**MULTISCALE MODELING OF LV GROWTH UNDER AUTONOMIC REGULATION OF BAROREFLEX FEEDBACK LOOP**

Hossein Sharifi1

Charles K. Mann1

Jonathan F. Wenk1,2\*

Kenneth S. Campbell3

1Department of Mechanical Engineering, University of Kentucky, Lexington, KY;

2Department of Surgery, University of Kentucky, Lexington, KY;

3Department of Physiology & Division of Cardiovascular Medicine, University of Kentucky, Lexington, KY;

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\*Corresponding Author:

Jonathan F. Wenk, Ph.D.

University of Kentucky

Department of Mechanical Engineering

269 Ralph G. Anderson Building

Lexington, KY 40506-0503

Phone: (859) 218-0658

Fax: (859) 257-3304

Email: jonathan.wenk@uky.edu

Introduction

**Abstract**

**Background**: Cardiac hypertrophy is an adaptive response of the heart muscle to ventricular overloading, mutations in sarcomeric proteins, or localized loss of contractile properties of the myocardium. However, if the underlying cause is not resolved, prolonged hypertrophy can increase the risk of heart failure and sudden death. The development of computational models on cardiac growth have increased significantly in recent years. These approaches can be used in predicting the progression of cardiac growth and could one day improve treatment plans for patient care. Although current models have been able to accomplish this goal with certain limitations, none of them consider the cross-bridge cycling of sarcomeres at the myosin level, nor do they account for the impact of baroreceptor in maintaining the arterial pressure during remodeling.

**Objective**: This study introduces a new growth model, incorporated with a multiscale model of cardiovascular function, which can predict the cardiac growth in response to valvular disorders like aortic stenosis and mitral regurgitation.

**Methods**: A multiscale model of cardiovascular function, named PyMyoVent, was extended by implementing a unified stress-driven growth module. The concentric growth law (wall thickening) was driven by the total stress in half-sarcomeres, whereas the passive stress drove the eccentric growth law (chamber dilation). Both growth laws were able to perform simultaneously. As we described in our previous work, the baroreflex feedback loop maintained the arterial pressure at the set-point level via continuous regulation of heart rate, myofilaments contractility, Ca2+ transient inside the cell, and the vascular tone.

**Results**: The model was able to predict the cardiac growth in response to different levels of severity for aortic stenosis and mitral regurgitation. In comparison to clinical data found in the literature, the model could appropriately predict both the trend and magnitude of change in the ventricular dimensions for both cases of valvular disorder. Furthermore, the model was able to capture the reverse cardiac growth (atrophy) in response to ventricular unloading.

**Conclusion**: A new multiscale model of the cardiovascular system is presented, which can predict cardiac growth while the arterial pressure is preserved via the baroreflex feedback loop.

**Keywords:** Multiscale Model, Cardiac Mechanics, Cardiac Growth, Concentric Hypertrophy, Eccentric Hypertrophy, Baroreceptor

**Introduction**

Cardiac diseases that exhibit hypertrophy can be caused by altered ventricular loading or mutations in sarcomeric proteins, which regulate cardiomyocytes (1-3). The growth and remodeling that are induced by cardiac hypertrophy can be categorized into two groups: 1) Concentric growth, where the ventricular wall mass and wall thickness increase in response to pressure overload condition, with little or no change in the ventricular chamber volume. 2) Eccentric growth, in which the ventricular chamber volume dilates due to volume overloading with small change in the wall thickness (4).

During past few decades, a variety of computational models on cardiac hypertrophy (5-10), along a number of review articles on the state of the art in cardiac growth and remodeling (11-14), have been developed. In addition to experimental studies with animal models or clinical studies with patients, these predictive models have brought new insights on the mechanisms of cardiac hypertrophy, and could one day contribute to the improvement of patient care.

The driving mechanical stimuli (myofiber stress or strain) utilized in these models are still open to debate. Some models (7, 9, 15, 16) employed a unified stimulus signal (either myofiber stress or strain), while others (10, 17) proposed a combination of different mechanical stimuli to simulate cardiac hypertrophies. In a recent work, Rondanina (18) tested different combinations of growth stimuli using a simple multiscale model in response to three different types of valvular disease. They showed that all four combinations of stress and strain stimuli resulted into stable growth, with the most reliable results stemming from the use of at least one stress-driven growth law. Mojumder et al. (19) showed finite element results of growth, which had a correlation with the changes in maximum fiber stress, but not the stretch, during pressure overloading.

Valvular disorders, such as aortic stenosis and mitral regurgitation, cause changes in the ventricular loading and cardiac function, but the arterial pressure and cardiac output normally remain unchanged (20-25). A major limitation to current modeling approaches is that they do not consider the effect of the baroreceptor feedback loop, which regulates arterial pressure. Most models usually capture the cardiac hypertrophy under constant heart rate, myocardial contractility, and vascular tone. Consequently, they have reported some mismatch in the predicted hemodynamics when compared to measured data. For example, Rondanina et al.’s (18) model predicted a 20% to 40% reduction in mean arterial pressure and cardiac output in response to aortic stenosis, aortic regurgitation, and mitral regurgitation. Also, Kerckhoffs et al. (9) reported a mismatch between the calculated peak LV cavity pressure and that measured in experiments, and posited that it could be due to the absence of fast baroreflex responses in their model. Rondanina et al. (26) recently investigated the influence of a hemodynamic feedback loop on the mechanical growth stimuli. They suggested using a mixed stress-strain growth model in conjunction with a model of hemodynamic feedback to capture more realistic cardiac growth and preserved cardiac pump function.

Furthermore, many current models have shown deficiencies in simulating reverse growth due to unloading of the ventricle. Ventricular unloading has been performed in clinical settings for different applications, including mitral valve (27) and aortic valve (28) treatments. Lee et al. (29) improved the strain-driven growth law proposed by Goktepe et al. (10) and introduced a new growth law that was able to capture the reversal growth in response to elimination of volume overloading. In a recent work, Arumugam et al. (30) proposed a growth model based on the concept of volumetric growth applied to a 3D model of biventricular geometry. Their model could simultaneously predict cardiac growth and reversal of growth in mechanical dyssynchrony.

In our recent work (Sharifi et al. 2021), we coupled a model of the baroreflex loop with a multiscale model of cardiovascular function (31). The baroreflex loop was able to maintain the arterial pressure at a user-defined setpoint level via continuous regulation of heart rate, myofilaments contractility, Ca2+ transient, and vascular tone. In current study we extend our previous work by adding a unified stress-driven growth sub-model, which is able to capture the cardiac growth in response to altered ventricular loading, and also is able to predict the reverse growth of the ventricle due to ventricular unloading.

**Methods**

***Overview***

This study extends our previous work (Sharifi 2021) by adding a sub-model for cardiac growth to a multiscale model of cardiovascular function named PyMyoVent. Fig 1 shows the overall flowchart of PyMyoVent and illustrates how sub-models communicate with each other. The original framework was initially published by Campbell et al. (31) where they showed how the variation in model parameters (like myosin rate constants) would change the system level parameters (like ventricular chamber volume or end-systolic pressure-volume relationship). The original framework was essentially built on four main sub-models: 1) myocyte electrophysiology model, 2) MyoSim model of contraction, 3) hemispherical model of single ventricle, and 4) circuit model of systemic circulation system. The activation pulse drives the Ca2+ transient in the electrophysiology model, which in turn drives the contraction model of half-sarcomeres. The change in half-sarcomere length and stress determines the blood pressure inside the ventricle chamber via Laplace’s law. Consequently, the blood flows into the lumped parameter model of circulation and updates the compartmental blood volume based on Ohm’s law. More details on the original framework can be find in Campbell et al.’s (31) study.

Diagram

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**Fig 1. Schematic flowchart of the multiscale model of cardiovascular function (PyMyoVent)**

***Baroreflex feedback loop model***

In our previous work (Sharifi et al. 2021) we enhanced the original framework of PyMyoVent (31) with a model of the baroreflex (Fig 1) to maintain arterial pressure at a user-defined setpoint level. The baroreflex model was designed to regulate the heart rate, myofilaments contractility, Ca2+ transient, and vascular tone. It was shown that the baroreflex loop was able to regulate the system towards a user-defined level of setpoint, as well as maintain the arterial pressure at the setpoint level under perturbed ventricular loading, such as acute blood loss or aortic stenosis. More information on the baroreflex loop is provided in the main work (Sharifi et al. 2021).

***Growth model***

The driving signal for the growth model is the stress in half-sarcomeres. Active contractile stress is the stimulus signal for the concentric growth, whereas the passive stress regulates the eccentric growth. Essentially, a deviation in sarcomeric stresses from their homeostatic levels (set-points) generates a growth signal, g, within the cardiomyocytes. The growth signal g is driven with the following system of ODEs (equation 1) that can be varied between 0 and 1.



where i represents the growth type (i.e. concentric or eccentric). kdrive is a constant rate factor. Si is the driving sarcomeric stress, Si,set is the homeostatic level of the driving signal, and gi is the growth signal for growth type i. It should be noted that both growth signals are operating during a simulation.

When the driving signal (half-sarcomere stress, Si) is above the set-point, the firing growth signal gi increases. Whereas, when it drops below the setpoint, the growth signal decreases. The growth signal then drives the change in the controlled parameters of the growth model, defined below.

*Eccentric growth*

Eccentric growth is controlled by the serial number of half-sarcomeres (nhs) around the circumference of the ventricle. The rate of change in the serial number of half-sarcomeres is controlled via equation 2, where γecc is the gain factor for eccentric growth law. According to equation 1, an increase in passive stress of half-sarcomeres (i.e. stimulus signal for eccentric growth), increases the serial number of half-sarcomeres and hence reduces passive stress until it is back to its setpoint level. A reduction in passive stress, on the other hand, reduces the serial number of half-sarcomeres and hence elevates the passive stress towards the setpoint.



***Concentric growth***

Concentric growth is governed by the change in ventricular wall volume (Vwall). Equation 3 defines the rate of change in the ventricle wall volume, where γcon is the gain factor for concentric growth law. The second term in equation 3 enforces the proportional gain in myocardial volume due to change in serial number of half-sarcomeres. It is well accepted in the literature (4) that during eccentric growth, the wall volume is not preserved and hence it changes as the serial number of half-sarcomeres changes. According to equation 1, if active contractile stress is above the setpoint level, the wall volume increases and brings back the elevated active stress towards the setpoint. Whereas, when the active stress drops below the setpoint, the wall volume decreases so the active stress in half-sarcomere increases back to setpoint level.



***Baseline simulation***

The current study is focused on representing human physiology. Thus, the model parameters were initially tuned to simulate the cardiovascular function of a healthy adult with a heart rate of 70 BPM, arterial pressure range of 110/70 mm Hg, cardiac output of ~ 5 liters/min, and ejection fraction of ~50% according to reference ranges in the literature (32, 33). In all simulations, the baroreflex sub-model was set to maintain the mean arterial pressure around the set-point level of 90 mm Hg. Two different types of valvular disorder were modeled by perturbing the steady state solution from the baseline simulation to investigate the ability of the model to capture cardiac growth. More details on each case are explained in the following sections.

***Pressure overloading (Aortic stenosis)***

Aortic stenosis (AS) is a valvular disease that creates pressure overloading to the left ventricle because of narrowing in the aortic valve area (34). Four different levels of AS severity (Table 1) were simulated by increasing the aortic resistance factor in the circuit model of circulatory system. Based on Poiseuille equation, resistance of a vessel has an inverted relation with the squared of cross-sectional area. For instance, a 500 percent increase in the aortic resistance is equivalent with a ~60 percent reduction in the aortic valve area, from a mean value of 2.5 cm2 for healthy adults (35-37) to a mean value of 1 cm2 for patients with aortic stenosis (35, 38-43).

|  |  |
| --- | --- |
| **Table 1.** Simulated different levels of AS severity | |
| % Increase in the aortic resistance | Equivalent % reduction in aortic valve area |
| 250 % | 46.55  (from 2.50 cm2 to 1.33 cm2) |
| 500 % | 60  (from 2.50 cm2 to 1.00 cm2) |
| 750 % | 65  (from 2.50 cm2 to 0.86 cm2) |
| 1000 % | 70  (from 2.50 cm2 to 0.70 cm2) |

***Volume overloading (Mitral regurgitation)***

Mitral regurgitation (MR) is a valvular disorder that causes improper closure of mitral valve, and consequently allows the blood to flow backward into the left atrium during systole and develop volume overloading (44). The backward blood flow through the mitral valve during systole is essentially controlled via a model parameter named “leaking factor” (Gleak in equation 4) that is zero for “baseline simulation”, representing a proper valve, and is nonzero for simulating an insufficient valve. The following values for “leaking factor” (Table 2) were used to simulate four levels severity for patients with MR (25, 45-49).



|  |  |
| --- | --- |
| **Table 2.** Simulated different levels of MR severity | |
| Gleak | Equivalent regurgitant volume (ml) |
| 5e-4 | 20 |
| 1e-3 | 30 |
| 2e-3 | 60 |
| 3e-3 | 80 |

***Model validation***

To validate our model, the simulated results were compared with clinical data from the literature, which was acquired by cardiac magnetic resonance (Table 3). Clinical data were categorized into three cases named “control volunteers”, “patients with AS”, and “patients with MR”. For each case, quantified data were collected from eight different studies. Ventricular dimensions were quantified with LV end-diastolic volume index (LVEDVi), LV end-systolic volume index (LVESVi), LV mass index (LVMi). Systolic function was assessed with LV stroke volume index (LVSVi) and ejection fraction (EF). An averaged body surface area of 1.9 m2 (50, 51) was used for indexing the simulated model results. Some studies in Table 3 did not report the measured LVSVi, so the absolute difference of reported LVEDVi and LVEDSi was used as LVSVi.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 3.** List of studies with quantified clinical data for LV dimensions and systolic function acquired by cardiac magnetic resonance. | | | | | | | | |
| **Control volunteers** | | | **Patients with AS** | | | **Patients with MR** | | |
| Study authors | Year | Study population | Study authors | Year | Study population | Study authors | Year | Study population |
| Lee et al. (41) | 2020 | 30 | Lee et al. (41) | 2020 | 191 | Liu et al. (49) | 2020 | 104 |
| Spath et al. (43) | 2019 | 41 | Everett et al. (40) | 2020 | 440 | Seldrum et al. (48) | 2019 | 59 |
| Seldrum et al. (48) | 2019 | 30 | Spath et al. (43) | 2019 | 159 | Bakkesstrom et al. (47) | 2018 | 46 |
| Lee et al. (52) | 2015 | 15 | Singh et al. (42) | 2019 | 174 | Polte et al. (53) | 2017 | 40 |
| Edwards et al. (25) | 2014 | 35 | Everett et al. (39) | 2018 | 61 | Myerson et al. (45) | 2016 | 152 |
| Chin et al. (35) | 2014 | 33 | Chin et al. (35) | 2014 | 133 | Edwards et al. (25) | 2014 | 35 |
| Barone-Rochette et al. (38) | 2013 | 20 | Barone-Rochette et al. (38) | 2013 | 128 | Schiros et al. (54) | 2012 | 94 |
| Schiros et al. (54) | 2012 | 51 | Steadman et al. (55) | 2012 | 41 | Uretsky et al. (46) | 2010 | 23 |
| Data were reported as mean ± standard deviation (SD) or median (interquartile range). | | | | | | | | |

**Results**

***Aortic stenosis***

Fig 2. shows model prediction in multiscale levels for 500% increase in the aortic resistance as an example for one of the pressure overloading cases. Elevated afterload increased the required active contractile stress in sarcomeres for pumping blood out of the ventricle but did not change the passive stress significantly. In response to these changes in growth stimulus signals, growth module increased the ventricle wall volume by roughly 25%, but the serial number of half-sarcomeres did not change significantly (~1.5%). Consequently, the ventricle chamber volume remained unchanged, but the ventricle wall thickness was increased by ~23% and 16% at end-diastole and end systole, respectively, and thus mimicked the concentric hypertrophy. In response to this level of narrowing in aorta compartment, the baroreflex feedback loop maintained the arterial pressure at setpoint level throughout the simulation by increasing heart rate, myofilaments contractility, and vascular tone.

Diagram

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**Fig 2. Multiscale response to aortic stenosis.** Growth algorithm was activated once the model was at steady state at time of 50 s (first vertical dashed lines). Aortic resistance increased by 500% from time point of 600 s (second vertical dashed line) to 900 s (third vertical dashed line). Baroreflex feedback loop was continuously regulating the arterial pressure to be maintained at setpoint level (middle column).

***Mitral regurgitation***

Fig 3. Illustrates model response to one of the volume overloading cases with regurgitant volume of 60 ml. Both passive and active stresses in half-sarcomeres were increased due to the increased ventricular preload. Thus, growth module increased the serial number of half-sarcomeres and ventricular wall volume by ~20% and ~45%, respectively. Ventricle chamber volume was increased by ~75% and ~93% at end diastole and end systole because of the addition of half-sarcomere in series. However, wall thickness remained unchanged and mimicked the eccentric hypertrophy. Arterial pressure was remained at the setpoint level via continuous regulation of the baroreflex feedback loop.

Chart, diagram

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**Fig 2. Multiscale response to mitral regurgitation.** Growth algorithm was activated once the model was at steady state at time of 50 s (first vertical dashed lines). Leaking factor increased from time point of 600 s (second vertical dashed line) to 900 s (third vertical dashed line) to develop a volume overloading with regurgitant volume of 60 ml. Baroreflex feedback loop was continuously regulating the arterial pressure to be maintained at setpoint level (middle column).

***Model prediction versus the clinical data***

Fig 4. compares predicted LV dimensions indexed with the measured clinical data (Table 3) for aortic stenosis and mitral regurgitation. For former case, as the severity of stenotic aortic valve increased model predicted almost no change for LV chamber volume, but significant increase for LV mass. Model prediction were in line with the clinical data in terms of both trend and magnitude. For latter case, as the severity of volume overloading intensified, model predicted more dilation in LV chamber volume and more addition of LV mass, which were completely following the reported trend for clinical data.

**Diagram

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**Fig 4. Comparison between simulated LV dimensions and the collected clinical data.** Simulated variables are indexed by averagebody surface area of 1.9 m2. Model predictions for different severity of disease are shown with “x” marker and clinical data are shown with “o” marker. = change in the aortic resistance factor, RV= regurgitant volume.

Fig 5. Illustrates predicted LV systolic function versus the measured values in clinical data (Table 3) for both types of valvular disorders. For aortic stenosis, model simulated a tiny decrease in the stroke volume indexed and ejection fraction as the change in the aortic resistance () increased, but both were still in the reported range for the clinical data. For mitral regurgitation, stroke volume followed the reported trend for patients as the severity of volume overloading was worsting. However, the calculated ejection fraction was lower than the reported data.

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**Fig 5. Comparison between simulated LV systolic function and the collected clinical data.** Simulated stroke volume is indexed by averagebody surface area of 1.9 m2. Model predictions for different severity of disease are shown with “x” marker and clinical data are shown with “o” marker. = change in the aortic resistance factor, RV= regurgitant volume.

*Reveres growth (MR)*

Fig 6. Shows an attempt in simulating the reverse growth in response to removal of volume overloading shown in Fig. 3. This event perturbed the steady state solution for the dilated LV and lessened both types of stimuli signals (half-sarcomere stresses). Reduction in the driving signals drove the growth module to reduce the ventricle wall volume and serial number of half-sarcomeres back to the baseline level at the original steady state. The baroreflex loop kept the arterial pressure at the setpoint level throughout the simulation.

Diagram, engineering drawing, schematic

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**Fig 6. Multiscale response to removal of volume overloading.** Growth algorithm was activated once the model was at steady state at time of 50 s (first vertical dashed lines). Leaking factor increased from time point of 500 s (second vertical dashed line) to 700 s (third vertical dashed line) to develop a volume overloading with regurgitant volume of 60 ml. Unloading started from time point of 1200 s (forth vertical dashed line) and ended at time point of 1400 s (fifth vertical dashed line). Baroreflex feedback loop was continuously regulating the arterial pressure to be maintained at setpoint level (middle column).

***Baroreflex feedback effects***

In another attempt, the impact of baroreflex feedback loop on the growth sub-model was investigated. Figure S1 shows model response to a similar simulation shown in Fig 2 for 500% increase in the aortic resistance while the baroreflex feedback loop was not activated. First, the arterial pressure could not remain unchanged in the normal range for a healthy adult as the growth sub-model was transitioning towards the steady state. If we exclude the transitional phase in the arterial pressure, it was dropped from 134/82 mm hg to 124/76.5 mm hg only due to the increased aortic resistance. Secondly, due to absence of the baroreflex feedback loop, the hemodynamics loading was quite sensitive to the regulation of the growth sub-model and hence it was required to use slower growth rates in the model so the simulation could have enough time to adopt the changes. Therefore, the required simulation time was increased by a factor of two.

**Diagram, engineering drawing

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**Fig S1. Multiscale response to aortic stenosis under no regulation of baroreflex feedback loop.** Growth algorithm was activated once the model was at steady state at time of 50 s (first vertical dashed lines). Aortic resistance increased by 500% from time point of 600 s (second vertical dashed line) to 900 s (third vertical dashed line). Baroreflex feedback loop was not activated and thus the arterial did not remain unchanged (middle column).

**Discussion**

This study integrated a unified stress-driven growth sub-model into a multi-scale model of cardiovascular function under continuous regulation of baroreflex loop (Sharifi et al. 2021). Total stress in half-sarcomeres was assumed as the stimulus signal for concentric hypertrophy while the passive stress was driving the eccentric growth of LV. The growth sub-model was not only able to capture both types of cardiac hypertrophy (i.e. concentric and eccentric), but also it could capture the revere growth in response to ventricular unloading.

***Model response***

The implemented growth sub-model governed the concentric hypertrophy by controlling the ventricle wall volume, while the eccentric hypertrophy was adapted by regulating the serial number of half-sarcomeres around the circumference of LV. Both growth laws were happening at the same time, meaning that at any given time step both parameters can change because of any perturbation in the driving growth signals (i.e. half-sarcomere stresses).

In response to pressure overloading, sarcomeres need to generate higher contractile force so the ventricle can overcome the elevated afterload and pump blood to the rest of the body. An initial adaptive mechanisms of the heart to compensate the elevated active contractile stress is to deposit more sarcomeres in parallel and hence increase the wall thickness which in turn alleviate the increased stress (56). Although this mechanism is initially considered as an adaptive event and the systolic function of LV remains intact, ultimately the prolonged pressure overloading can end up to heart failure and patient’s death (57). According to hemispherical geometry of the left ventricle in our model, ventricle wall thickness can be derived via equation 5 Based on this equation, for a given chamber volume, wall thickness increases if the wall volume grows.



Current model defines the blood pressure inside the ventricle via *Laplace’s law* (equation 6). According to this law, for a fixed blood pressure (peak aortic pressure) and given chamber volume, as the wall thickness increases the total stress in myofiber would decrease. Therefore, an increase in the fiber cross-sectional area and wall thickness of the ventricle results into generating of higher contractile force with lower myofiber stress (58).



During volume overloading, as blood move backward from LV to the veins (last compartment before LV in the model) the preload increases and causes LV to fill with more blood during diastole. Excessive filling of LV stretches more the half-sarcomeres and consequently increases the passive stress in half-sarcomeres. Overstressed half-sarcomeres then starts the process of sarcomerogenesis (59) by changing the serial number of half-sarcomeres in a way to re-establish the optimal length at which the peak force happens (58). Essentially, it is well accepted that an increase or decrease in the number of sarcomeres would elevate or reduce the associated optimal length for a given peak stress (58), respectively. Therefore, by increasing the number of half-sarcomeres in the model, peak stress happens in a longer length and thus the circumference of LV would increase and end up to the dilation of LV.

***Compare to other existing models***

In recent years, a large number of computational models on cardiac growth and remodeling have been introduced. In one of the earliest model, Lumens et al. (60) proposed a simple mechanical model of the ventricle mechanics lumped with a model of circulation (61). In their model the blood volume and peripheral resistance were being regulated while the model could adapt the volume of ventricles and vessels in response to chronic and acute pulmonary hypertension. In a recent work, Witzenburg and Holmes (62) showed the impact of hemodynamic reflex on the ventricular remodeling in time of myocardial infarction (MI). They essentially used a compartmental model that was able to capture the ventricular remodeling in response to MI (15), and varied four model parameters reflecting the hemodynamic reflex that occurs in response to MI. They showed the variation in these hemodynamic reflex parameters, like heart rate or systematic vascular resistance, could explain the remodeling variation in patients with MI and consequently can be targeted for therapies of ventricular remodeling. Rondanina and Bovendeerd (26) also investigated the importance of hemodynamic feedback on the stimulus signal for the cardiac growth. They used a compartmental model of left ventricle and circulation lumped with a growth model and a hemodynamic feedback model where the cardiac output and mean arterial pressure were being controlled by regulation of peripheral resistance and the total stressed blood volume, respectively.

In addition to simple compartmental models, finite element (FE) models of the heart have done an excellent job in better understanding of the mechanics of cardiac growth and remodeling. Theory of “kinematic growth” is one of the most common approach in capturing cardiac growth and remodeling which is mainly used in FE modeling. Based on this theory, that was initially proposed by Rodriguez et al. (6) , the volumetric growth of the ventricle is defined on the concept of continuum of mechanics where the total deformation gradient is decomposed into plastic and elastic components. Three main advantages of FE models can be summarized as: 1) Its patient-specific geometry of the heart that is mainly acquired from MRI imaging (63), 2) Its ability in capturing the cardiac torsion at the time of heart contraction (64), and 3) Incorporating base to apex or transmural variation in contractile properties and fiber alignment (65).

One big major limitation of existing models is the absence of a more physiologically realistic model of sarcomere mechanics. Ultimately, they use a time-varying elastance model of LV mechanics that does not simulate the dynamically coupled interaction of myofilament in myosin level. However, in this study we used a more accurate model of sarcomere mechanics named MyoSim (66, 67). In this model the myosin heads of thick filaments can move across three different configurations from super-relax state (SRX) to disordered-relax (DRX) and force generating (FG) states based on the availability of binding sites on thin filaments activated by the Ca2+ molecule inside the cell. This model has recently been used in two FE models of left ventricle (68, 69), but the cardiac hypertrophy was not investigated.

Also, existing computational models of cardiac growth and remodeling mainly focus on the geometry of the ventricle and paid less attention to the hemodynamics of the heart and baroreflex feedback loop in presence of cardiac growth mechanism. According to the collected data in Table 3, patients with valvular disorders had approximately the same range for arterial pressure as in the healthy volunteers. The baroreflex feedback loop in this study was able to regulate the cardiovascular function in various time and length scale levels (Sharifi et al. 2021). It essentially could maintain the arterial pressure at the setpoint level via continuous regulation of heart rate, vascular tone, contractility of myofilaments and Ca2+ transients based on the received signal from the baroreceptor.

Furthermore, the current model could appropriately predict the reverse growth of LV after unloading of the ventricle (Fig. 6). In computational models, reverse growth occurs when the driving signal (e.g. cell stress) falls below the homeostatic level and creates a negative growth signal. Yoshida et al. (70) investigated the cardiac hypertrophy and its regression when the pressure-overloading was lifted. They used the strain-driven growth law proposed by Kerckhoffs et al. (9) which had the best performance in capturing cardiac hypertrophy in a comparison between eight growth laws (13). However, they were unsuccessful in predicting reverse growth that was typically reported in the animal data. Lee et al. (29) improved the growth law proposed by Goktope et al. (10) and could capture cardiac atrophy when the volume overloading was removed. In contrast to existing models, our model was properly able to reflect the effect of ventricular unloading on capturing the reverse growth of the ventricle (atrophy). This provides an ideal computational framework for evaluating different valvular treatments of the heart.

Eventually, in contrast to admired works (9, 10, 29, 71) in computational modeling of cardiac hypertrophy based on the “kinematic growth” theory, this work did not use any constraint on the growth signals. The growth sub-model continues the regulation of controlled parameters (i.e. ventricle wall volume and serial number of half-sarcomeres) until the simulation reach to a new steady state and maintain the stimuli signals at the homeostatic level.

***Future perspective***

Introduced model in this study has created a robust multiscale framework for simulating the cardiovascular function. This new framework can predict any change in the ventricular size and dimensions in response to any alteration in the ventricular loading while the arterial pressure is being regulated with the baroreflex feedback loop. Therefore, in addition to simulating acute changes in valvular functions, it can be useful in investigating the effects of other types alterations in ventricular loading. For example, left ventricular assisting device (LVAD) is a mechanical pump that is being used to help the weakened hearts to pump blood. It has been reported that using LVAD in patients with severe heart failure could help in unloading of the ventricle and myocardium recovery (72). The effect of LVAD can be simulated by defining a new compartmental blood flow from LV to aorta and then the influence of ventricular unloading on the recovery of ventricle can be evaluated.

Furthermore, current model can investigate effect of mutant sarcomeric proteins on the cardiovascular function and cardiac growth. For instance, hypertrophic cardiomyopathy (HCM) is caused by mutations in thick and thin contractile myofilaments of the sarcomere. It has been generally seen that the mutations in HCM result in myocyte hypercontractility and excessive ATPase usage (73). The current framework can evaluate the effect of mutant sarcomere on the organ level by perturbing the detachment rate factors of myosin heads.

***Limitations of current work***

The current study is built upon the previous works using similar model framework, and hence it still includes some of the limitations explained in the previous works (Sharifi et al. 2021, (31)). The following limitations are particularly related to the new growth sub-model introduced in this study. First, the current model only can capture uniform changes in the ventricular size and dimensions. This mainly is due to the simplified 1-D hemispherical geometry of LV used in this framework. Because of this assumption, the complex torsional motion of the heart (64), longitudinal and transmural variation of contractile properties (65), and variational in myofibers orientations (74) are ignored. Therefore, all half-sarcomeres in the model experience a uniform loading at each given time step of a simulation and thus grow uniformly in response to overloading.

Second, the current model can only quantify the cardiac growth (i.e. change in the ventricular size and dimension), but not the myofiber disarray. Variation in myocardium environment like hemodynamic overloading or pathological stimulus can result into a change in the architecture of myofiber and produce myofiber disarray (75). For example, hypertrophic cardiomyopathy not only leads to asymmetrical change in the wall thickness, but also it can result into the myofibrillar disarray and myocardial fibrosis (73). However, this model has assumed the myofibers are circumferentially embedded at the ventricle base and their orientations remain constant throughout a cardiac cycle.

**Conclusion**

This study has implemented a new growth sub-model into an existing multiscale model of cardiovascular function. The growth sub-model was stress-driven where the concentric growth (wall thickening) was driven by total stress and the eccentric growth (ventricle dilating) was driven by passive stress in half-sarcomeres. The multiscale model was coupled with a baroreflex feedback loop so the arterial pressure could remain unchanged during the whole simulation while the ventricle was growing. Although simplistic, the growth algorithm could capture both the correct trend and the final magnitudes for ventricular dimensions compared to the clinical data in the literature. The growth sub-model was also able predict the reversal growth due to unloading of the overloaded ventricle.

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