	1.09	24.35	10.72
3	0.28	1.30	1.40	1.28	0.04	1.95	1.09	20.24	18.52
4	0.28	1.26	5.05	1.33	0.08	1.94	1.09	8.90	21.87
5	3.28	0.74	1.27	3.77	0.85	1.25	1.09	44.51	12.29
6	4.83	0.64	2.91	5.02	0.99	2.25	1.09	67.86	5.60
7	2.53	0.74	2.04	3.16	0.70	0.40	1.09	32.38	6.80
8	3.24	0.19	1.43	3.71	1.38	1.66	1.09	43.98	9.39
9	1.74	0.19	1.84	2.44	1.22	0.20	1.09	22.56	8.51
10	1.78	0.74	0.10	2.52	0.63	0.46	1.09	21.76	9.81
11	1.46	0.43	2.03	2.21	0.95	0.63	1.09	18.48	5.32
12	2.67	0.37	0.81	3.25	0.63	0.55	1.09	34.72	9.71
13	2.21	0.38	0.21	2.88	1.01	0.11	1.09	27.73	9.56
14	1.93	0.74	0.06	2.65	0.64	0.32	1.09	23.87	9.31
15	2.22	0.74	1.94	2.90	0.68	0.09	1.09	28.16	8.57
16	1.74	0.24	3.76	2.41	1.33	0.02	1.09	23.92	5.24
17	1.18	0.99	0.28	0.53	0.39	0.72	0.74	14.99	9.73
18	0.59	0.79	0.30	1.83	0.67	0.71	0.74	7.11	8.19
19	0.29	0.88	0.39	1.57	0.57	0.80	0.74	12.37	4.21
20	0.29	1.02	0.33	1.58	0.44	1.05	0.74	6.95	8.69
21	0.29	0.96	0.38	1.56	0.49	1.06	0.74	8.41	6.68
22	0.06	0.88	0.36	1.55	0.57	1.03	0.74	9.40	5.11
23	0.00	0.96	0.38	1.32	0.49	0.97	0.74	5.44	6.71
24	0.00	0.84	0.42	1.30	0.62	0.95	0.74	5.29	5.25

Table 2.6: Cumulative Z-scores for the model geometries

The model with the minimum cumulative Z-score, highlighted in bold, represents the selected model geometry for normal human fetal growth

Model	Cumulative Z-score		
	Pre-Growth	Post-Growth	TOTAL
1	9.57	11.43	21.01
2	11.12	35.07	46.19
3	7.33	38.76	46.09
4	11.03	30.77	41.80
5	12.24	56.81	69.05
6	17.72	73.46	91.18
7	10.65	39.18	49.83
8	12.70	53.37	66.07
9	8.71	31.07	39.78
10	7.32	31.57	38.89
11	8.80	23.80	32.59
12	9.37	44.42	53.79
13	7.88	37.29	45.17
14	7.42	33.17	40.60
15	9.67	36.73	46.40
16	11.47	29.16	40.63
17	4.84	24.72	29.56
18	5.63	15.29	20.93
19	5.24	16.58	21.82
20	5.46	15.63	21.09
21	5.47	15.09	20.56
22	5.19	14.51	19.71
23	4.87	12.16	17.03
24	4.87	10.55	15.41

With all criteria weighed equally, Models 23 and 24 have the lowest cumulative Z-score of 4.87, but the latter model is the best predictor of shape from mid gestation to term and therefore yields the absolute minimum cumulative Z-score, making it the working model for normal fetal LV growth for this study.

2.2.2 Model for Normal Human Fetal LV Growth

Using the method of cumulative minimum Z-scores, Model 24 was chosen as the working reference model for normal growth in the human fetal left ventricle. The refined FE mesh at mid gestation is shown in Figure 2.8 followed by the normal pressure-volume inflation curve. Normal growth is quantified from mid gestation to term and classified as volumetric and shape growth of the LV cavity and wall.

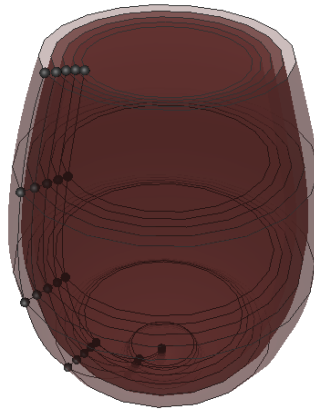


Figure 2.8: Refined mesh of Model 24, the working reference model for normal human fetal LV growth.

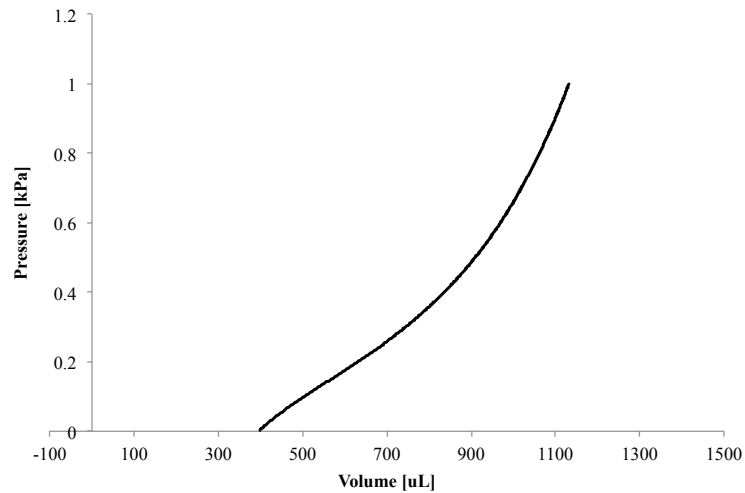


Figure 2.9: Inflation curve describing the normal pressure-volume relations at mid gestation in a human fetal LV.

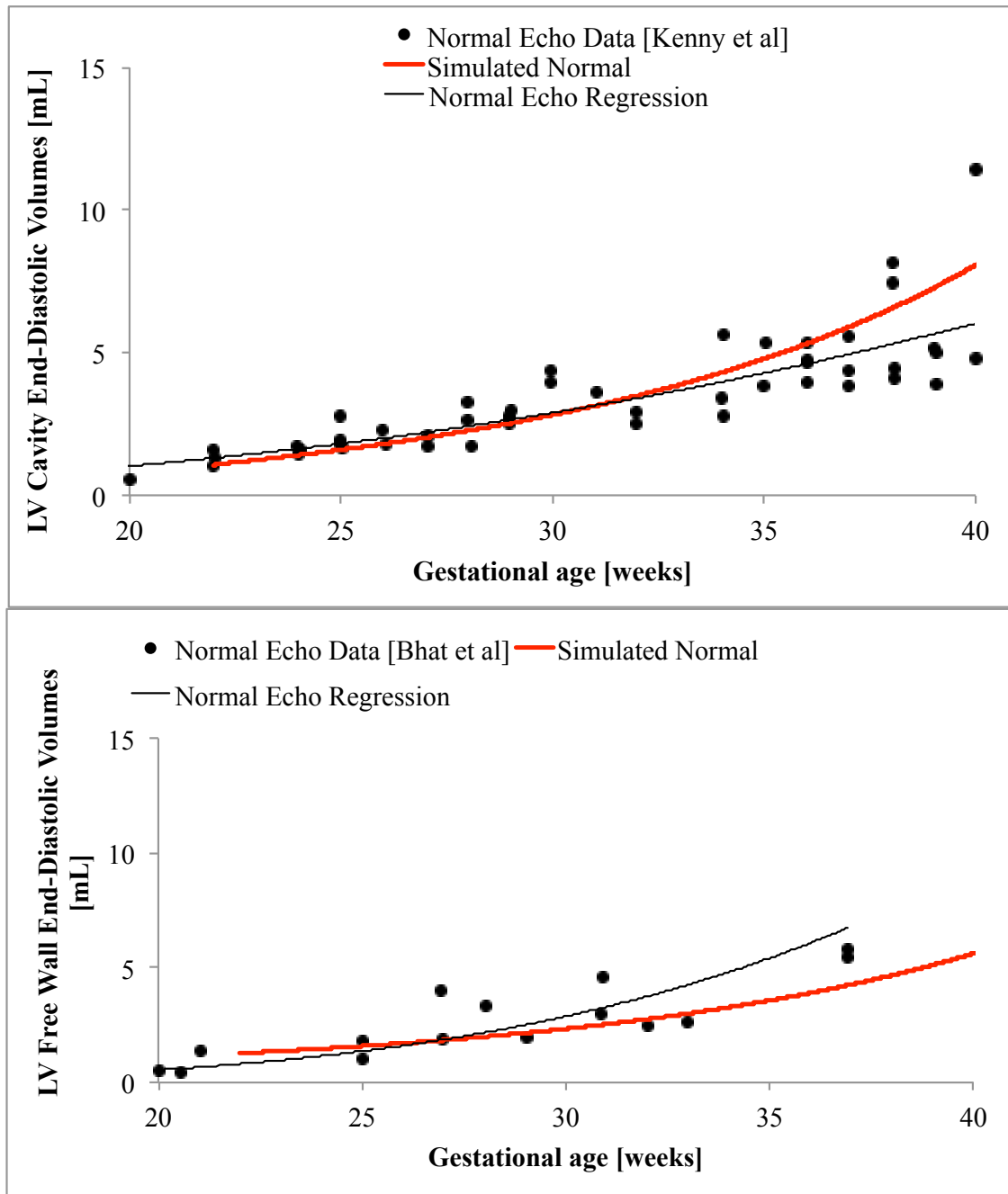


Figure 2.10: Simulated normal volumetric growth in the fetal LV cavity (top) and free wall (bottom) from mid gestation to birth.

Simulated growth is compared to normal echocardiographic data derived from [73, 90]

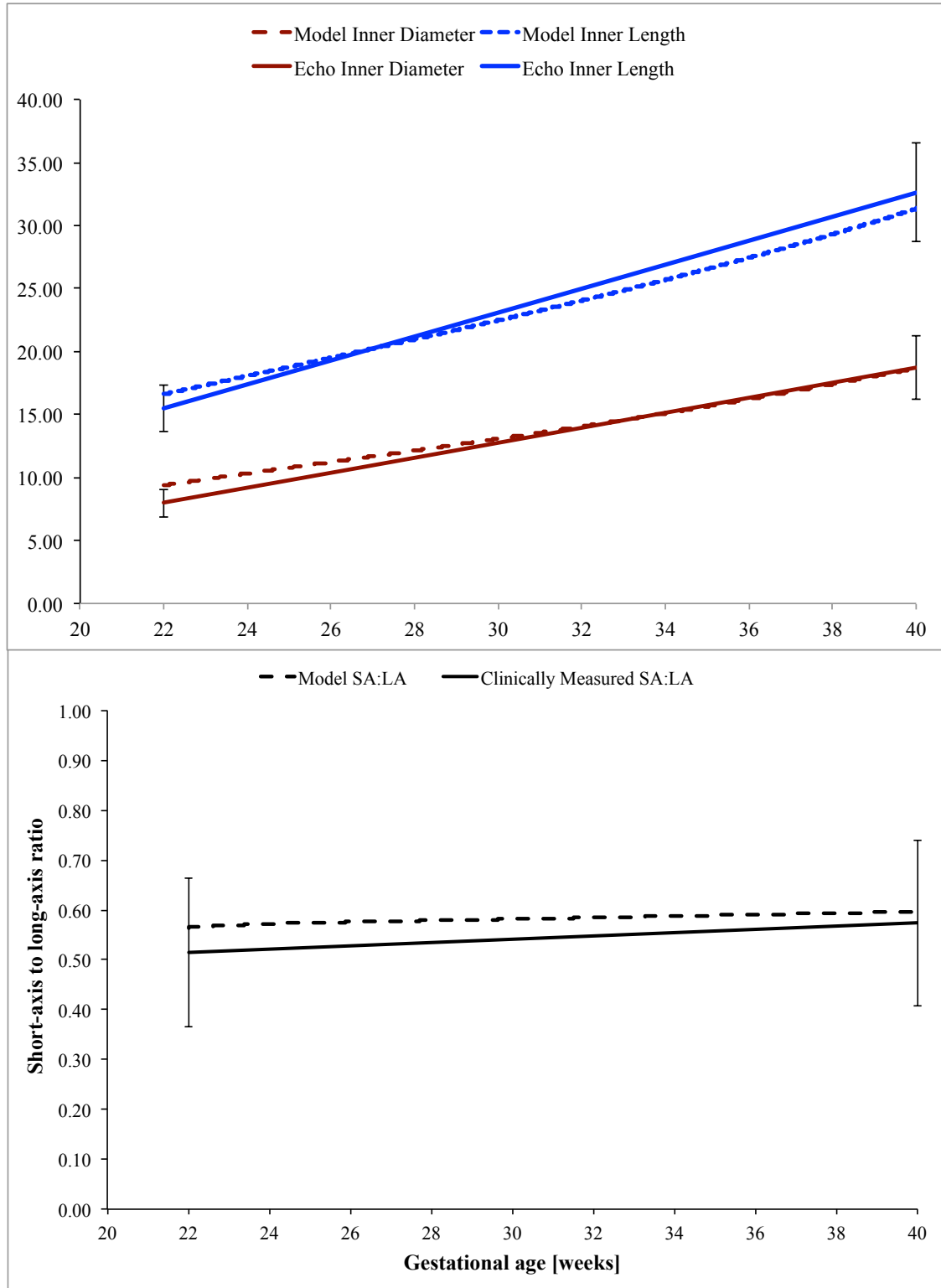


Figure 2.11: Simulated normal shape growth in the fetal LV cavity from mid gestation to birth. Simulated growth is compared to echocardiographic measurements of short- and long-axis dimensions (top) along with their ratio (bottom) [71].

2.3 Discussion

The goal of the statistical analysis was to identify the model that best satisfied experimental and clinical data for normal fetal LV dimensions and end-diastolic measures of function at mid gestation and best predicted shape growth from mid gestation to birth. The selected model would then serve as the working reference model for normal growth in the human fetal LV.

2.3.1 Statistical Analysis using Z-scores

Model 24 was chosen as the best-fit geometry, serving as the reference model for normal fetal LV growth based on a scoring method of least Z-scores. Another method commonly used is sum of absolute errors, which is calculated as the sum of the absolute values of the residuals between the observed and expected mean values. However, the method of Z-scores was preferred in this study because the equation takes into consideration the sample size of the varying data sets that were used to extract LV dimensions and measures of end diastolic function.

Z-scores are commonly used and have major advantages for the presentation of data in various scientific fields [77-80]. However, they remain an imperfect approximation and the drawbacks are important to note. First, Z-scores are based on the mean and standard deviation of experimental data, which are only estimates of values that vary widely within the population. Second, to have statistical confidence in the experimental mean requires an extremely large sample size, particularly with studies conducted on human patients due to the heterogeneity presented patient to patient. Not all

the datasets used had a large sample size, especially at a specific time point. For instance, the Johnson study reported intracardiac pressure measurements from 39 normal fetuses during 20 to 40 weeks gestation [72]. However, for this study, only the data from mid gestation (22 weeks) was of interest, which had a sample size of 4 fetuses. Inappropriate averaging of data across insufficient numbers of patients that may not adequately represent the variance in the normal population can lead to under- or overestimation of Z-scores. Thirdly, as with any manual measurements, a degree of variability is unavoidable and may lead to Z-scores that incorrectly amplify errors in measurements [77]. Another criticism of presenting data in the form of Z-scores is that resetting to a common metric may lead to loss of the meaningful nature of raw data. However, this was accounted for in this study by presenting the Z-score distribution along with its corresponding raw data point as extracted from literature and the 24 models.

Developing the fetal LV growth model involves a three-stage process of refining the unloaded mesh to fit experimental data, inflating the mesh to a prescribed preload at mid gestation, and then growing the inflated model from mid gestation to term. This process has a sequential nature of methods, requiring optimization of the geometry at each stage and therefore allowing elimination of geometries after a given stage. However, it was of interest to conduct an unbiased statistical test of all 24 geometries without taking the sequential nature of the workflow into account during the analyses. Z-scores were computed for all geometries at each stage to get a comprehensive overview of the developed geometries from mid gestation to term. In addition, the selection criteria for this study were all weighed equally; i.e. the selected geometry was required to best-fit experimental and clinical data for unloaded geometry, end-diastolic geometry and clinical

measures of function at end-diastole. However, there may be interest in weighing the criteria differently or in investigating which parameters growth is most sensitive to at any given stage. For this reason, Z-scores were reported at each stage and an elimination process was not chosen to present the data.

Lastly, it is important to emphasize that the 24 geometries were developed in an iterative process, learning from the previous geometry. This serves as explanation for why the later geometries better fit the experimental and clinical data, as specific features of the model became intelligible over time. One such example is with the measurement of the short-axis dimension. Clinically and experimentally, the LVEDD is measured at the plane below the mitral valve. This measurement was thought to correspond to the base plane of our LV geometry so for geometries developed prior to Model 19, the inner diameter was obtained from the base level. For Model 19 and consequent geometries, the inner diameter was extracted from the more clinically relevant level corresponding to our geometry: the level between the base and mid, referred here as “next to base”. Similarly, the normal preload applied to the models was adjusted after the development of Model 20, prior to which the geometries were inflated at a comparatively lower preload (600 Pa). 0.75 kPa was chosen as the normal preload at mid gestation for the consequent geometries based on the pressure measurements presented in the study by Johnson et al [72]. While this iterative learning process may have affected the development of the 24 geometries, conducting a statistical analysis and disregarding the sequence of the methods used to develop the geometries addressed this bias and led to the selection of the best fit geometry that satisfied all of the selected criteria for a normal fetal LV model, and henceforth the working model for the remainder of this study.

2.3.2 Model for Normal Human Fetal LV Growth

The single ventricle fetal growth model presented here has several limitations worth noting. The fetal growth model was approximated with a truncated ellipsoid without the RV and, hence, circulation. This is a simplified, idealized geometry that fails to take into account the loading on the septum from the RV, which would affect fiber and cross-fiber strains. Hence, the results presented here represent LV free wall growth rather than septal growth. This simplification of geometry may explain discrepancies in LV short- to long-axis ratio measurements between simulation and experiment.

In the current model, the growth law developed by Kerckhoffs assumes that end-diastolic fiber strains serve as the growth stimulus based on a previously proposed hypothesis [48, 61, 82, 90]. Volumetric growth is linearly related to biomechanical stimuli, derived from an imbalance in fiber and cross-fiber strains. However, cardiac hypertrophy and remodeling can also be triggered by neurohormonal factors and their downstream signaling pathways [91]. The model presented here only considers normal LV growth as a result of changes in biomechanical stimuli.

In the model, growth will continue indefinitely because the fiber and cross-fiber strains are not able to reach their zero set points due to the constant 0.75 kPa pressure that is prescribed. The fixed set point values in the model can be gradually increased to halt growth, as demonstrated by Kerckhoffs in [25]; however, in our study, fiber and cross-fiber strains are assumed to be zero because the hemodynamic load is low in the fetal heart, which would lead to approximately zero average strains. Another assumption is that the growth rate constants in fiber and cross-fiber direction remain constant throughout fetal growth. The model can be tuned further to match experimental and

clinical data by incorporating variable growth rates and passive material properties that change temporally and spatially within the ventricular wall.

CHAPTER 3

Growth Model Sensitivity

3.1 Methods

With any complex systems consisting of multiple variables, it can be informative to perform a sensitivity analysis, whereby the levels of key parameters are adjusted systematically in order to quantitatively measure the impact that different parameters have on outcomes of the system as well as to understand the interaction behavior between the variables. Greater understanding of the sensitivity of a computational model to the input parameters is extremely valuable in improving the predictive capacity of the model. This is especially useful when modeling a process as complex and responsive to stimuli as fetal ventricular growth. Computational models offer the ideal platform to conduct this type of analysis as they can overcome the shortcomings inherent to studying growth behavior in the fetus in-utero. The objective of this aim was to conduct a growth model sensitivity analysis to comprehensively test the role of specific model parameters in resulting volumetric and shape growth of the normal fetal LV at birth.

3.1.1 Study Design

The parameters that were of interest in this study and their clinical significance are listed in Table 3.1. Using the values of these parameters from the normal growth model as reference points, several cases were designed to isolate the impact of one or multiple variables.

Table 3.1: Input parameters of interest in the study of growth model sensitivity

Input Parameter	Description/Clinical Significance
V_0	Initial Unloaded Volume
EDV- V_0	Ventricular filling
EDP	Preload
Cpass (wall stiffness)	Ventricular wall material properties
WT	Average Wall Thickness
Short- to long-axis ratio (SA:LA)	Cavity Shape

Each case was purposefully designed to target the effect of one variable while keeping all others same as the normal model when applicable. However, the nature of the growth model requires that multiple variables are interdependent, making it difficult to discern the effect of a single variable on growth. For instance, with all other parameters held constant, ventricular filling cannot be varied in a model without inducing a change in preload. For this reason, a different model must be developed introducing a third variable that is independent of the other two, which then allows us to keep either ventricular filling or preload constant in the initial case. For cases with co-variables such as these, multiple cases were designed to isolate the effect of the single variable. Within

each case, the target variable was varied across a range of values centered about the normal reference value. The cases along with their target variable(s) and associated co-variable(s) are listed in Table 3.2. By taking a logical approach in the case design, we were able to generate linear regression equations describing the effect of a single parameter on volumetric and shape growth relative to the normal model. The outputs of interest for each case were the percentage growth of LV cavity and wall volume, cavity shape, and average wall thickness relative to normal growth from mid gestation to birth.

Table 3.2: Overview of cases designed to discern the effect of the target variable on growth

Case Number	Target Variable(s)	Co-Variable(s)
1-3	EDV- V_o , EDP	Cpass
4A-B	EDV- V_o , EDP	None
6A	SA:LA	V_o , EDV- V_o , EDP
6B	SA:LA, WT	None
7A-L	Cpass (asymmetric)	V_o , EDV- V_o , EDP

Since the effect on growth was of interest in this study, four growth parameters were considered: LV cavity volume, wall volume, cavity shape, and wall thickness. Briefly, the change in volumetric and shape growth from mid gestation to birth was calculated as %Growth. Then the effect of each input parameter on these growth outputs was represented as $d(\%Growth)/d(\text{Target Variable})$ derived from linear regression equations where $x = \%$ change in the Target Variable and $y = \%Growth$, both relative to normal. This output parameter can be used to make conclusions about the relative contribution of a given parameter towards growth. For every unit of increase in x , y

changes by the output parameter dy/dx , hence implication that a relatively higher magnitude $d(\% \text{Growth})/d(\text{Target Variable})$ indicates greater contribution of that variable towards growth.

3.1.2 Growth Model Sensitivity Analysis

The cases listed in Table 3.2 will be presented here in two sections: one, in which the models within the cases are of same initial, unloaded volume equivalent to that of the normal fetal LV model; and the other, in which the unloaded volume varies.

Overview of Cases with V_o = same

Cases 1-3

Cases 1, 2, and 3 were designed to isolate the effect that ventricular filling and preload have on growth. In Case 1, the normal unloaded mesh was inflated to 1kPa and then the growth law was applied at varying preloads. Since the unloaded volume is constant, these growth models exhibit varying ventricular filling ($EDV - V_o$). In this case, two parameters, preload and ventricular filling, are changing making it difficult to make conclusions about their individual contribution to growth. For this reason, a third variable C_{pass} , the stress-scaling coefficient, is introduced in Cases 2 and 3 as it can be independently varied without affecting the other two parameters. This also allows us to keep ventricular filling constant in Case 2 while preload varies, and vice versa in Case 3. Because in both cases C_{pass} is varied in the same degree relative to normal, we are able to discern the individual contribution of preload on growth by comparing cases 1 and 2, and the impact of ventricular filling by comparing Cases 1 and 3.

The resulting inflation curves and volumetric cavity growth were plotted. Along with volumetric LV cavity growth, linear regression equations were generated for Cases 1 and 3 describing growth (relative to normal) in the other output variables: LV wall volume, cavity shape, and wall thickness, where growth is quantified as change in the output from 22 to 40 weeks. This procedure was repeated for Cases 1 and 2 with preload as the independent variable. These generated slopes can be used to make conclusions about the relative contribution of a given parameter, in this case ventricular filling and preload, towards growth. Briefly, the slope of a regression equation is a measure of both the direction and magnitude of the relationship between the independent and dependent variables. For every unit of increase in the independent variable, growth changes by the slope value, hence the implication that a relatively higher magnitude of slope indicates greater contribution of that independent variable towards growth. Of course, a positive slope value indicates positive correlation with growth and vice versa, and the strength of correlation is indicated by the R^2 value.

Case 6B

Case 6B was designed to quantify the effect of LV cavity shape on volumetric and shape growth by either changing short-axis to long-axis ratio or average wall thickness of the LV. To achieve this, four unloaded geometries were created with the same unloaded volume as the normal unloaded geometry. Two geometries were developed by changing the location of the epicardium nodes uniformly along the LV to yield a thick-walled LV (Thick; WT: +30%) and a thin-walled LV (Thin; WT: -30%) relative to normal. The other two were developed by manipulating the overall shape of the LV to yield

“TallNarrow” (SA:LA: -17%; WT: -10%) and “ShortWide” (SA:LA: +26%; WT: -5%) geometries, both of which had thin walls relative to the normal.

Case 7 (V_o = same)

Case 7 was designed to investigate whether increasing the stress scaling coefficient to induce ventricular wall stiffness asymmetrically rather than symmetrically, as in Cases 2 and 3, has an impact on fetal LV growth. The endocardial, mid-wall, and epicardial elements of the LV free wall normally exhibit a stress of 0.33 kPa. For this case, the stress scaling coefficient was increased to 1.00 kPa for the endo, mid, and epi elements individually, while the remaining elements exhibited normal wall stiffness. These meshes were grown from mid gestation to birth at (a) a constant preload of 0.75 kPa, and at (b) a constant ventricular filling of 430 μ L. Regression equations were generated for Case 7 (b) allowing us to compare LV volumetric and shape growth as a gradient of position in the LV free wall.

Overview of Cases with $V_o \neq$ same

Case 4

Case 4 was designed to discern the individual contribution of ventricular filling (4A) and preload (4B) to growth, as in Cases 1-3, but with an unloaded volume differing from that of the normal model. Within each case, five geometries with varying initial unloaded volumes were generated by changing the focus of the mesh, which induces a size change in the LV while maintaining the proportion (i.e. SA to LA ratio). While the short- and long axis dimensions and wall thickness are different from normal at mid gestation, the dimensions are the same between 4A and 4B, enabling us to compare the two models and derive conclusions about the target variables.

Case 6

Case 6 was designed to quantify the correlation between shape and growth by varying either the short- or long-axis dimensions in the initial unloaded mesh, resulting in four geometries with non-proportional changes in the ratio and therefore varying unloaded volumes. Two geometries were developed by decreasing or increasing the short-axis dimension relative to normal to yield a narrow (Narrow; SA: -32%) or wide (Wide; SA: +32%) LV, respectively. Decreasing or increasing the long-axis dimension relative to normal yielded another set of geometries with a LV short (Short; LA: -13%) or tall in length (Tall; LA: +10%), respectively. The four geometries were then inflated and grown at (a) a constant preload of 0.75 kPa, and at (b) a constant ventricular filling of 383 μL .

Case 7 ($V_o \neq \text{same}$)

As in Case 7 with unloaded volume held the same as normal, this case was designed to discern the individual contribution of asymmetric wall stiffness on growth. As before, the stress scaling coefficient was increased to 0.66 kPa and 1.00 kPa for the endo, mid, and epi elements individually, while the remaining exhibited normal wall stiffness, or in combination. These meshes were grown from mid gestation to birth at (a) a constant preload of 0.75 kPa, and at (b) a constant ventricular filling of 543 μL .

Using the generated regression equations, the percentage growth relative to normal was predicted given a 10% decrease for each parameter with the constraint that unloaded volume is same as normal. This was repeated for the cases where unloaded volume varies from that of the normal model.

3.2 Results of Growth Model Sensitivity Analysis

As in the methods, the results for the growth model sensitivity analysis presented here will be divided into two sections: one, in which the models within each case have the same initial, unloaded volume as that of the normal model; and another, in which the unloaded volume varies as its own independent parameter.

3.2.1 Overview of Cases with $V_o = \text{same}$

Cases 1-3

Table 3.3 shows the list of parameters for each case where the ones marked with ‘x’ represent the parameters with values varying from those in the normal model. Figures 3.1-3.3 describe the resulting inflation and LV cavity volumetric growth for each case. To reiterate, in these cases the individual effect of preload and ventricular filling on growth is isolated given three cases where a third variable, C_{pass} , is used to hold one of the two parameters constant.

Table 3.3: List of parameters within each case where those varying from normal are marked with ‘x’

Cases	V_o	EDP	EDV-V_o	C_{pass}
1		x	x	
2		x		x
3			x	x

In Case 1, the models grown at higher EDPs grow more in terms of LV cavity volume, which is clinically accurate as increase in ventricular preload dramatically

increases ventricular stroke volume by altering the force of contraction of the myocardium. The inflation curves for Cases 2 and 3 show that models with increased ventricular wall stiffness require higher pressures to reach the same EDV as more compliant LVs. When EDV- V_o is held constant as in Case 2, there is no observed difference in the growth between the differentially stiff LVs; however, this is not observed in Case 3 when EDP is held constant.

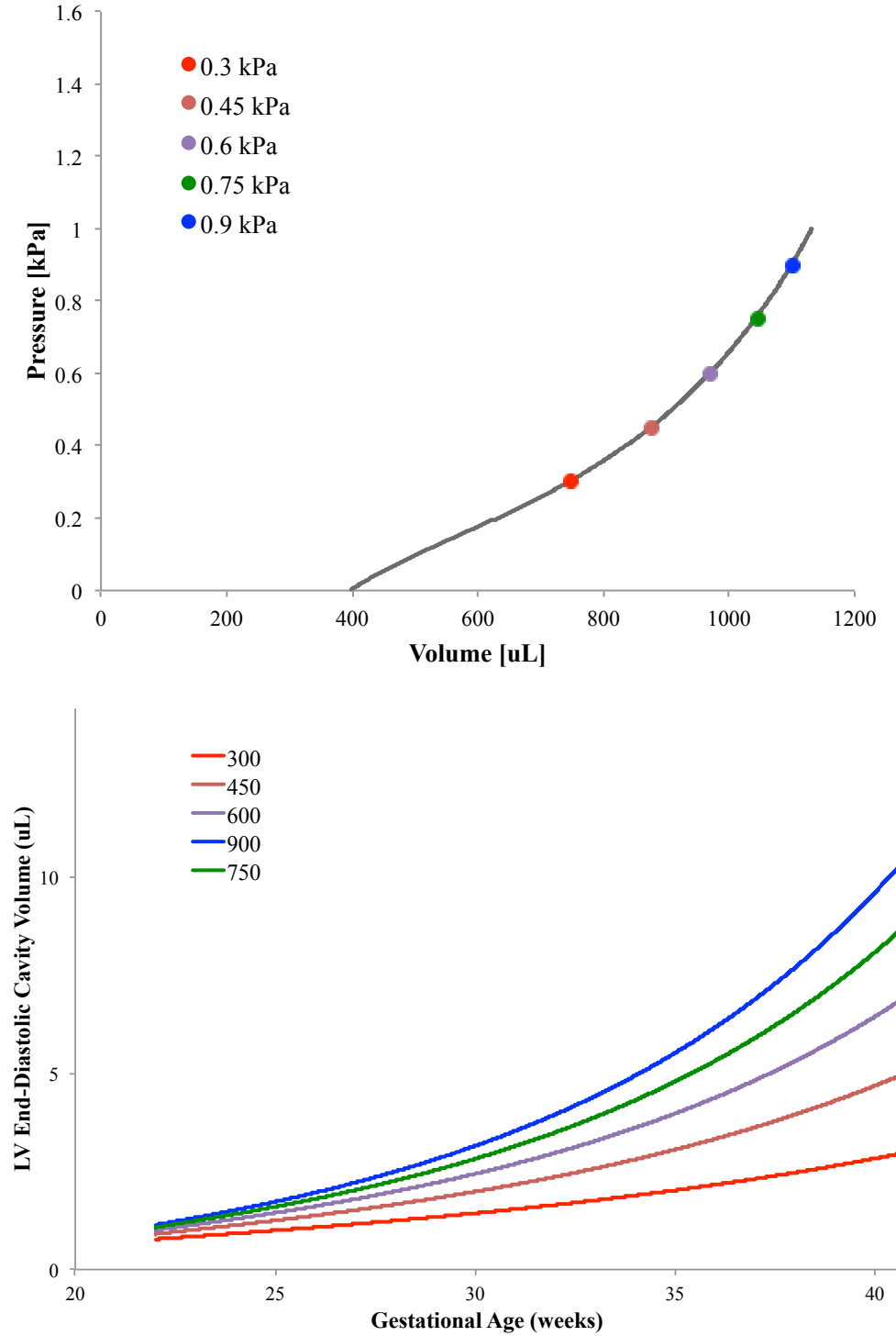


Figure 3.1: Case 1 Inflation Curve (top) and LV Cavity Volumetric growth (bottom).

The inflation curve displays the varying preloads at which the model was set to grow (normal preload: 0.75 kPa); the resulting volumetric growth curves from mid gestation to term are shown.

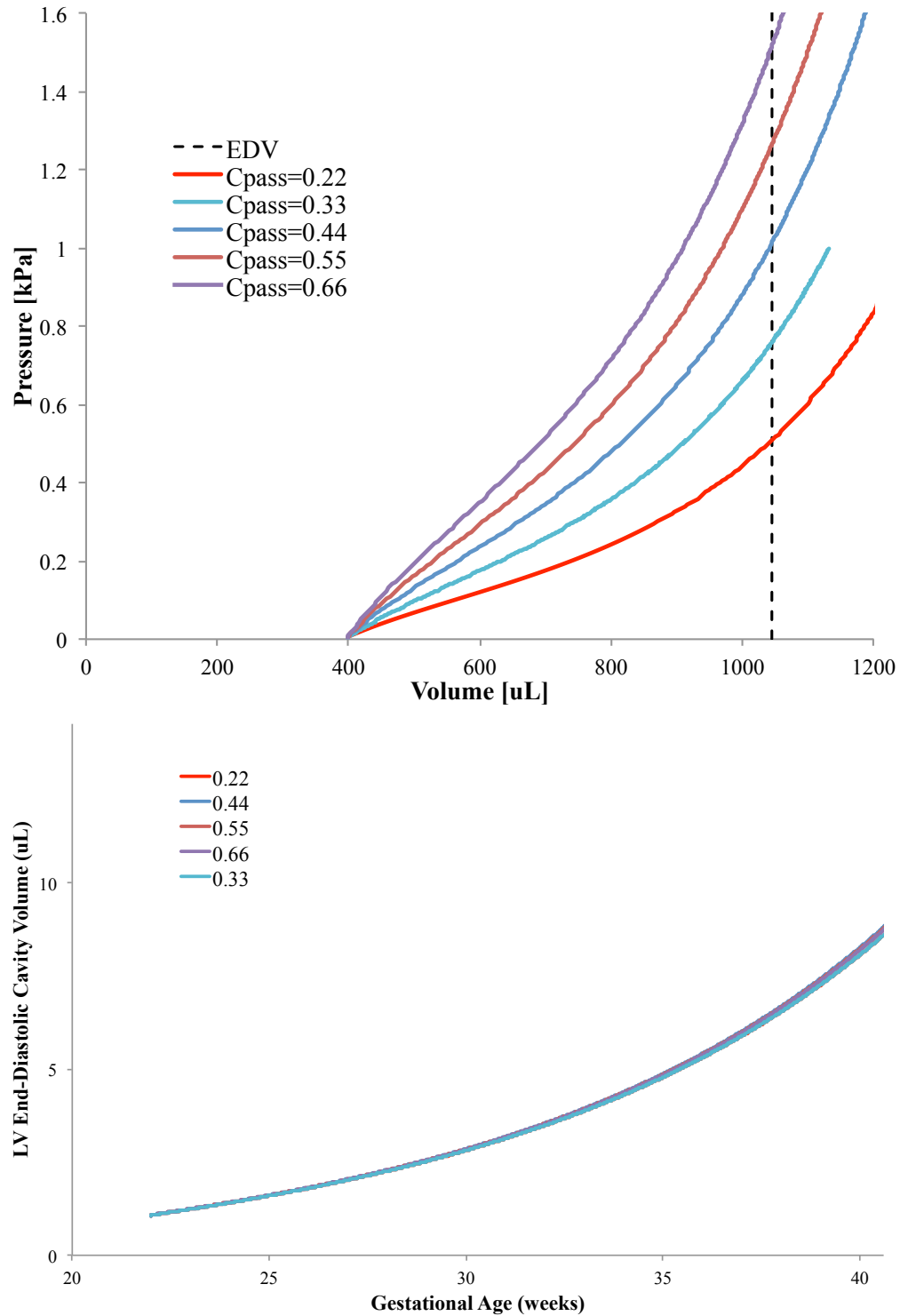


Figure 3.2: Case 2 Inflation Curve (top) and LV Cavity Volumetric growth (bottom).

The inflation curve displays the models of varying ventricular wall stiffness (normal Cpass: 0.33 kPa) inflated at same EDV-Vo; the resulting volumetric growth curves from mid gestation to term are shown.

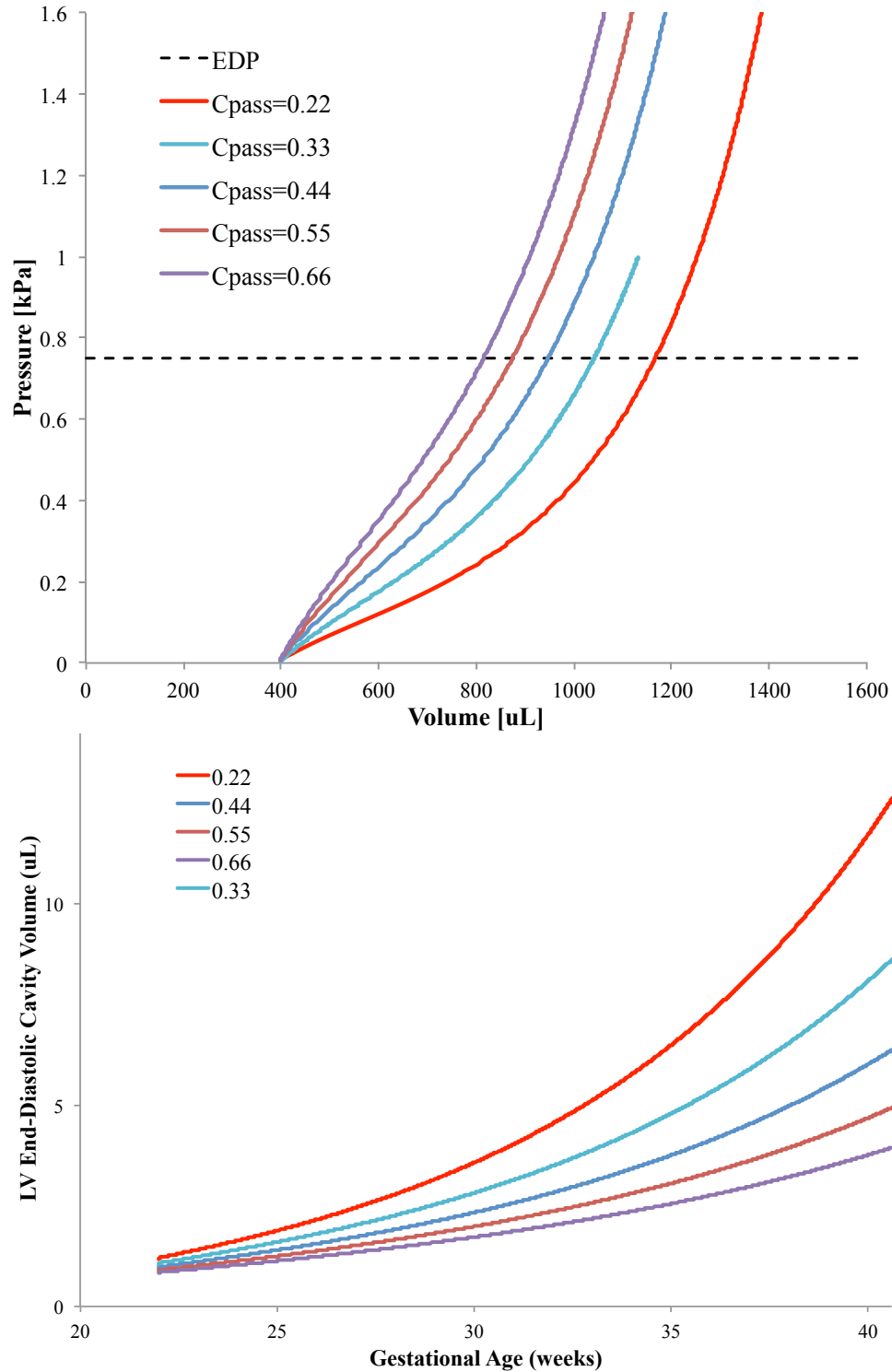


Figure 3.3: Case 3 Inflation Curve (top) and LV cavity volumetric growth (bottom)

The inflation curve displays the models of varying ventricular wall stiffness (normal Cpass: 0.33 kPa) inflated at same EDP; the resulting volumetric growth curves from mid gestation to term are shown.

Comparing growth as a result of percent change in a given parameter allows us to see if the observed growth behavior in these cases follows any particular trend. In Cases 1 and 3, this trend is clearly a linear regression with positive correlation with volumetric LV cavity growth.

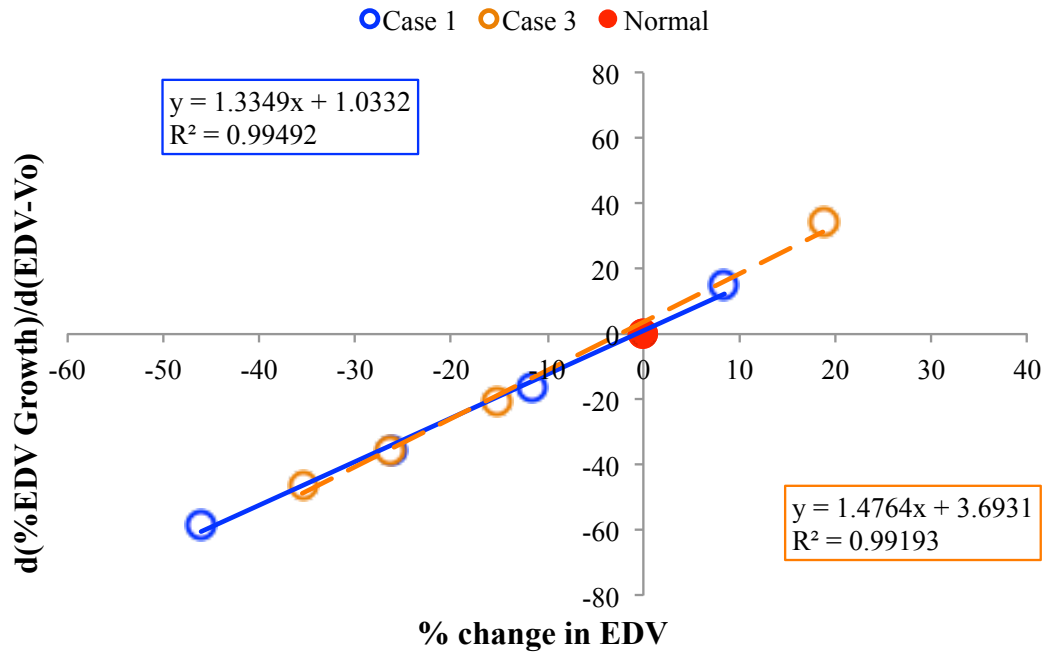


Figure 3.4: Linear regression lines fitted to the data in Cases 1 (open blue circles) and 3 (open orange circles)
High R^2 values indicate strong positive correlation between EDV-Vo and LV cavity volumetric growth relative to normal (red circle)

When comparing the growth behavior observed in Cases 1 and 2 (Table 3.4, Figure 3.5) with EDP as the independent variable, there are three possible outcomes regarding the correlation between preload and growth:

- (a) positive – this would imply that Cpass has an equal and opposite (i.e. negative) correlation with growth, and that ventricular filling has no correlation with growth

- (b) negative – this would imply that ventricular filling has a strong positive correlation with growth, and that Cpass has an equal and opposite (i.e. positive) correlation with growth
- (c) none – this would imply that ventricular filling has a positive correlation with growth, and Cpass has no correlation with growth

From these hypotheses, it is evident that there is no case for ventricular filling having a negative correlation with growth.

Table 3.4: Representation of the input parameters in Cases 1 and 2, and the relative contribution of EDP towards growth

Input parameters varying from normal values are marked by 'x'; outputs are $d(\% \text{Growth})/d(\text{EDP})$ where %Growth is relative to normal and growth is quantified for cavity volume, cavity shape, wall volume, and wall thickness

Target Variable: EDP		
INPUTS	Case 1	Case 2
EDP	x	x
EDV-Vo	x	
Vo		
Cpass		x
SA:LA		
SA		
LA		
WT		
d(%Growth)/d(EDP)	Case 1	Case 2
LV Cavity Volume	0.912	0.012
LV Cavity Shape	0.256	-0.001
LV Wall Volume	0.945	0.011
LV Wall Thickness	0.402	-0.025

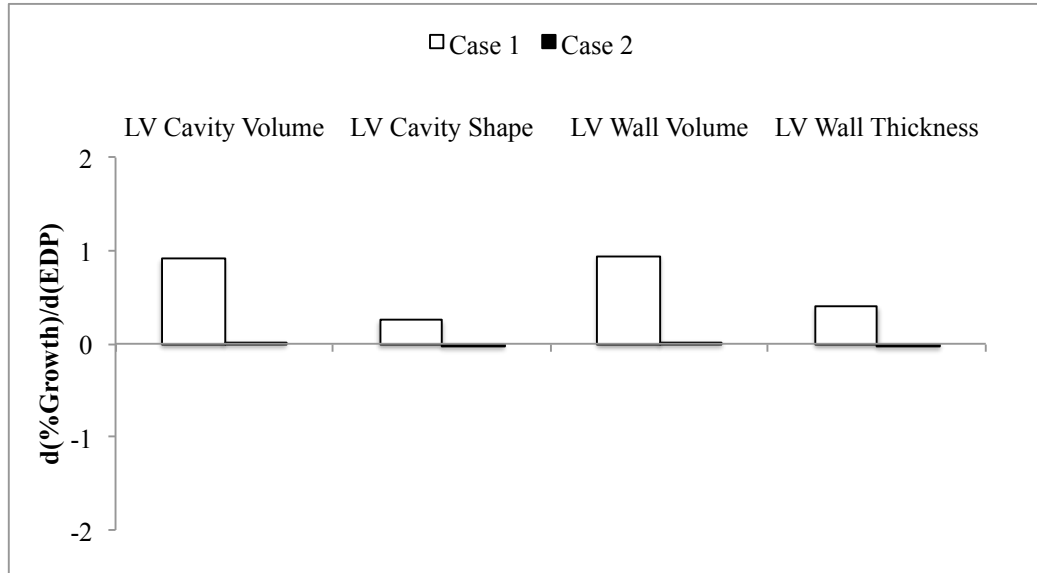


Figure 3.5: A visual representation of %Growth in the LV cavity and free wall as it changes with respect to EDP in Cases 1 and 2.

Table 3.5: Representation of the input parameters in Cases 1 and 3, and the relative contribution of EDV-Vo towards growth

Input parameters varying from normal values are marked by 'x'; outputs are $d(\% \text{Growth})/d(\text{EDV-Vo})$ where %Growth is relative to normal and growth is quantified for cavity volume, cavity shape, wall volume, and wall thickness

Target Variable: EDV-Vo		
INPUTS	Case 1	Case 3
EDV-Vo	x	x
Vo		
EDP	x	
Cpass		x
SA:LA		
SA		
LA		
WT		
d(%Growth)/d(EDV-Vo)	Case 1	Case 3
LV Cavity Volume	1.335	1.476
LV Cavity Shape	0.386	0.341
LV Wall Volume	1.380	1.546
LV Wall Thickness	0.561	0.896

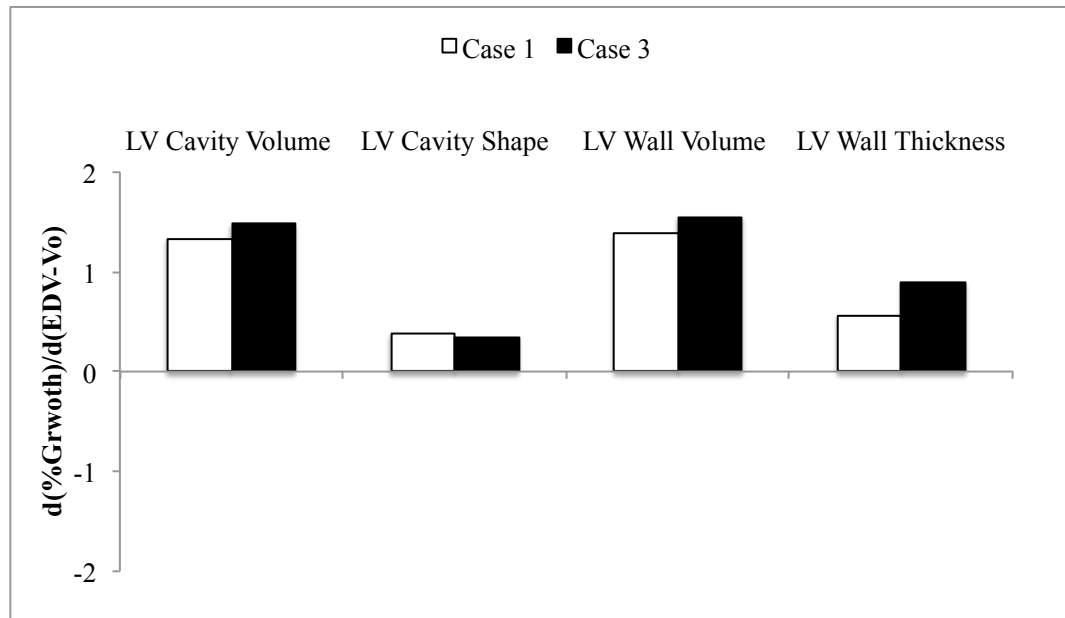


Figure 3.6: A visual representation of %Growth in the LV cavity and free wall as it changes with respect to EDV-Vo in Cases 1 and 3.

To test these hypotheses, Cases 1 and 3 must be compared with ventricular filling as the independent variable (Table 3.5, Figure 3.6). The magnitude of the slopes of volumetric and shape growth are almost equal, indicating ventricular filling contributes equally to the growth in both cases. Again, three hypotheses can be constructed regarding the relationship between ventricular filling and growth with different implications:

- (d) positive – this implies preload and Cpass have no correlation with growth
- (e) negative – this implies that preload has a positive correlation with growth and Cpass has a significantly strong positive correlation with growth

Simply by process of elimination, hypothesis (a) and (e) can be disregarded as they are not mutually compatible, leaving hypothesis (d) and, as a result, hypothesis (a) to be true. This cross-case analysis enables us to conclude that ventricular filling has a positive correlation with growth while preload and Cpass have no correlation with growth. To confirm this, regression equations were generated with Cpass as the independent variable,

the results of which validate that ventricular filling is clearly the dominating variable contributing to LV volumetric and shape growth when unloaded volume is same as normal.

Table 3.6: Representation of the input parameters in Cases 2 and 3, and the relative contribution of Cpass towards growth

Input parameters varying from normal values are marked by 'x'; outputs are $d(\% \text{Growth})/d(\text{Cpass})$ where %Growth is relative to normal and growth is quantified for cavity volume, cavity shape, wall volume, and wall thickness

Target Variable: Cpass		
INPUTS	Case 2	Case 3
Cpass	x	x
EDV- V_o		x
EDP	x	
V_o		
SA:LA		
SA		
LA		
WT		
$d(\% \text{Growth})/d(\text{Cpass})$	Case 2	Case 3
LV Cavity Volume	0.012	-0.590
LV Cavity Shape	-0.001	-0.140
LV Wall Volume	0.011	-0.618
LV Wall Thickness	-0.026	-0.352

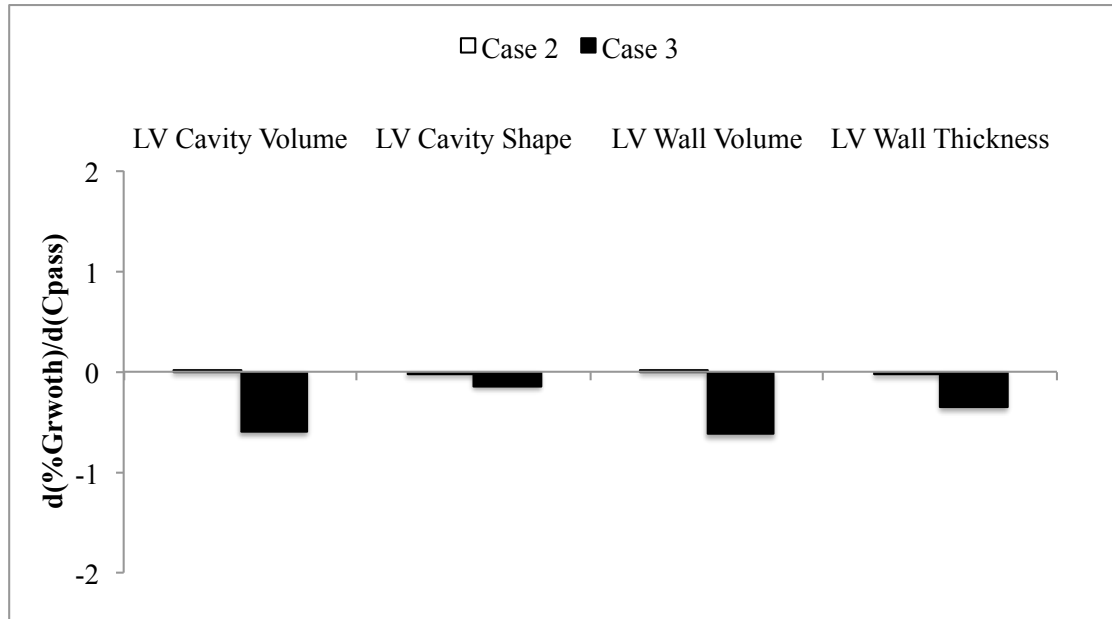


Figure 3.7: A visual representation of %Growth in the LV cavity and free wall as it changes with respect to Cpass in Cases 2 and 3.

Case 6

Case 6 studies the effect of shape on growth by varying either wall thickness to generate thick- and thin-walled LVs or SA:LA to generate ShortWide and TallNarrow geometries, all of equal unloaded volume, preload, ventricular filling, and material properties. The effect of increased wall thickness on growth is clear in that a thin-walled LV grows larger in size and volume than a thick-walled counterpart. Hence, increase in wall thickness has a negative correlation with volumetric and shape growth. The trend for growth in the ShortWide and TallNarrow geometries is relatively insignificant controlled to the normal LV; however, it is conclusive that the ShortWide LV grows more than the TallNarrow (Figures 3.17-3.19). Increasing short-axis and long-axis dimensions simultaneously seem to have a counteracting effect on growth, which may explain this behavior. In addition, the individual effect of SA:LA is inconclusive as wall thickness

was a co-variable in the case of TallNarrow and ShortWide due to the constraints of the model.

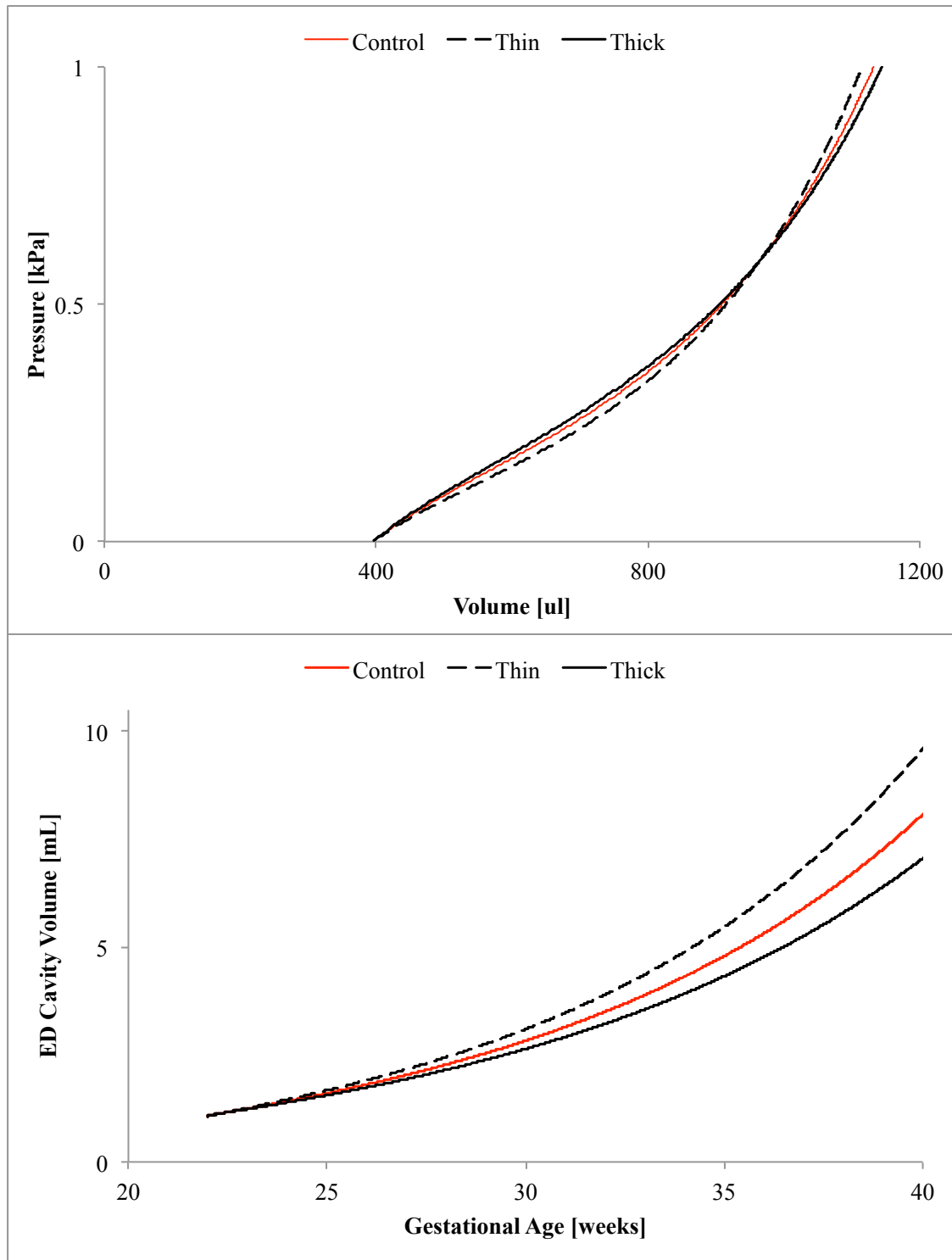


Figure 3.8: Case 6 Inflation Curve (top) and LV cavity volumetric growth (bottom)

The inflation curve displays the models of varying wall thickness inflated at normal EDP and EDV- V_0 ; the resulting volumetric growth curves from mid gestation to term are shown.

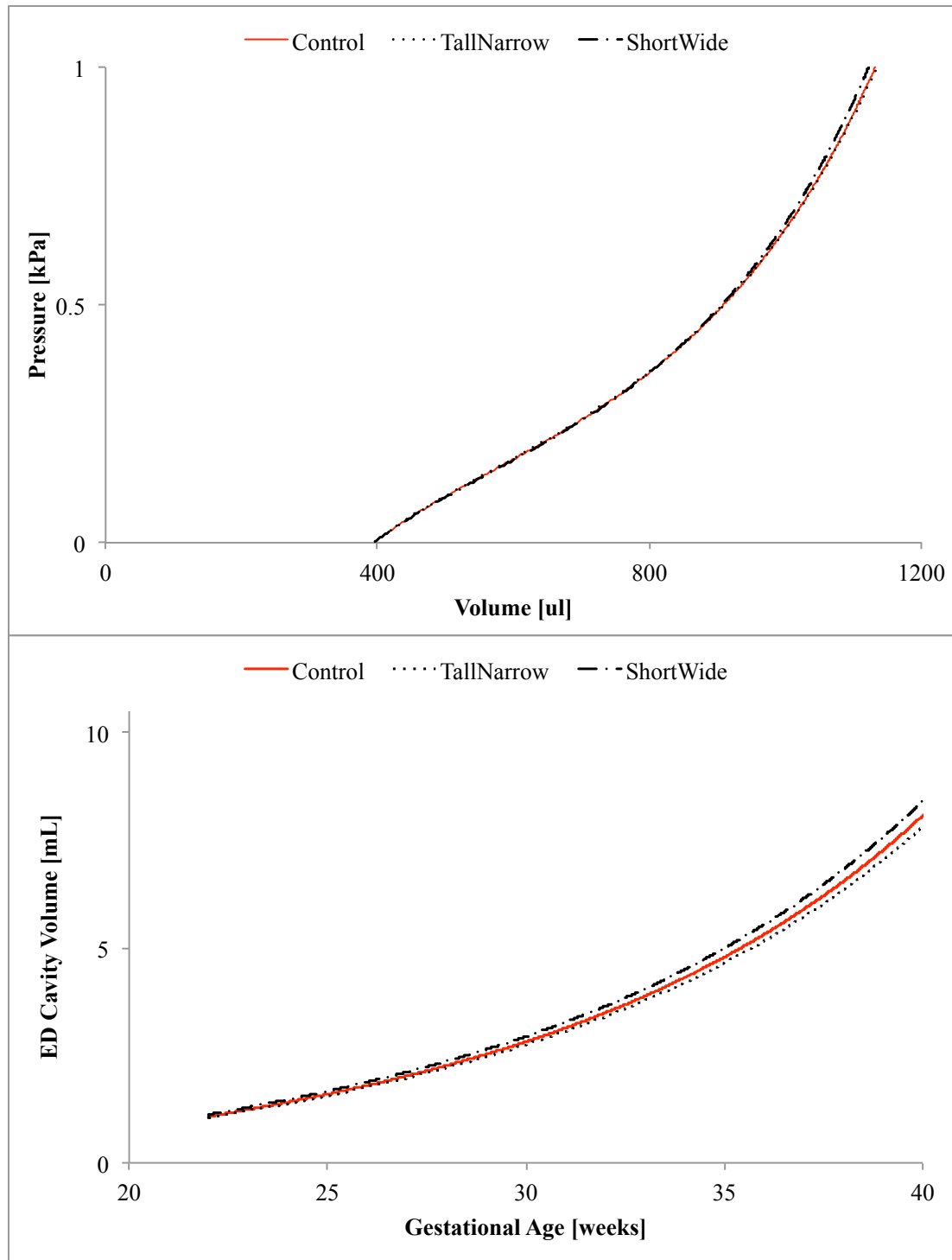


Figure 3.9: Case 6 Inflation Curve (top) and LV cavity volumetric growth (bottom)

The inflation curve displays the models of varying SA:LA inflated at normal EDP and EDV- V_0 ; the resulting volumetric growth curves from mid gestation to term are shown.

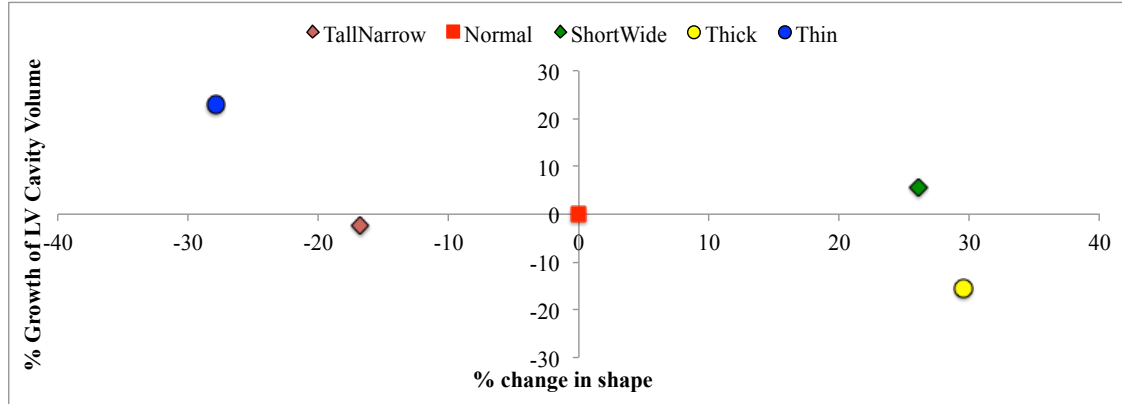


Figure 3.10: Case 6 comparing the effect of shape on %Growth of LV cavity volume

Effect of shape is represented as either change in wall thickness (thin to thick) or SA:LA (TallNarrow to ShortWide) at mid gestation; % Growth is relative to normal growth from mid gestation to birth.

Table 3.7: Representation of the input parameters in Case 6B, and the relative contribution of wall thickness towards growth

Input parameters varying from normal values are marked by 'x'; outputs are $d(\%Growth)/d(WT)$ where %Growth is relative to normal and growth is quantified for cavity volume, cavity shape, wall volume, and wall thickness

Target Variable: Wall Thickness	
INPUTS	Case 6B: Thick/Thin
WT	x
EDV-Vo	
EDP	
Vo	
Material Properties	
SA:LA	
SA	
LA	
$d(\%Growth)/d(WT)$	
LV Cavity Volume	-0.664
LV Cavity Shape	0.243
LV Wall Volume	-0.858
LV Wall Thickness	-0.940

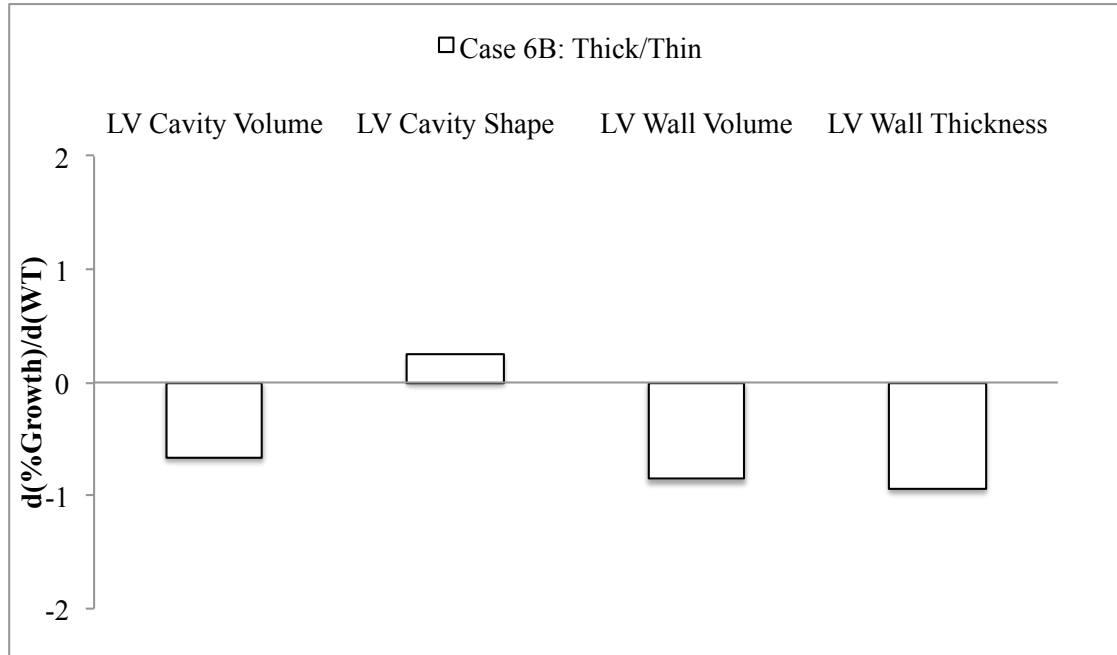


Figure 3.11: A visual representation of %Growth in the LV cavity and free wall as it changes with respect to wall thickness in Case 6.

Table 3.8: Representation of the input parameters in Case 6B, and the relative contribution of SA:LA towards growth

Input parameters varying from normal values are marked by 'x'; outputs are $d(\%Growth)/d(SA:LA)$ where %Growth is relative to normal and growth is quantified for cavity volume, cavity shape, wall volume, and wall thickness

Target Variable: SA:LA	
INPUTS	Case 6B: ShortWide/TallNarrow
SA:LA	x
EDV- V_o	
EDP	
V_o	
Material Properties	
SA	x
LA	x
WT	x
$d(\%Growth)/d(SA:LA)$	
LV Cavity Volume	0.189
LV Cavity Shape	-0.298
LV Wall Volume	0.039
LV Wall Thickness	0.020

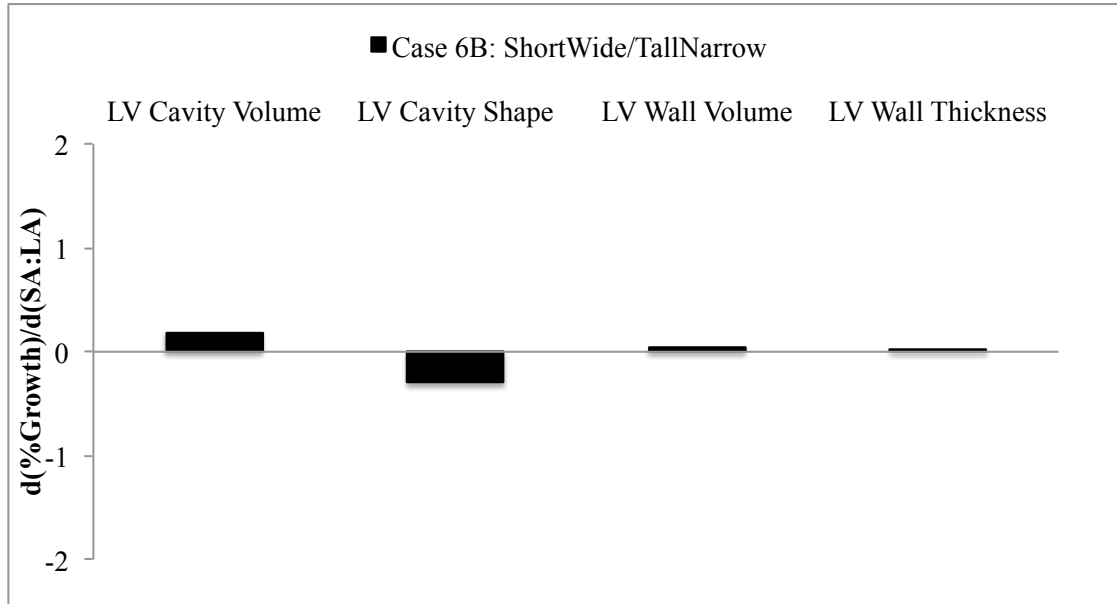


Figure 3.12: A visual representation of %Growth in the LV cavity and free wall as it changes with respect to SA:LA in Case 6.

Table 3.9: Representation of the input parameters in Case 6B, and the relative contribution of SA towards growth

Input parameters varying from normal values are marked by 'x'; outputs are $d(\% \text{Growth})/d(\text{SA})$ where %Growth is relative to normal and growth is quantified for cavity volume, cavity shape, wall volume, and wall thickness

Target Variable: SA	
INPUTS	Case 6B: ShortWide/TallNarrow
SA	x
EDV- V_0	
EDP	
V_0	
Material Properties	
SA:LA	x
LA	x
WT	x
$d(\% \text{Growth})/d(\text{SA})$	
LV Cavity Volume	0.450
LV Cavity Shape	-0.758
LV Wall Volume	0.095
LV Wall Thickness	0.389

Table 3.10: Representation of the input parameters in Case 6B, and the relative contribution of LA towards growth

Input parameters varying from normal values are marked by 'x'; outputs are $d(\% \text{Growth})/d(LA)$ where $\% \text{Growth}$ is relative to normal and growth is quantified for cavity volume, cavity shape, wall volume, and wall thickness

Target Variable: LA	
INPUTS	Case 6B: ShortWide/TallNarrow
LA	x
EDV- V_o	
EDP	
V_o	
Material Properties	
SA:LA	x
SA	x
WT	x
$d(\% \text{Growth})/d(LA)$	
LV Cavity Volume	-0.349
LV Cavity Shape	0.565
LV Wall Volume	-0.072
LV Wall Thickness	-0.148

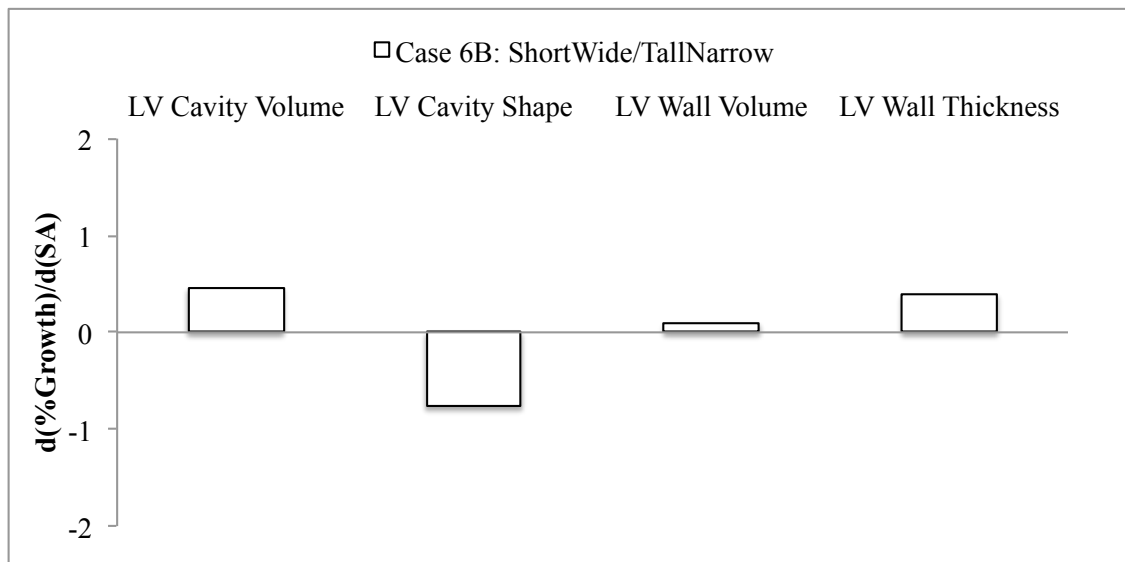


Figure 3.13: A visual representation of $\% \text{Growth}$ in the LV cavity and free wall as it changes with respect to SA in Case 6.

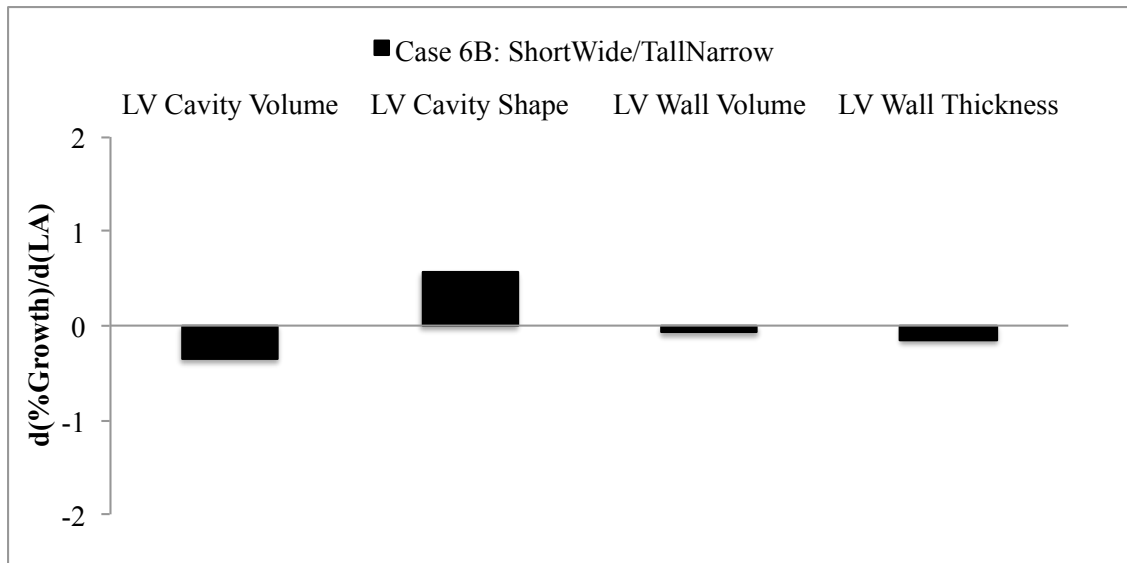


Figure 3.14: A visual representation of %Growth in the LV cavity and free wall as it changes with respect to LA in Case 6.

Case 7

This case was an exploration of the effect of asymmetric ventricular wall stiffness on growth. From Cases 2 and 3, we concluded that ventricular wall stiffness when induced symmetrically throughout the endocardial, mid-wall, and epicardial elements of the LV free wall has relatively insignificant effect on growth. The results from Case 7 confirm this conclusion that ventricular filling is a dominant driving force in fetal LV growth, so it must be held constant in order to truly observe the effects of another variable (Figure 3.17).

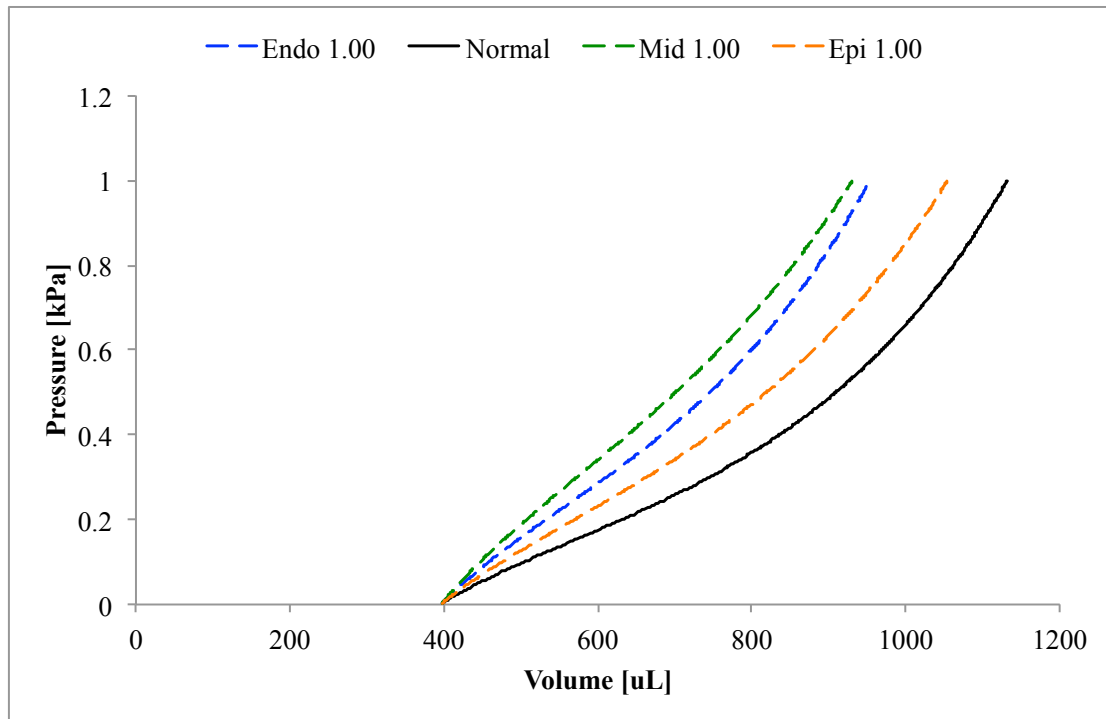


Figure 3.15: Case 7 Inflation Curves of models with asymmetric wall stiffness

The normal LV free wall ($C_{pass} = 0.33$ kPa for all elements) inflation curve is compared to models of asymmetric and increased wall stiffness ($C_{pass} = 1.00$ kPa)

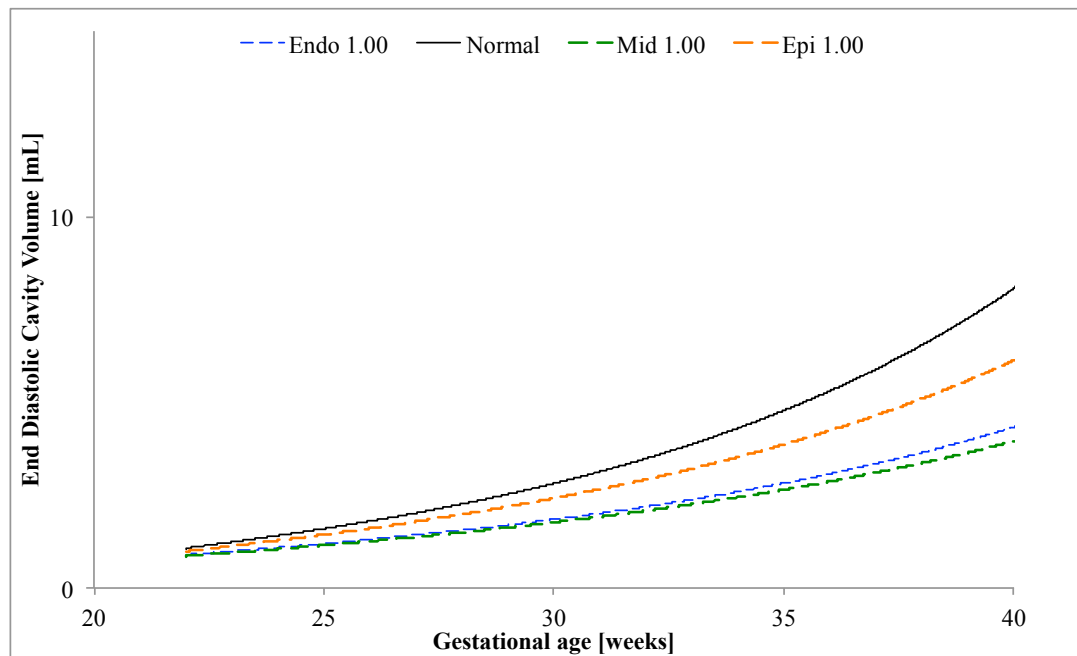


Figure 3.16: Case 7 LV cavity volumetric growth in models of asymmetric wall stiffness when grown at same EDP

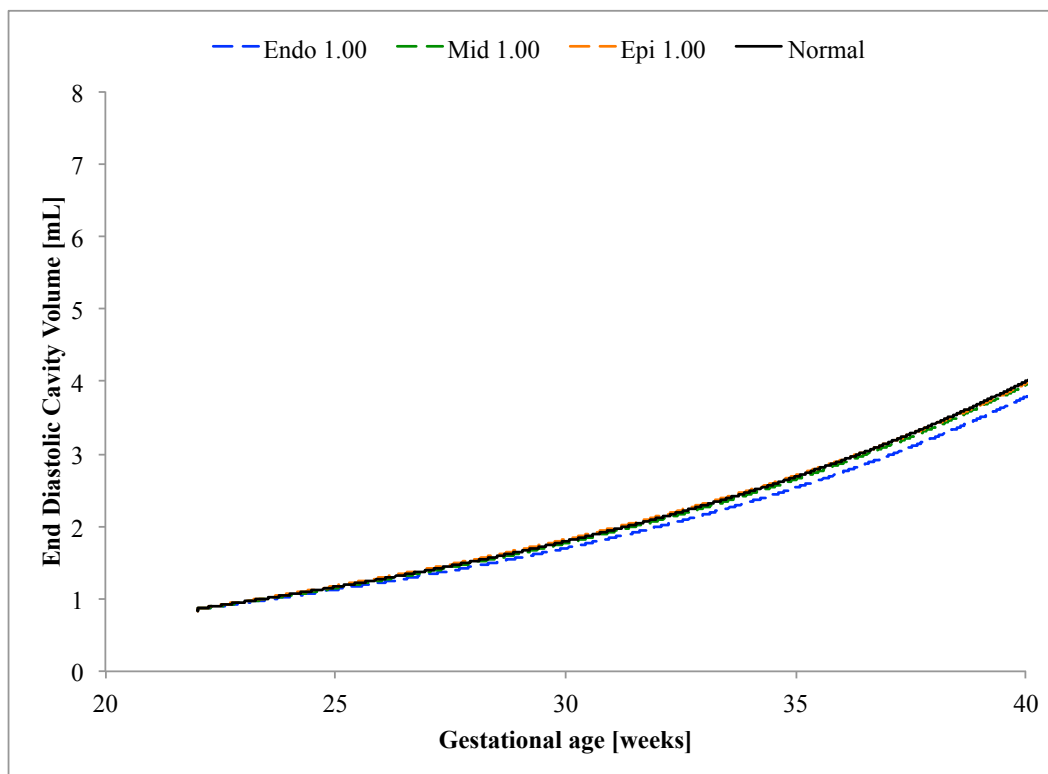


Figure 3.17: Case 7 LV cavity volumetric growth in models of asymmetric wall stiffness when grown at same EDV- V_0

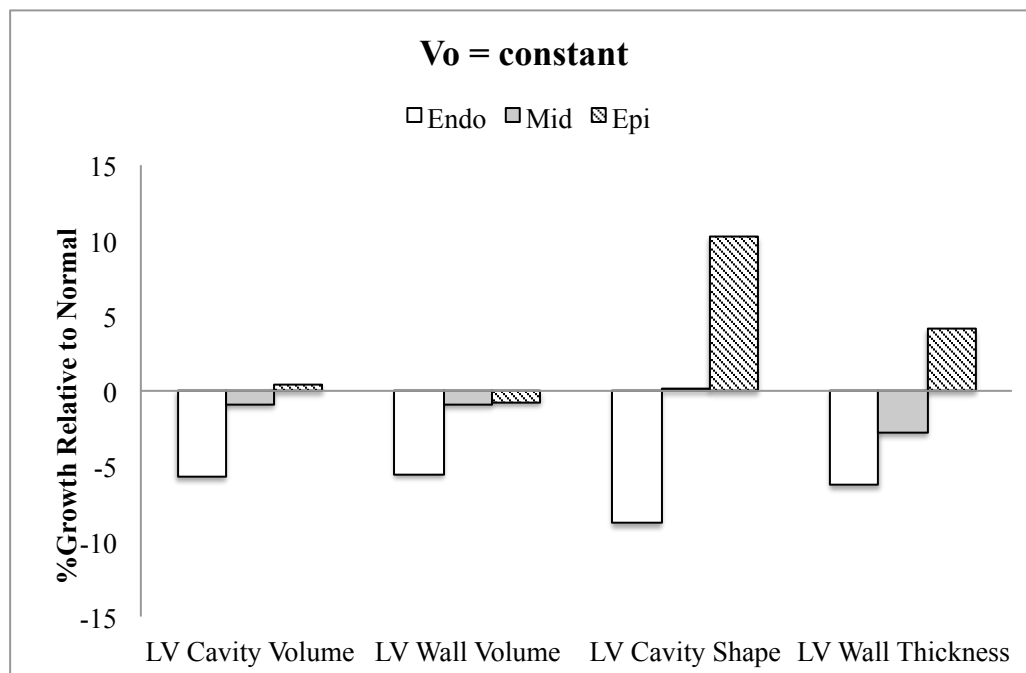


Figure 3.18: A visual representation of %Growth in the LV cavity and free wall for the models of asymmetric wall stiffness in Case 7

From Figure 3.18, we can conclude that when unloaded volume and ventricular filling are held constant, increasing the stiffness in the endocardial, mid-wall, and epicardial elements has a positive correlation with growth of the LV cavity shape (SA:LA, WT) as a gradient of position in the free wall from endocardial to epicardial elements. Increasing the stiffness of the endocardial elements has a decreased effect on volumetric growth whereas relatively insignificant change in growth is observed for the stiffer mid-wall and epicardial elements.

3.2.2 Overview of Cases with $V_o \neq \text{same}$

Case 4

Interestingly, when unloaded volume is variable, preload is the dominating variable contributing to volumetric cavity and wall growth with a positive correlation. This is a direct reversal of the hierarchy observed when unloaded volume is controlled for.

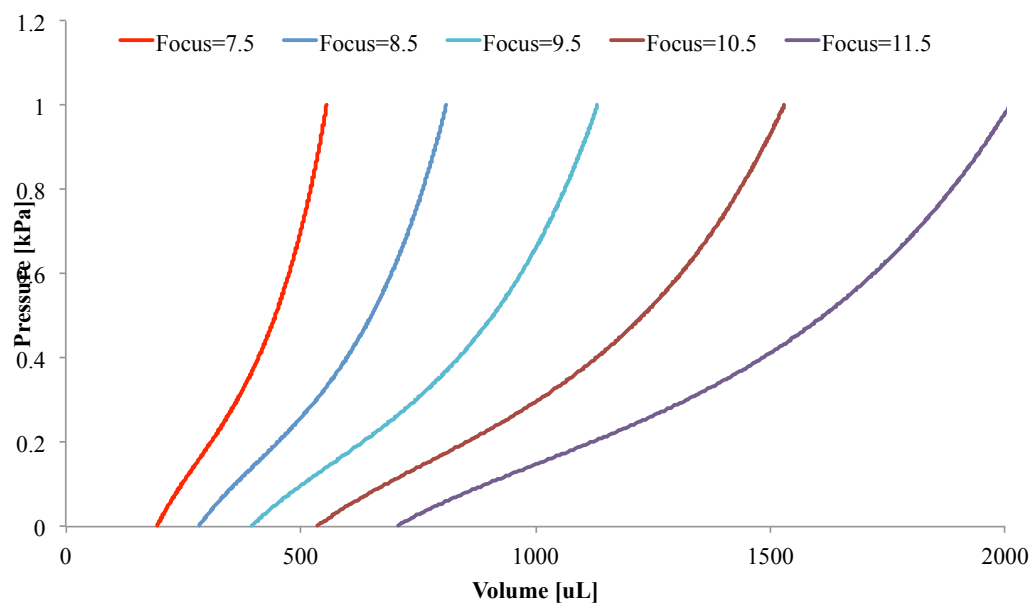


Figure 3.19: Case 4 Inflation Curves for models of varying foci, thereby differential unloaded volumes (normal focus: 9.5)

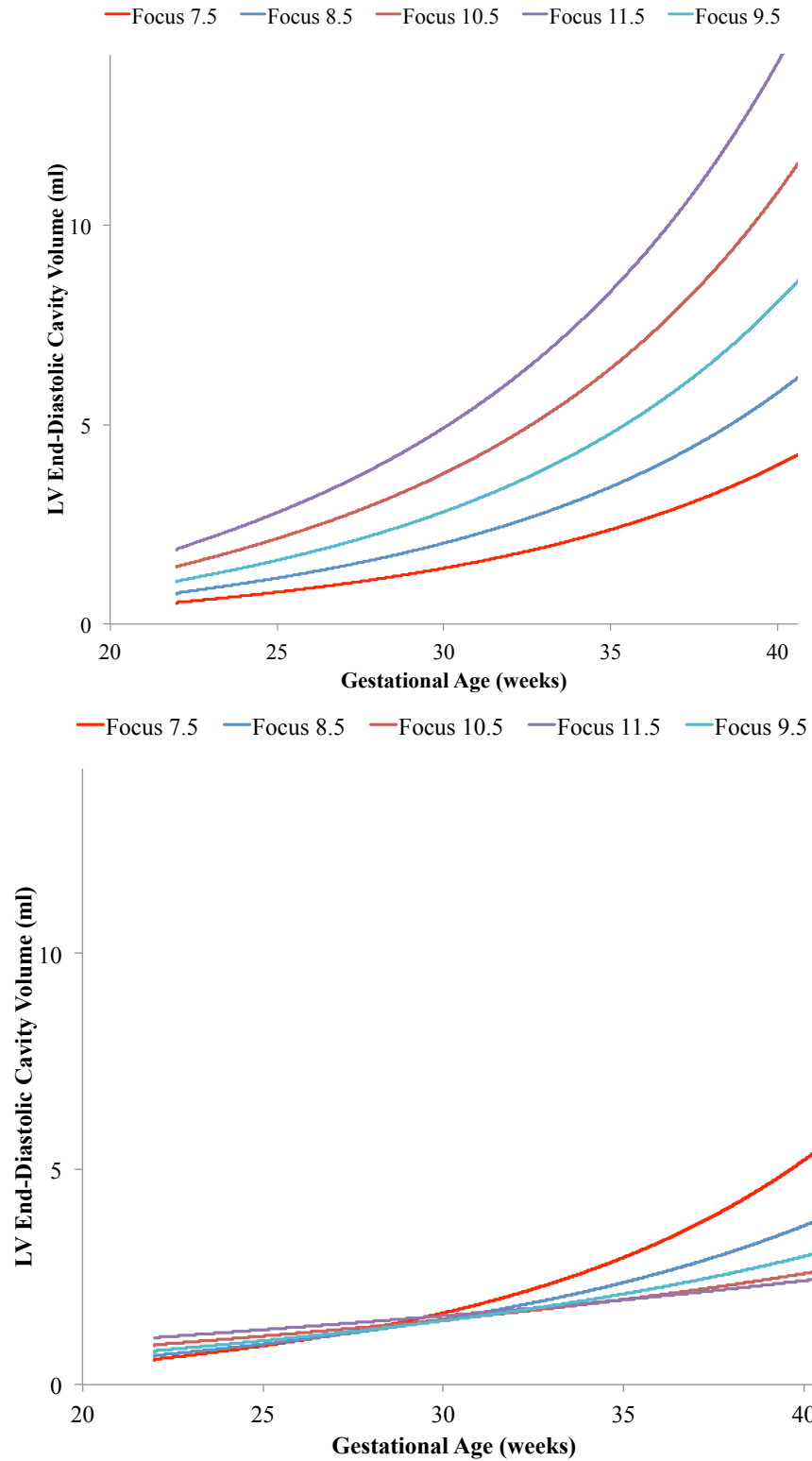


Figure 3.20: Case 4 LV cavity volumetric growth in models of varying foci, grown at same EDP (top) and same EDV-Vo (bottom)

Table 3.11: Representation of the input parameters in Case 4A, and the relative contribution of EDV-Vo towards growth

Input parameters varying from normal values are marked by 'x'; outputs are $d(\% \text{Growth})/d(\text{EDV-Vo})$ where %Growth is relative to normal and growth is quantified for cavity volume, cavity shape, wall volume, and wall thickness

Target Variable: EDV-Vo	
INPUTS	Case 4A
EDV-Vo	x
Vo	
EDP	x
Cpass	
SA:LA	
SA	
LA	
WT	
$d(\% \text{Growth})/d(\text{EDV-Vo})$	
LV Cavity Volume	-0.021
LV Cavity Shape	0.063
LV Wall Volume	0.014
LV Wall Thickness	0.168

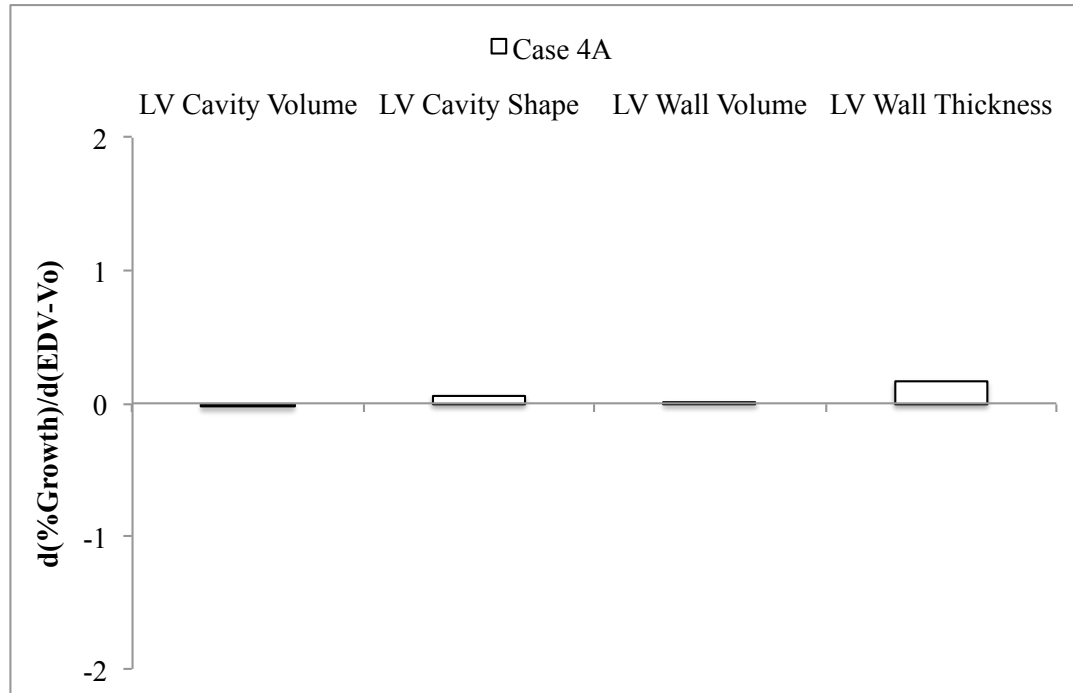


Figure 3.21: A visual representation of %Growth in the LV cavity and free wall as it changes with respect to EDV- V_o in models of varying foci.

Table 3.12: Representation of the input parameters in Case 4B, and the relative contribution of EDP towards growth

Input parameters varying from normal values are marked by 'x'; outputs are $d(\% \text{Growth})/d(\text{EDP})$ where %Growth is relative to normal and growth is quantified for cavity volume, cavity shape, wall volume, and wall thickness

Target Variable: EDP	
INPUTS	Case 4B
EDP	x
EDV- V_o	
V_o	x
C _{pass}	
SA:LA	
SA	
LA	
WT	
$d(\% \text{Growth})/d(\text{EDP})$	
LV Cavity Volume	0.908
LV Cavity Shape	0.149
LV Wall Volume	0.938
LV Wall Thickness	0.002

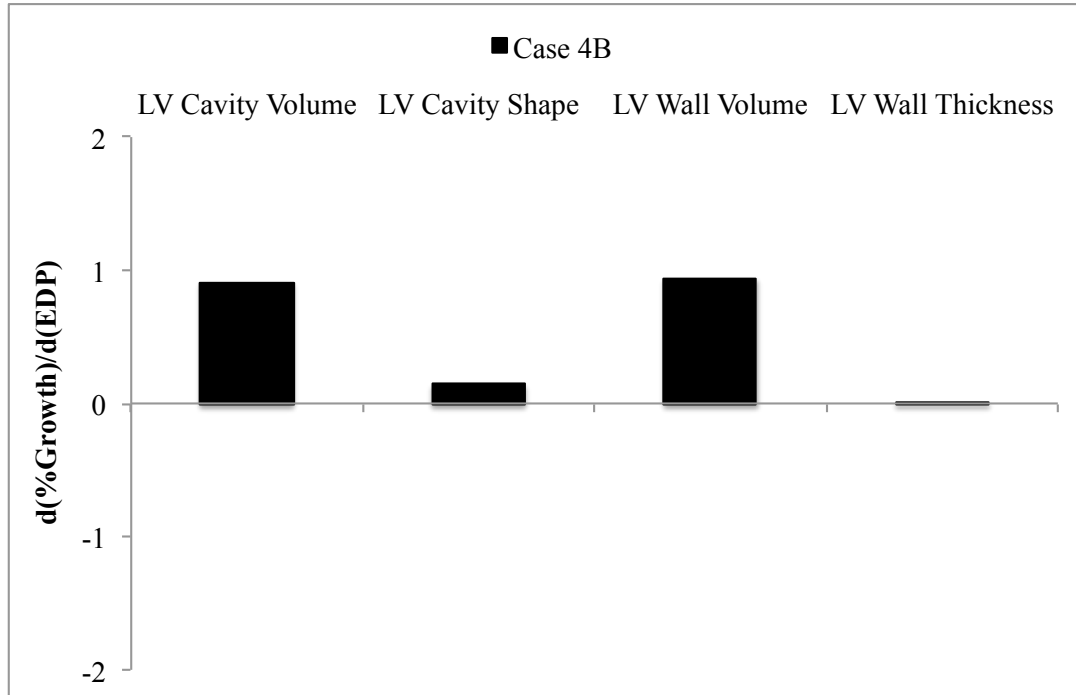


Figure 3.22: A visual representation of %Growth in the LV cavity and free wall as it changes with respect to EDP in models of varying foci.

Case 6

Case 6 compared the effect of shape on growth when volume is varied and with either EDP held constant or ventricular filling held constant. No other parameters including LV wall thickness are changed. It is expected that the Wide geometry would grow more in cavity volume than the Narrow; this phenomenon is observed when EDP is held constant (Figure 3.24 top). However, this observation is completely the opposite when EDV-Vo is held constant (Figure 3.24 bottom), suggesting the complex stimuli-responsive behavior of volumetric growth when unloaded volume is not variable. This reversal is also observed in the Tall and Short geometries, where the Tall LV grows more than the Short in the first case (constant EDP) and vice versa. This phenomenon is confirmed numerically when the volumetric and shape growth outputs ($d(\% \text{Growth})/d(\text{Target Variable})$) are plotted individually with EDV-Vo and EDP as the

target variables (Figures 3.25, 3.26). The results from this case are not as conclusive as the previous cases and needs further investigation before claiming the individual contribution of shape on volumetric and shape growth when unloaded volume is not constant.

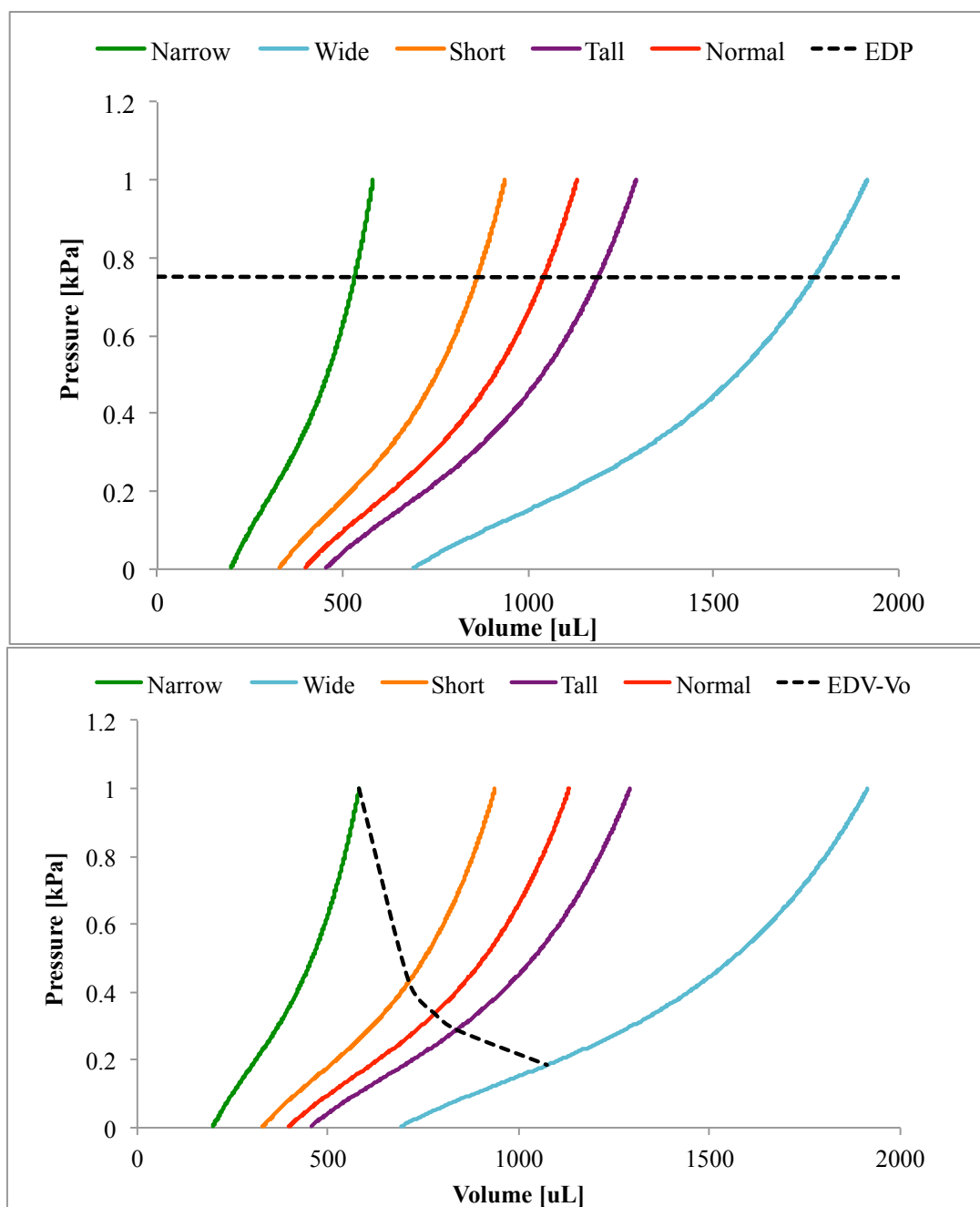


Figure 3.23: Case 6 Inflation curves for models of varying shape, set to grow at same EDP (top) and same EDV-Vo (bottom)

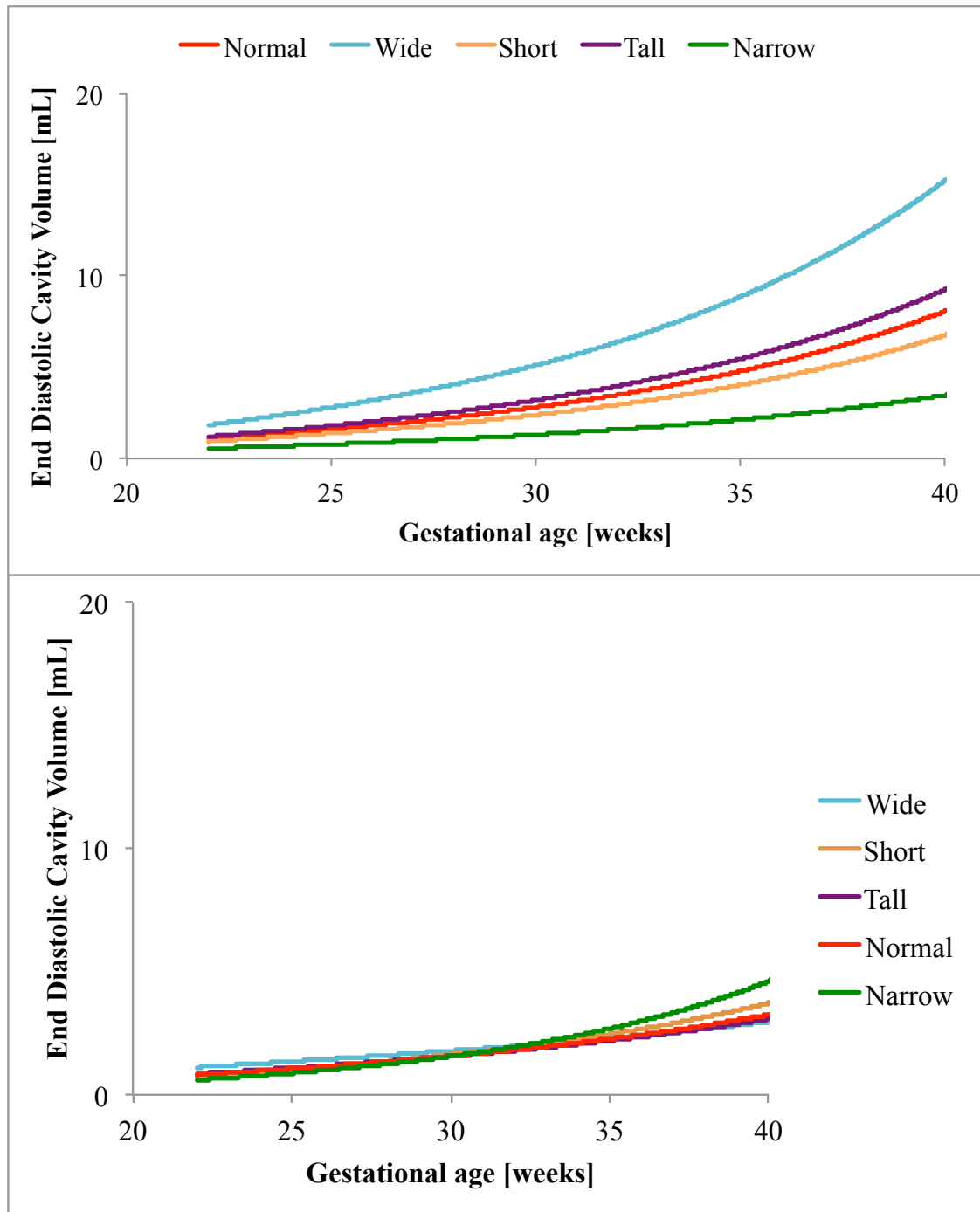


Figure 3.24: Case 6 LV cavity volumetric growth in models of varying shape, grown at same EDP (top) and same EDV-Vo (bottom)

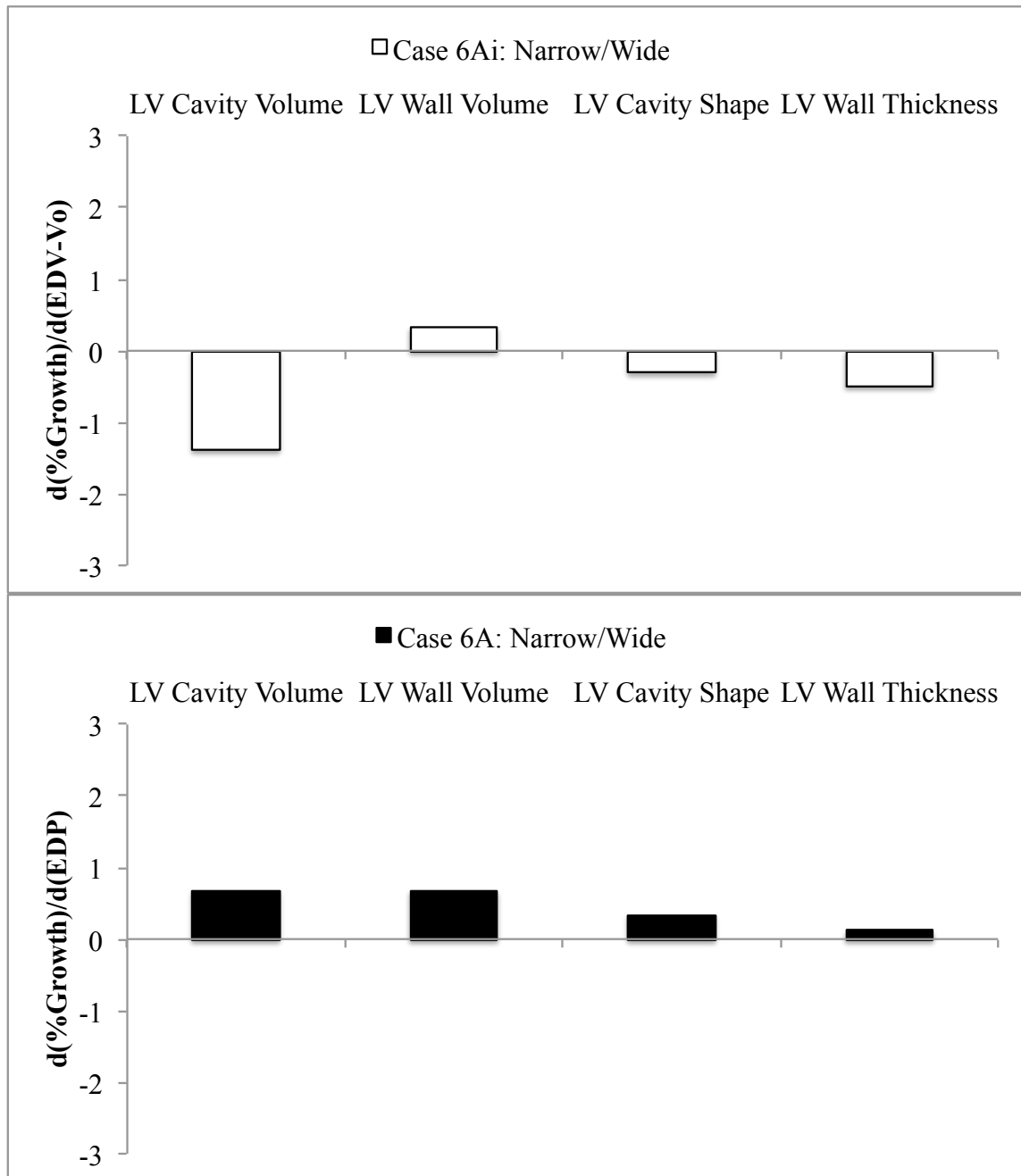


Figure 3.25: A visual representation of %Growth in the LV cavity and free wall as it changes with respect to EDV-Vo (top) and EDP (bottom) in models of varying width.

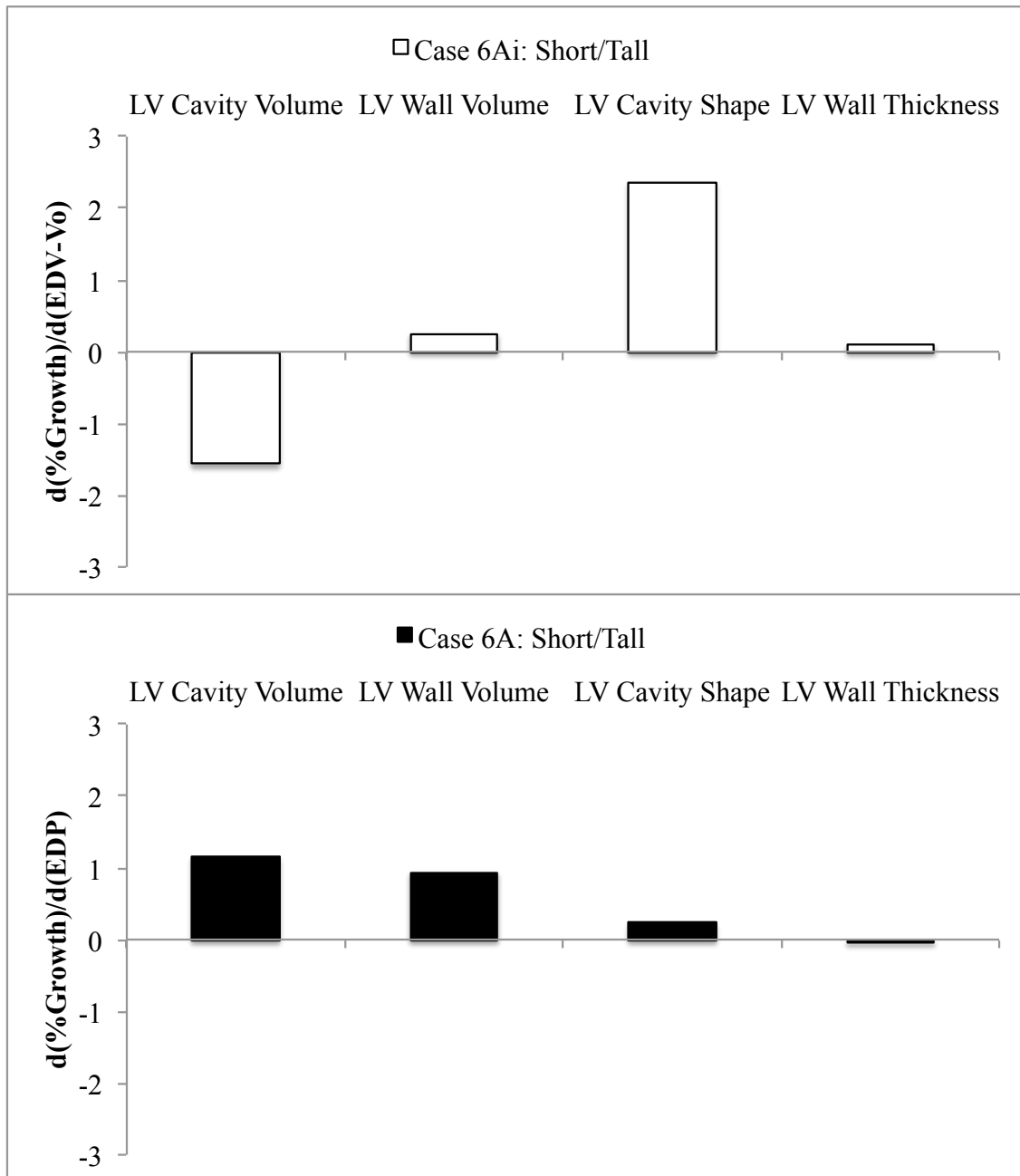


Figure 3.26: A visual representation of %Growth in the LV cavity and free wall as it changes with respect to EDV- V_0 (top) and EDP (bottom) in models of varying length.

Case 7

The results from this case introduce a contradiction to our earlier claim that when unloaded volume is constant and same as normal, preload is the dominating variable contributing to growth rather than ventricular filling. Discussion of this can be found in

Chapter 3.3. Regression equations for this case were generated with C_{pass} as the independent variable when ventricular filling is constant. With this constraint, we conclude that when unloaded volume is varying between the endocardial, mid-wall, and epicardial elements, increasing the wall stiffness of the myocardium non-uniformly results in decreased volumetric and shape growth. LV cavity shape decreases most significantly in a gradient from endocardial to epicardial elements of the wall. Finally, increasing stiffness in the endocardial and epicardial elements results in significantly reduced wall thickness growth (endo: -40%; epi: -70%) compared to the normal.

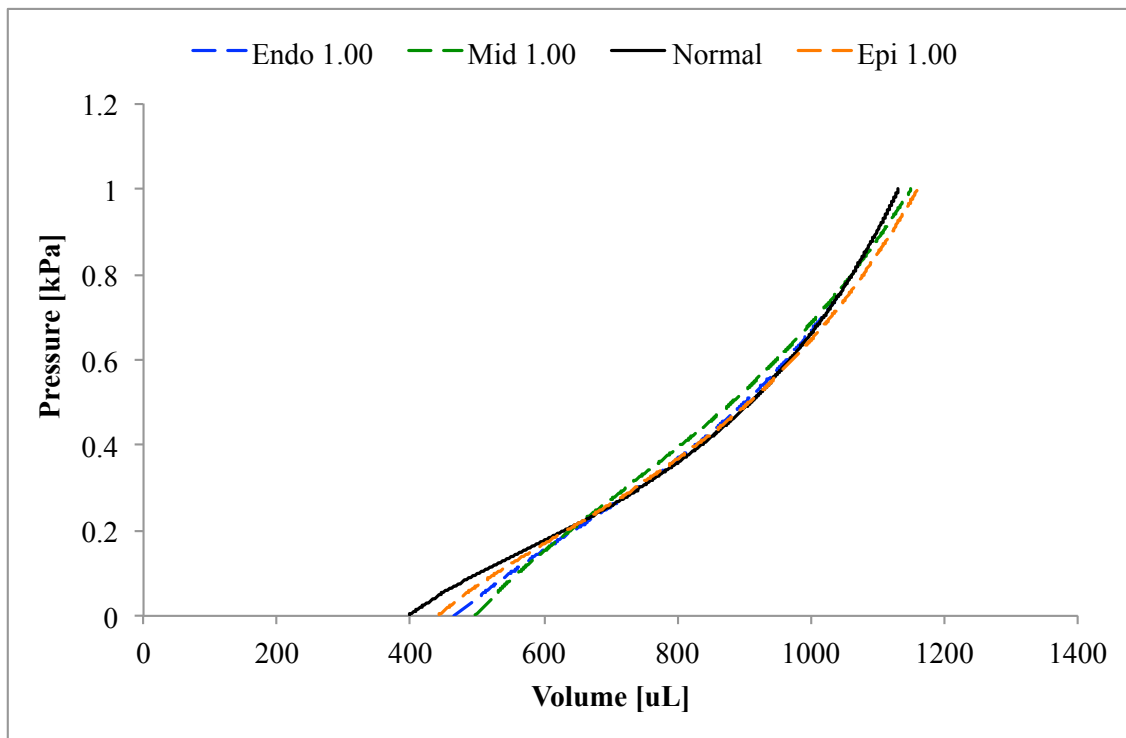


Figure 3.27: Case 7 Inflation Curves of models with differential wall stiffness and unloaded volume
The normal LV free wall ($C_{pass} = 0.33$ kPa for all elements) inflation curve is compared to models of asymmetric and increased wall stiffness ($C_{pass} = 1.00$ kPa) as well as differential unloaded volumes

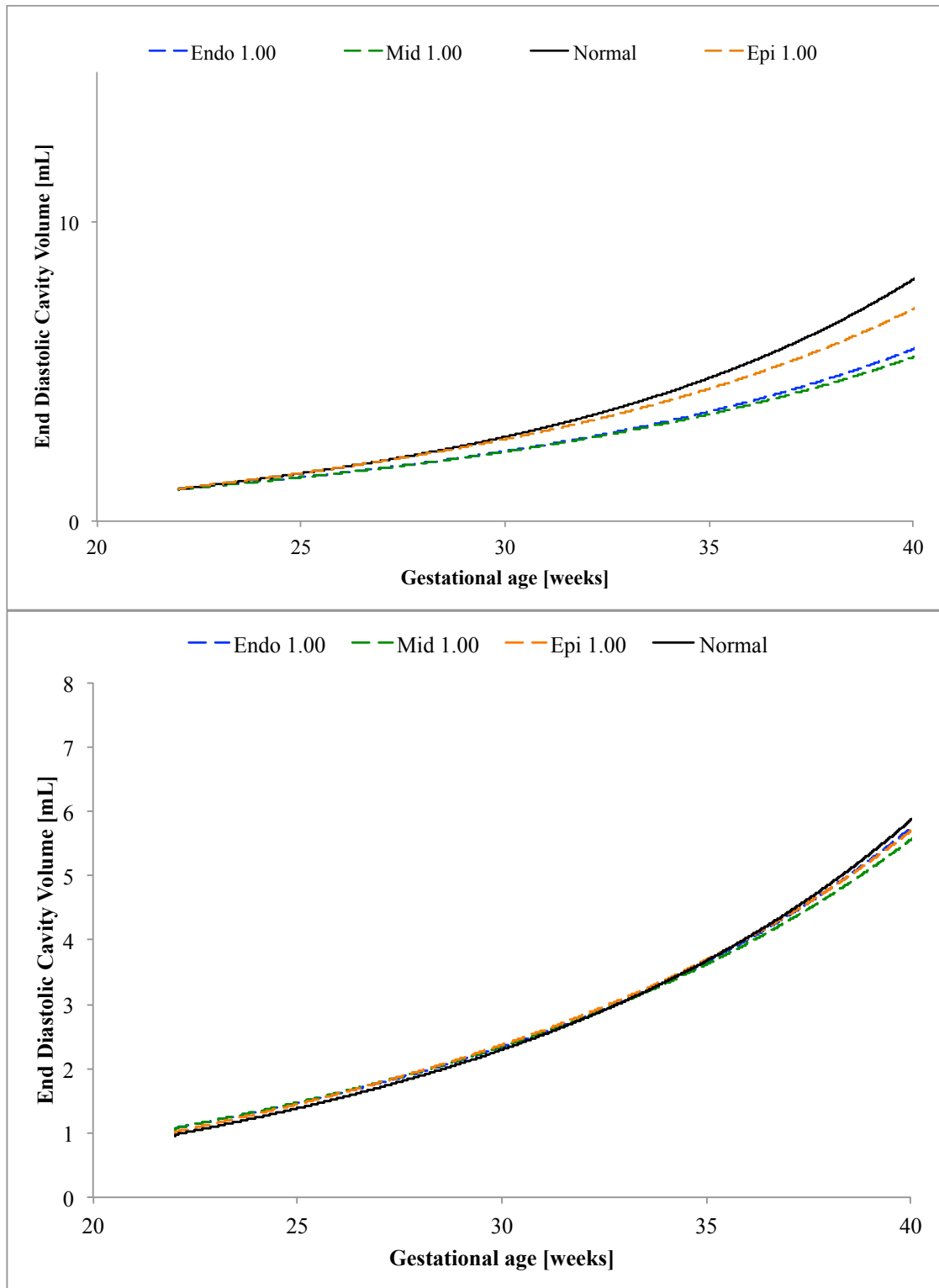


Figure 3.28: Case 7 LV cavity volumetric growth in models of asymmetric wall stiffness when grown at same EDP (top) and same EDV-Vo (bottom)

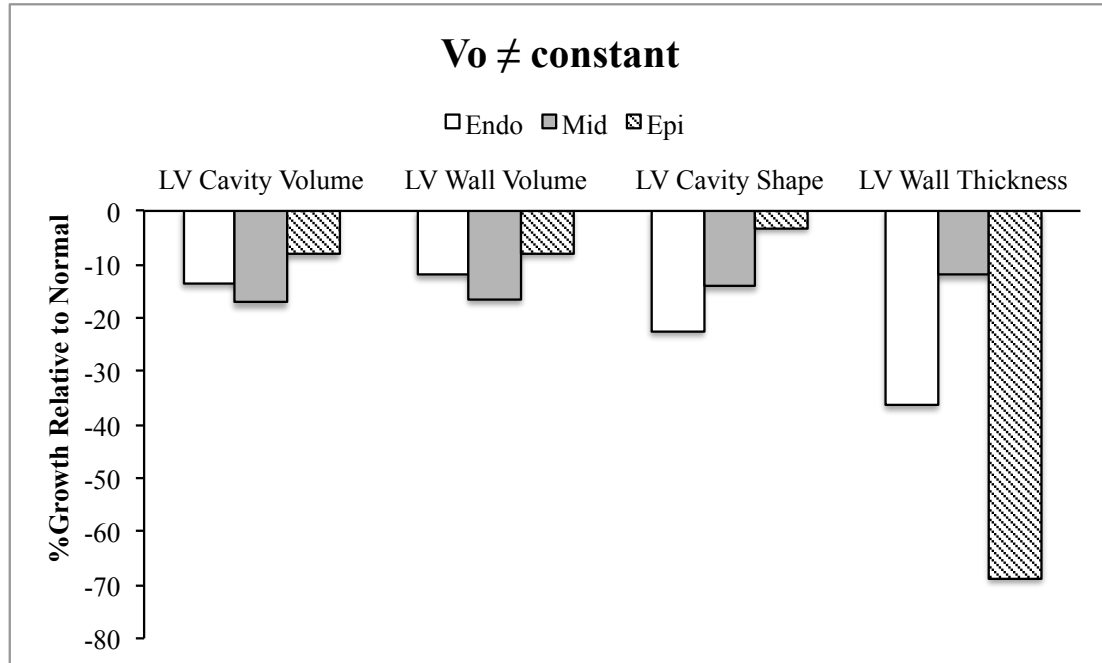


Figure 3.29: A visual representation of %Growth in the LV cavity and free wall for the models of asymmetric wall stiffness and differential unloaded volumes in Case 7

3.2.3 Summary of Growth Model Sensitivity Analysis

I. Growth model sensitivity Analysis ($V_o = \text{same}$)

Using the regression equations listed in Table 3.13, the percentage growth relative to normal was predicted given a 10% decrease for each parameter with the constraint that unloaded volume is same as the normal model.

Table 3.13: Regression equations describe the effect of the target variable on growth when unloaded volume is same as normal

The linear equations predict change in %Growth at birth relative to the normal model (Y), where growth is quantified for LV cavity volume, wall volume, cavity shape, and wall thickness. The input (X) is the percent change in the target variable value relative to normal at mid gestation.

Target Variable	Regression Equation describing %change in growth relative to normal			
	LV Cavity Volume	Wall Volume	Cavity Shape	Wall Thickness
EDV- V_o	$Y = 1.34 * X + 1.03$	$Y = 1.38 * X + 0.84$	$Y = 0.39 * X + 0.16$	$Y = 0.56 * X - 0.23$
WT	$Y = -0.66 * X + 2.84$	$Y = -0.86 + 3.57$	$Y = 0.24 * X - 0.27$	$Y = -0.94 * X + 1.10$
Cpass	$Y = 0.01 * X + 0.96$	$Y = 0.01 * X + 0.56$	$Y = -0.0006 * X + 0.2$	$Y = -0.03 * X - 0.25$
EDP	$Y = 0.01 * X + 0.94$	$Y = 0.01 * X + 0.55$	$Y = -0.0006 * X + 0.2$	$Y = -0.02 * X - 0.27$

Table 3.14: %Growth in LV cavity and free wall from mid gestation to birth

Normal	%Growth from mid gestation to birth:			
	Cavity Volume	Wall Volume	Cavity Shape	Wall Thickness
	672.6	339.6	37.8	-8.09

Table 3.15: Inducing a 10% decrease in the input parameters and the observed effect on growth at birth when unloaded volume is same as normal

%Growth is quantified at birth as relative to normal

10% decrease in	%Growth Relative to Normal			
	LV Cavity Volume	LV Wall Volume	LV Cavity Shape	LV Wall Thickness
EDV- V_o	-12.3	-12.96	-3.69	-5.84
WT	+9.47	12.14	-2.70	+8.35
Cpass	+0.836	0.455	+0.21	+0.005
EDP	+0.817	0.439	+0.208	-0.025

II. Growth model sensitivity Analysis ($V_o \neq$ same)

Using the regression equations listed in Table 3.16, the percentage growth relative to normal was predicted given a 10% decrease for each parameter without any constraint on unloaded volume.

Table 3.16: Regression equations describe the effect of the target variable on growth when unloaded volume is varying

The linear equations predict change in %Growth at birth relative to the normal model (Y), where growth is quantified for LV cavity volume, wall volume, cavity shape, and wall thickness. The input (X) is the percent change in the target variable value relative to normal at mid gestation.

Target Variable	Regression Equation describing %change in growth relative to normal			
	LV Cavity Volume	Wall Volume	Cavity Shape	Wall Thickness
EDV-V _o	$Y = -0.02 * X + 0.06$	$Y = 0.01 * X - 0.51$	$Y = 0.06 * X + 0.95$	$Y = 0.17 * X + 0.32$
C _{pass}	$Y = -0.19 * X + 1.02$	$Y = -0.19 * X + 0.96$	$Y = -0.20 * X + 2.00$	$Y = -0.47 * X + 20.3$
EDP	$Y = 0.91 * X - 6.47$	$Y = 0.94 * X - 5.13$	$Y = 0.15 * X - 4.78$	$Y = 0.002 * X - 14.35$

Table 3.17: Inducing a 10% decrease in the input parameters and the observed effect on growth at birth when unloaded volume is varying from normal

%Growth is quantified at birth as relative to normal

10% decrease in	%Growth Relative to Normal			
	LV Cavity Volume	LV Wall Volume	LV Cavity Shape	LV Wall Thickness
EDV-V _o	+0.268	-0.650	+0.326	-1.357
C _{pass}	+2.963	+2.908	+4.032	+24.984
EDP	-15.549	-14.517	-6.265	-14.273

3.3 Discussion

Depending on the mechanical stimulus that regulates tissue growth, we expect that functional and structural parameters will influence the course of mechano-sensitive growth in the heart. The goal of this study was to gain an understanding of the individual parameters that mediate normal growth in the fetal LV model, and gain insight into the sensitivity of growth towards certain parameters more than others.

The case results were divided into two categories, the distinction between which was unloaded LV chamber volume. We learned that it was crucial to make this distinction, specifically when predicting growth behavior using the model, because unloaded volume appears to play an important interactive role with the other parameters.

To reiterate, when unloaded volume is constant and the same as our normal model, we concluded that ventricular filling is the dominating variable contributing to LV volumetric and cavity growth, and that growth is least sensitive to changes in pressure preload. However, when unloaded volume varies from that of the normal model, this observed trend completely flips with preload being the dominating variable mediating growth. This is challenged in one case when material properties are introduced as a variable by inducing stiffness in the elements of the myocardial wall. In that case, ventricular filling is again the dominating variable and change in preload has seemingly no individual effect on growth, suggesting that stiffness of the myocardial wall suppresses the effect on growth typically observed by changing preload. This hypothesis must be tested further when unloaded volume is constant and variable in order to elucidate the nature of the potential interactive behavior between preload and material properties.

Categorizing the growth model sensitivity analysis by unloaded volume can also be useful in its application clinically. The cases with unloaded volume held constant can shed insight into normal growth behavior of the fetal heart, specifically when the LV is of a size similar to our assumed normal (397 μL) but more importantly when determining clinical intervention or drug therapies for a specific patient. There are clinical cases such as in ventricular septal defect, where the fetal patient has a cardiac malformation that must be surgically repaired by placing a shunt or performing reconstruction surgery. For these procedures, it is difficult to predict the growth behavior of the fetus including the size, shape and mechanical consequences. Our growth model sensitivity analysis would be useful here as it can predict the growth behavior in terms of volume and shape,

including wall thickness growth, given the percent change in the parameter of interest. On the other hand, the analysis with unloaded volume varying from that of a normal fetal LV at mid gestation can be extremely useful when predicting LV growth for a patient with a heart significantly different in size, as in the case of HLHS.

While the growth model sensitivity analysis improves understanding of normal growth in the fetal LV, there are several limitations of this method worth discussing. First, the method is based on a logical approach of case design and inference that is not established as a statistical method of sensitivity analysis. Second, within each case, there are only a few points above and below the normal reference value that are used to generate linear regression lines. While the nature of normal growth predicted by the model is, in fact, mostly linear, there is a definite need to increase the number of data points in order to improve confidence in the resulting correlation behavior between the parameters and growth. Third, in some cases the independent variable was not varied by the same degree above or below the normal reference value due to the complex iterative nature of developing these unloaded geometries. However, this limitation can also be vastly improved by increasing the number of data points, resulting in a more comprehensive analysis within each case.

Fourth, the individual effects of a few parameters could not be elucidated completely, specifically in the case of short-axis to long-axis ratio when unloaded volume is constant. As mentioned previously, manipulating the unloaded geometry in order to understand the effect of SA:LA while keeping all other parameters (unloaded volume, preload, ventricular filling, wall thickness) constant is difficult and often involves compromise. In the case above, wall thickness could not be controlled for, which

complicates the conclusions that can be made. However, because we know the individual effect of wall thickness as in the case of Thick versus Thin, it is still possible to make inferences about the effect of SA:LA by assuming that wall thickness plays the same role. For example, the ShortWide and TallNarrow geometries were 5% and 10% thinner than normal, respectively. Based on the regression equation with wall thickness as the independent variable and focusing on just volumetric cavity growth, one can predict that a 5% and 10% thinner LV would grow 6% and 9% more than normal. The ShortWide geometry does grow approximately +6%, most likely suggesting that the changes in SA:LA did not contribute to growth at all. On the other hand, the TallNarrow geometry grows 2.5% less than normal. This is peculiar and may be due to the limitation that the SA:LA for TallNarrow was varied by only -17% while ShortWide was varied by +27%. Further work must be done to account for this variability before making conclusions about the relative contribution of SA:LA towards growth.

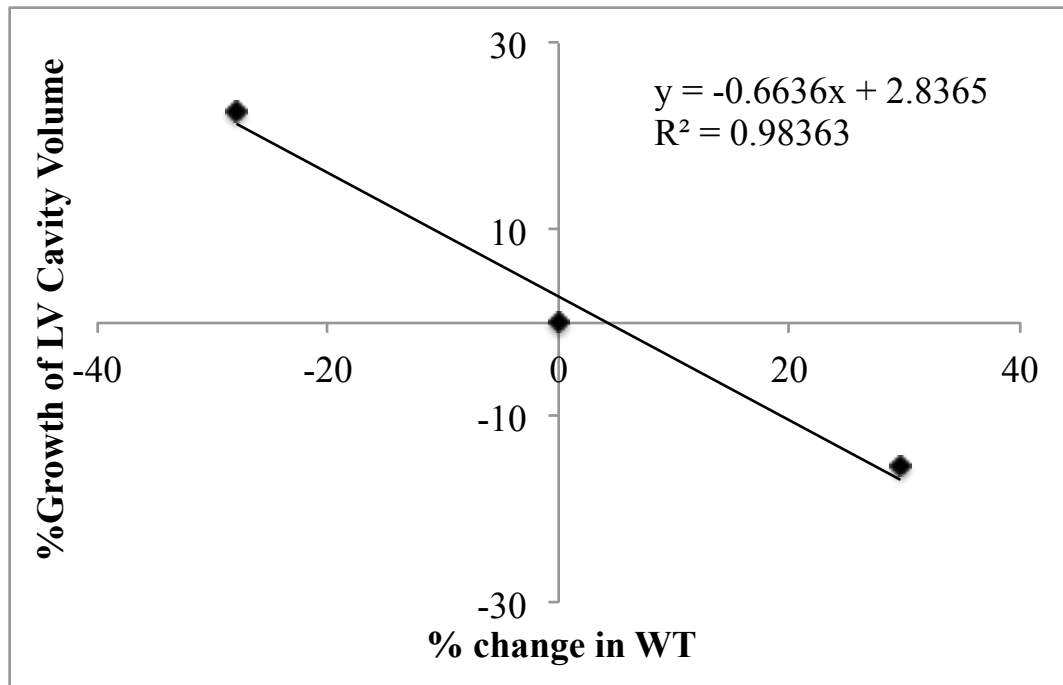


Figure 3.30: Linear regression line describing the effect of change in wall thickness on LV cavity volumetric growth

It is also necessary to design a case with thick- and thin-walled LVs that vary in their unloaded volume. This can be done by changing the location of the endocardial elements in addition to the epicardial elements, as in Case 6 Thick versus Thin. This would present an interesting clinical case of a dilated and hypertrophic heart that can provide insight into how wall thickness interacts with unloaded volume to contribute to volumetric and shape growth of the LV.

CHAPTER 4

Reverse Growth

Although a number of models describe the process of ventricular remodeling, there are few that describe its reversal. Reverse modeling of the ventricles has been observed clinically after mitral valve repairs or implantation of a LVAD. These interventions lead to a reduction in ventricular loading after sufficient and prolonged unloading of the ventricles [84]. The growth law as described in this study, developed by Kerckhoffs et al, was used to model ventricular growth in the fetus from mid gestation to birth. The objective of this aim was to adapt the growth law in the reverse direction and to model fetal LV growth from mid gestation to an in vivo unloaded state.

4.1 Methods

The previously described growth law was applied such that the magnitude of the growth rates were constant as in forward growth, but the direction of growth was negative to yield reverse growth while keeping all parameters the same. The time calibration was adjusted to calculate gestational age in the reverse direction. The growth

law was applied to the reference model of normal fetal growth and allowed to grow backwards. LV dimensions were extracted from the model at the earliest time point and compared to short-axis, long-axis, and average wall thickness dimensions of the normal fetal LV in both an unloaded state and loaded state, as reported in literature. Thorough mapping of end-diastolic cavity and wall volumes, wall mass, and EDPs from early gestation (5 weeks) to birth was conducted [73, 92-97]. This comprehensive overview of fetal development was used to compare the compatibility of our results with clinically and experimentally observed features of left ventricular growth in the normal fetus.

4.2 Results

The LV fetal growth model was able to reverse grow from 22 weeks gestation to approximately 15 weeks gestation at which point the LV cavity volume was near zero (9 μL) in the model. However, the resulting mesh at this time point had a warped element (Figure 4.1), so reverse growth behavior in the model was analyzed from mid gestation up until the point that the mesh exhibits no warping of any elements and associated nodes, which occurred at 17.2 weeks gestation. LV cavity and wall volumetric growth in the forward and reverse direction as described by the model is shown in Figure 4.2.

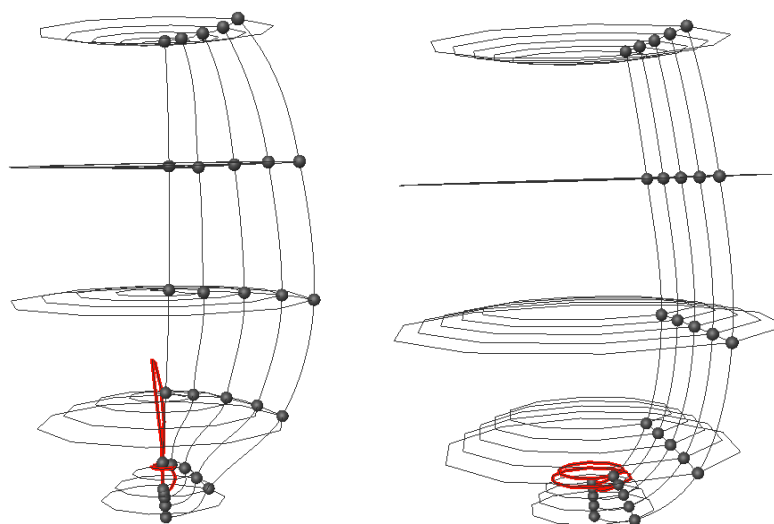


Figure 4.1: Mesh reverse grown from 22 weeks to 15 weeks displays warped element (left) not present at 17.2 weeks (right)

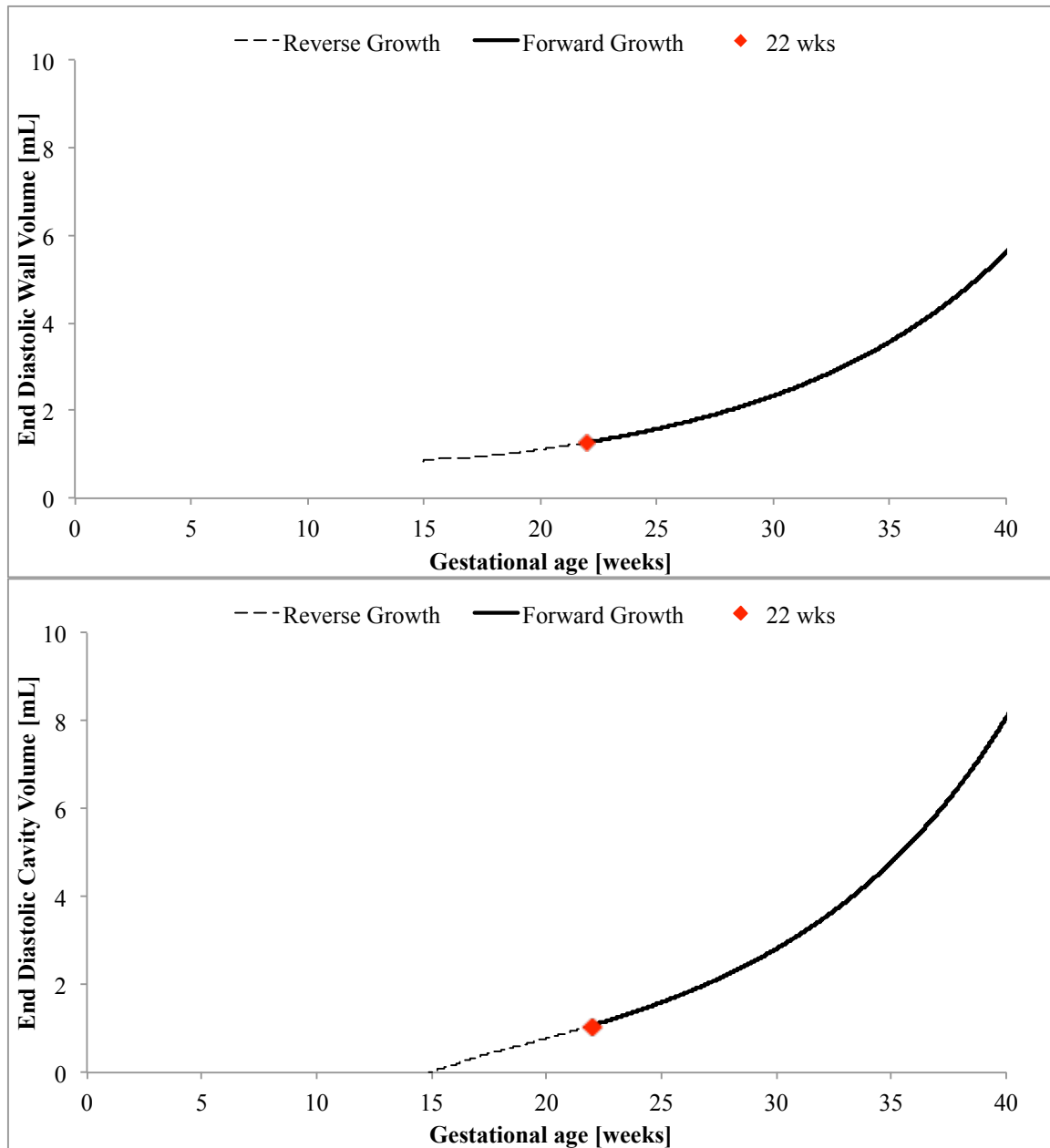


Figure 4.2: Simulated volumetric growth in forward and reverse direction

Forward growth was previously simulated from 22 to 40 weeks gestation; the growth law is applied in the reverse direction from 22 weeks to simulate reverse growth. The red diamond represents the initial point of growth in forward and reverse direction

4.3 Discussion

Myocardial hypertrophy and extracellular matrix (ECM) remodeling can be defined as changes in the heart geometry and function that occur over an extensive period of time as a result of pathology (heart disease, CHD) or physiology (growth and development, pregnancy, aging etc.). Hypertrophy and ECM remodeling can be similar in some cases. For instance, cellular hypertrophy is the response in both hypertensive heart disease and post-natal heart development due to pressure overloading. Remodeling may initially behave as a compensatory mechanism to normalize function under pathophysiological stimuli. This explains why during pressure loading, LV wall thickness increases as it normalizes wall stresses [81].

Hypertrophy-related changes in the LV geometry can be classified into concentric and eccentric hypertrophy. During concentric hypertrophy, the LV wall thickens with minimal change in chamber volume whereas during eccentric hypertrophy, the LV wall thins and the chamber volume decreases significantly. The mechanism behind this type of wall thickening and LV dilation is explained by the parallel and serial addition of sarcomeres in the myocytes, respectively. Hypertrophy and remodeling, in addition to geometrical changes, can also induce functional changes that affect myocardial contraction at the myocyte level. Increased myocardial stiffness, which can impair diastolic filling, is a hallmark of diastolic heart failure with preserved ejection fraction. This increase in myocardial stiffness has been attributed to a delayed relaxation of the myocyte's contraction. These global changes that occur during growth and remodeling can be traced to the geometrical and functional changes in the myocytes [81].

Several computational models based on the concept of finite volume growth have been developed, as described previously [61, 63 82, 83]. These ventricular growth models were developed with either ventricular myofiber stress as the stimulant of growth or with ventricular myofiber and/or myocardial cross-fiber strain as the primary stimulant. Guccione et al recently presented a constitutive strain-drive growth model capable of describing both ventricular remodeling and reverse modeling under pathological conditions. The model was able to predict key features in the end-diastolic pressure-volume relationship that is observed experimentally and clinically during ventricular growth and reverse growth [84].

The goal of this aim was to adapt our growth law in the reverse direction to test its ability to predict LV growth at time points prior to mid gestation. Model compatibility with clinically and experimentally observed LV dimensions in healthy fetuses were compared at 17.2 weeks gestation (Figure 4.3). Figure 4.4 shows LV cavity and wall volumetric growth derived from echocardiographic measurements from multiple studies.

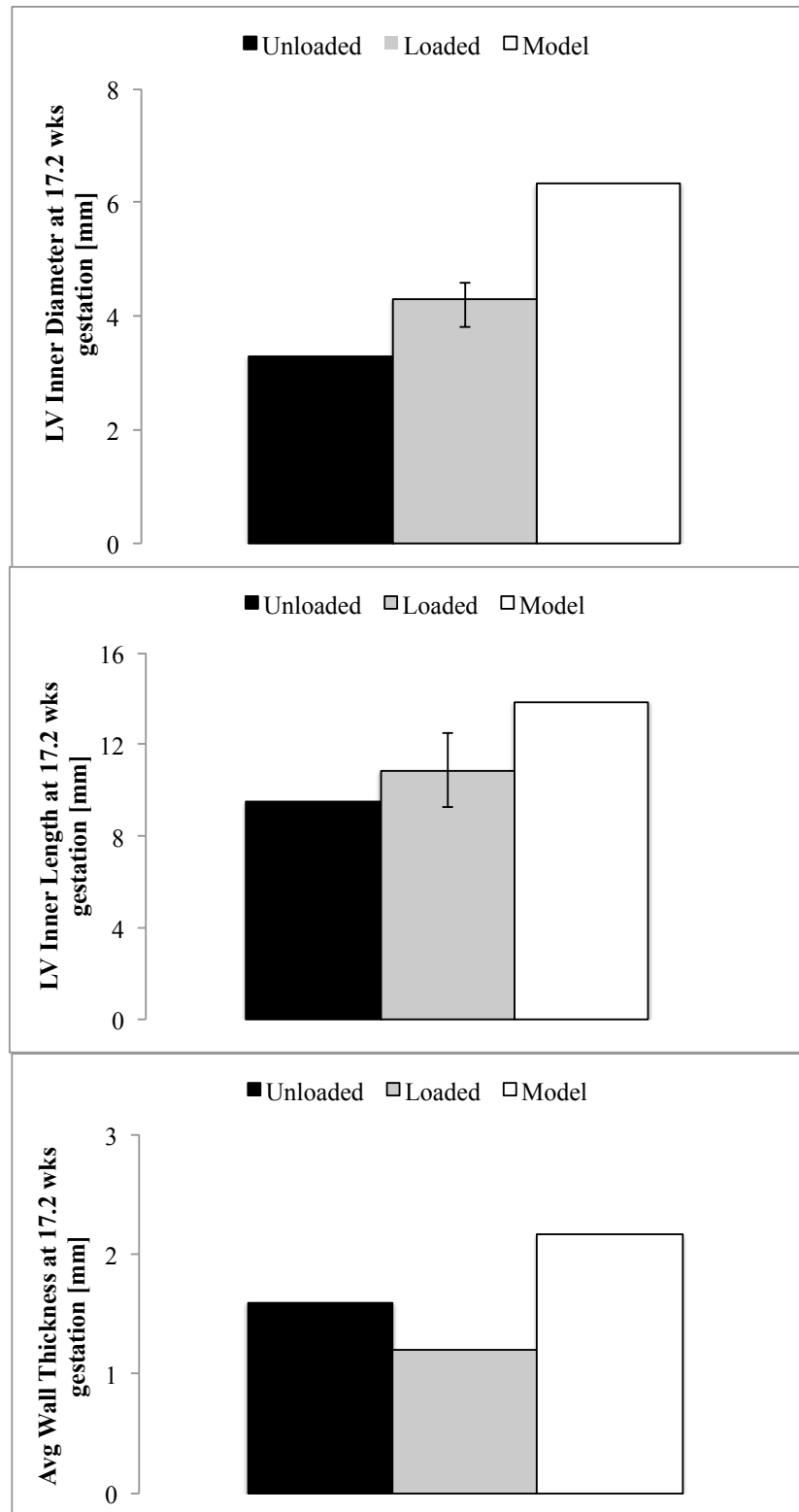


Figure 4.3: LV dimensions at 17.2 weeks gestation as reported in literature compared with values from reverse growth model

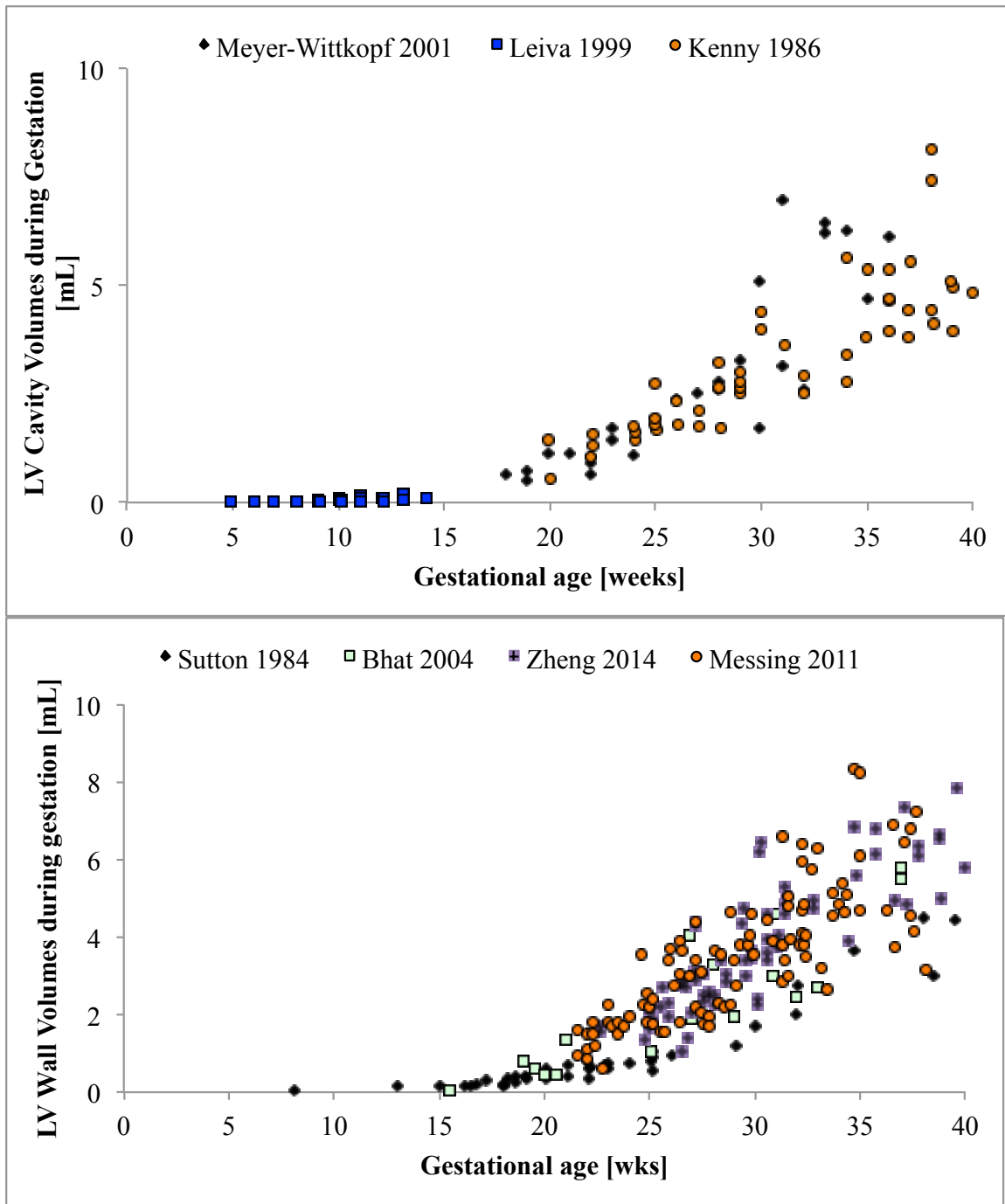


Figure 4.4: Mapping of LV Cavity (top) and free wall (bottom) volumes from 5-40 weeks gestation, as reported in literature [73, 92-97]

It is noteworthy that the model when grown in the reverse direction has an applied preload of 0.75 kPa as in the forward direction. The fetal LV from mid gestation to term can be modeled with a constant preload, as described earlier, because the EDP does not change significantly until birth. The growth model was developed based on this assumption that may not apply prior to mid gestation. The pressure in the LV prior to 22 weeks gestation is significantly lower and exhibits a relatively steeper slope over time as the heart continues to develop and grow in size during early gestation.

The strain-based growth law in both forward and reverse direction does not account for the dynamics of pressure development or myocardial stiffness during growth. While this may be a valid assumption after mid gestation, this is a limitation when modeling growth in early gestation. The growth law utilized in this model can be modified to incorporate remodeling by varying the passive stiffness of the myocardium dependent on either volume or time. For example, Kerckhoffs et al previously used the growth law to predict concentric and eccentric cardiac growth during pressure and volume overload [63]. However, remodeling prior to mid gestation was not studied in our model of reverse growth.

CHAPTER 5

Patient-Specific Case Study of HLHS

5.1 Methods

The following section will discuss the workflow of developing a patient-specific model of HLHS based on clinical echocardiography measurements and test the hypothesis that (a) a patient presenting a severely hypoplastic ventricle at mid gestation will exhibit significant decrease in volumetric growth at term, and (b) that the model can accurately predict the dimensions of the patient's ventricle at late-gestation.

5.1.1 Clinical Measurements

In cases of suspected fetal cardiac abnormality, patients are referred for fetal echocardiography in order to observe development of fetal cardiac structures and associated flow patterns in real-time. The fetal studies were conducted in the Pediatric Cardiology division of the Primary Children's Hospital, Salt Lake City, Utah, following guidelines set by the American Society of Echocardiography. All patient data are retrospective and de-identified, and were not acquired specifically for this study. The

studies were IRB approved and conducted at 23.1 weeks gestation with a follow-up at 30.1 weeks; fetal age was determined by standard protocols by obstetricians.

Measurements of the hypoplastic LV were made retrospectively by a pediatric cardiologist at Rady Children's Hospital, San Diego, California. The measurements taken were of the left ventricular internal and external diameters (width) at the base and mid-level, as well as the inner and outer length of the cavity. Figure 5.1 displays a screenshot with the measurements taken for this patient at the first time point. Measurements were only made when the image quality allowed clear definition of the structures in the four-chamber projection of the fetal heart at the end of diastole.



Figure 5.1: Screenshot of LV end-diastolic measurements obtained for HLHS patient at first time point (23.1 weeks)

5.1.2 Mesh Generation

The left ventricular measurements obtained at end-diastole as described above were used to calculate the wall thickness at the base, mid, and apex levels. Table 5.1 lists the LV measurements corresponding to the HLHS patient at 23.1 weeks used to generate a FE mesh in a prolate spheroidal coordinate system as described in Chapter 2.1.2. The resulting surface mesh was refined to generate a mesh of 30 nodes and 20 elements

representing the end-diastolic geometry of the patient's LV at 23.1 weeks gestation. The accuracy of the generated mesh was verified by ensuring that the short-axis diameter and wall thickness at the base and mid-level, along with the length of the LV cavity agreed to within 1% of the measurements from the clinical data.

Table 4.1: LV dimensions of the HLHS patient at 23.1 weeks gestation retrospectively measured from fetal echocardiographic images

LV Dimension	Echo measurement [mm] at 23.1 weeks
Inner Diameter (base)	5.8
Outer Diameter (base)	8.8
Inner Diameter (mid)	5.8
Outer Diameter (mid)	8.8
Inner Length	7.1
Outer Length	9.4

The measurements from the patient's ultrasonic examination are obtained in-vivo and hence correspond to a loaded state of the heart. In order to simulate growth in the developed FE mesh and perform biomechanics simulations, it is required to obtain the unloaded reference geometry for the patient LV. The unloaded state was modeled from the end-diastolic ventricular geometry at a normal preload, using the method described by Krishnamurthy et al [69]. The passive material properties used in the normal reference state are also assumed to be the same for the patient myocardium. Briefly, the unloading algorithm first inflates the initial geometry to the measured EDP. The deformation gradient between the inflated mesh and the fitted end-diastolic mesh is then computed, and this deformation gradient is applied inversely to get a new unloaded geometry estimate that is consistent with respect to the nodal positions of the initial geometry. This process is iterated until the projection error between the surfaces of the measured and loaded geometries is lower than the fitting error. This yields the unloaded geometry that,

when loaded to the measured EDP, deforms to the measured end-diastolic geometry developed previously with the same passive material properties [63, 69].

The unloaded ventricular geometry constitutes the anatomic model of the patient LV. The anatomic model and the passive constitutive model comprise the patient-specific fetal LV model. The model is inflated to the EDP to obtain the deformed nodal properties, which are inputted as initial conditions for the growth model. This method is the same as described for setting up the growth model of a normal fetal LV, as described earlier. The model is allowed to grow to term and LV dimensions are extracted at 30.1 weeks gestation to compare with the measured echocardiographic data at that time point.

5.2 RESULTS

In a case study, using echocardiographic data (LV geometry) from a HLHS patient at 23.1 weeks, the patient-specific growth model with normal preload and is able to predict a hypoplastic LV at birth and replicate clinical measurements of LV dimensions at 30.1 weeks. The model predicts a 50% reduction in LV EDV (1.1 mL) and a 60% reduction in LV wall volume (2.1 mL) at birth, consistent with the patient diagnosis of a severely hypoplastic LV.

The model replicates LV short-axis inner diameters at the base (6.5 mm) and mid level (7.4 mm), inner length (8.5 mm) and outer length (10.5 mm) with error ranges shown in Figure 5.3. The patient-specific model is not able to accurately replicate the LV wall thickness measurements at base and mid (-50% error); possible theories and limitations are discussed in Chapter 5.3.

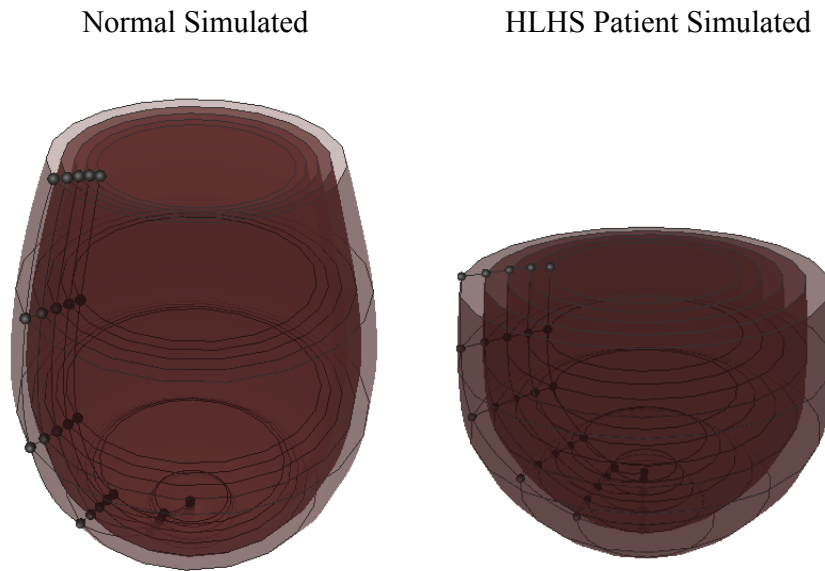


Figure 5.2: Three-dimensional FE models based on echocardiographic mid gestation data in normal (left) and HLHS (right) cases

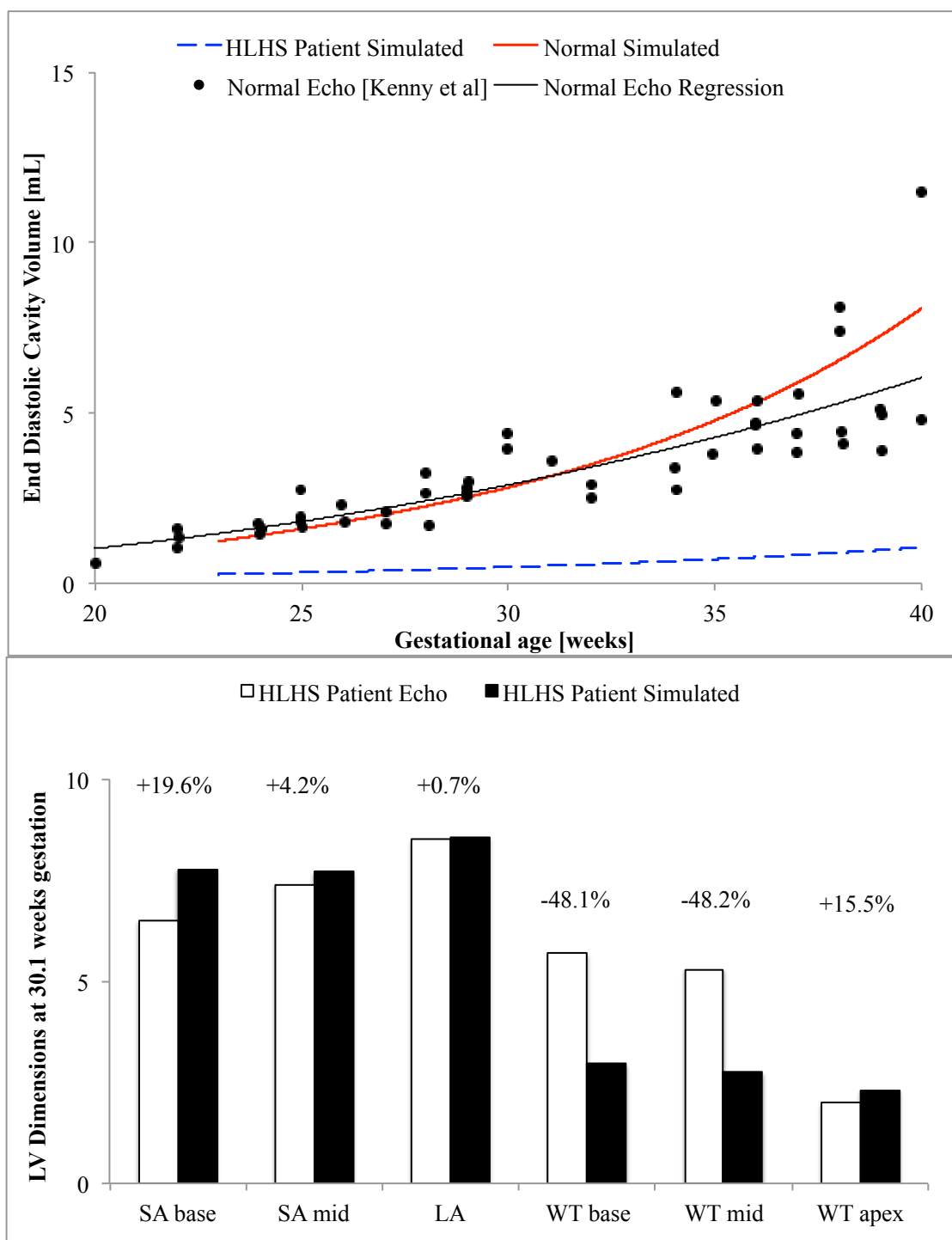


Figure 5.3: Simulated LV cavity volumetric growth (top) and dimensions in HLHS patient (bottom)
 LV cavity volumetric growth from mid gestation to birth is compared between the echocardiographic normal, simulated normal, and simulated HLHS cases (top); LV dimensions are compared between patient echocardiographic data obtained at 30.1 weeks gestation and predicted dimensions from simulated HLHS model

5.3 DISCUSSION

Hypoplastic left heart syndrome (HLHS) is a complex congenital heart defect in which the left-sided cardiac structures of the heart are severely underdeveloped, resulting in obstruction of blood flow from the left ventricular outflow tract to the systemic circulation. It has been reported that HLHS occurs in 0.016 to 0.036% of all live births in Canada and the United States, and accounts for 23% of neonatal deaths as a result of congenital heart malformations [85, 86]. Without treatment, 95% of newborns affected by HLHS die during the first month of life, and none survive beyond 4 months [87]. Features of HLHS include varying degrees of hypoplasia presented in the LV or ascending aorta, and mitral and aortic valve atresia or stenosis. A typical HLHS heart is compared with a normal heart in Figure 5.4.

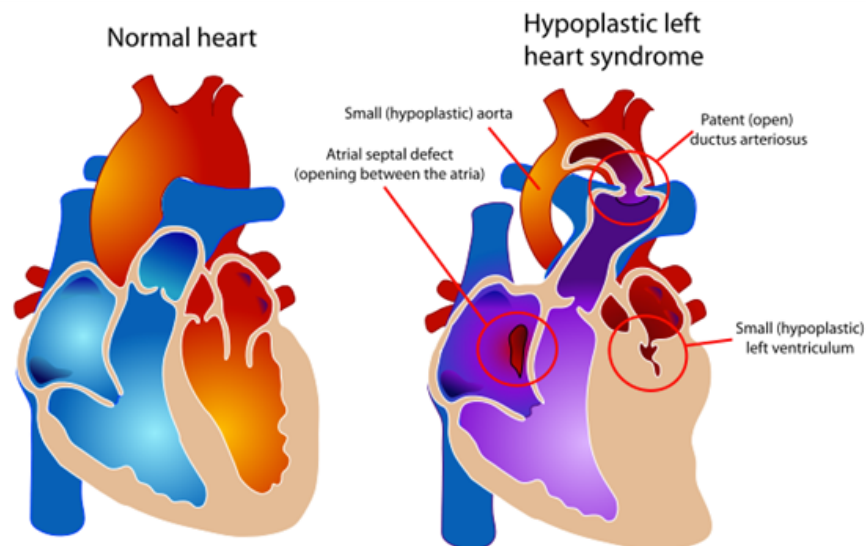


Figure 5.4: Diagram of a typical heart compared with one with HLHS [88]

The syndrome can be diagnosed by fetal echocardiography between 18 and 22 weeks of gestation. However, HLHS goes undetected in most newborns and the normal

physiological changes that occur upon birth lead to severe hemodynamic disturbances in the infant. The clinical presentation of HLHS occurs as systemic and coronary perfusion is critically decreased, leading to metabolic acidosis, tissue hypoxia, and eventually vascular shock or death. Presently, HLHS is managed by a three-stage palliative reconstructive surgery that creates unobstructed systemic blood flow from the right ventricle to the aorta (Norwood, Stage 1) and connects the superior and inferior vena cava (Fontan, Stage 2) to the pulmonary arteries, facilitating the transition to a physiologically normal circulation. The last stage involves closure of the fenestration, resulting in the right ventricle pumping oxygenated blood through a reconstructed aorta and deoxygenated blood returning directly to the lungs. Survival rates for all infants with combined three-staged procedures has been reported to be 63 to 80% at one year of age and 58 to 72% at five years of age [86]. An alternative to surgery is infant heart transplantation, which has reported survival rates of 76% at five years and 70% at seven years, but many infants die while awaiting a donor heart due to complications [86].

Although fetal echocardiography allows an accurate prenatal diagnosis of HLHS at mid gestation, providing the opportunity to plan management and counseling for the family, Galindo et al reported an overall survival rate of 36% for these prenatally diagnosed fetuses [89]. The outlook for fetuses affected by HLHS is poor due to the limitations posed by early diagnosis via fetal echocardiography and inability to predict the outcome of the fetal hypoplastic heart upon birth. Patient-specific computational modeling of developing fetuses with HLHS could serve to improve prenatal diagnosis by providing insight into the biomechanics and growth behavior of the affected ventricle.

Our model was based on patient-specific LV geometry at mid gestation and was able to replicate short-axis and long-axis dimension data from late-gestation. It was not able to replicate wall thickness measurements at the base and mid level, though it predicted wall thickness at the apex level accurately. This is likely due to the altered geometry as it plays a significant role in altering strain distribution, thereby leading to differential addition of sarcomeres in series or parallel. A greater understanding of the strain distribution may shed insight into the mechanism underlying the significant wall thickening observed in hypoplastic hearts; however, our study did not explore this facet of fetal growth. Our HLHS model predicts a severely hypoplastic LV at birth in comparison to the normal simulated LV. Our conclusions from the growth model sensitivity analysis (Chapter 3.2) support this prediction as we observed reduced volumetric growth in a thick-walled LV.

Fetal LV dimensions obtained from pre-recorded echocardiographic images are valuable measurements as they provide the most clinically relevant and accurate inflation about ventricular structure in HLHS patients. Despite the retrospective method used, these images contain several types of artifacts as they are taken in real time. In addition, hypoplastic ventricles are of smaller scale relative to normally developing ventricles, which compounds the difficulty of taking accurate measurements. While measurements were only made when the structures were visibly clear and delineated, there is the possibility of introducing error due to manual handling of data. For this case study, six dimensional measurements were provided at different planes; increasing the number of data points and including flow data would allow for more constraints on the developed mesh and, therefore, a more faithful patient-specific geometry. In addition, measurements

at more than two time points would be valuable in validating the patient-specific model and its predictive capability. For future studies, protocols need to be developed to ensure consistent methods between patients and, if possible, reduce manual error by having multiple experts obtain measurements.

It is noteworthy that the ventricular geometry was imaged at end-diastole when the heart experiences a significant amount of load. An unloading algorithm developed by Krishnamurthy et al was used to predict the unloaded configuration of the 3D FE model under normal preload and passive material properties, which may not hold true for the patient-specific case [69]. It is impossible to obtain unloaded geometry from echocardiographic images and presently it is not standard protocol to obtain a measure of preload via fetal cardiac catheterization in utero. However, the predicted unloaded geometry is able to successfully deform to the measured end-diastolic geometry, demonstrating promising results. Repeating this with a larger set of patients would serve to validate the algorithm as well as the ability of the growth model to predict dimensions at a future time point.

CHAPTER 6

CONCLUSIONS

The single ventricle growth model for a normal human fetal LV presented here was developed based on experimental and clinical geometric and functional data. The model is able to accurately represent normal volumetric and shape growth of the fetal LV from mid gestation to birth. The model is also capable of simulating reverse growth from mid gestation to an *in vivo* state of near zero LV cavity volume, providing a comprehensive overview of fetal growth from the onset of cardiac function to birth. The sensitivity of the growth model to several model parameters was quantified, which led to an understanding of the individual clinically relevant parameters that mediate normal growth in the fetal LV. Finally, a patient-specific growth model for HLHS was developed that was able to replicate clinical echocardiographic measurements for LV shape at a later time point and predict severe hypoplasia at birth.

Patient-specific and clinically relevant computational models offer potential for studying the complex biomechanical and electrophysiological behavior of the heart in its normal and diseased states. For this reason, significant efforts have been made to develop protocols for building specific models and demonstrate the predictive capabilities of these

models by comparison with experimental results and clinical measurements. Incorporation of growth and remodeling in patient-specific and clinically relevant computational models offers the capacity to understand the complex mechanisms and biomechanical stimuli underlying normal cardiac development as well as in pathophysiology. The next step is to explore the clinical feasibility of these computational models and the benefits they can offer to physicians in optimizing clinical outcomes and surgical interventions. A main focus of this study was to develop a physiologically relevant FE model describing normal growth in the human fetal model that can ideally be used as a clinical tool, especially considering the limited scope of fetal cardiac computational models.

The developed single ventricle model for normal fetal growth is a significant step towards building patient-specific models based on fetal echocardiography data. Since ventricular geometry is one of the major model parameters that determine cardiac function, the focus of this study was to optimize the single ventricle geometry. In the future, it would be invaluable to generate a bi-ventricular mesh of the fetal heart with circulation in order to improve the physiological relevance of the model as well as understand the interaction effects between the ventricles in a normal and diseased state. This would be specifically useful in a clinical case such as HLHS because the right ventricle often compensates for the reduced function in the LV. Identifying the biomechanical stimuli that drive this behavior and quantifying the consequential effects on cardiac growth would shed insight into the defect.

The methods developed in this thesis serve to facilitate understanding of fetal growth behavior undergoing normal development and provide a benchmark model for

normal growth in the human fetal LV, enabling comparison with patient-specific fetal LV models. This is, to the best of our knowledge, one of the first computational models that describe cardiac growth behavior in the human fetus by integrating information from multiple clinical measurements and predicts patient diagnoses based on mid gestation echocardiographic geometry. Ultimately, with further refinement, the model has potential to aid physicians in surgical planning to achieve optimal therapeutic outcomes. Computational models such as these will be invaluable tools in understanding the complex stimuli-responsive behavior of organ-level fetal growth.

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