Multiscale modeling of cardiac valve disease using cell-level signals to regulate concentric and eccentric myocardial growth

Hossein Sharifi 1, Austin G. Wellette-Hunsucker 2, Charles K. Mann 1, Jonathan F. Wenk 1,3, Kenneth S. Campbell 2

1Department of Mechanical Engineering, University of Kentucky, Lexington, Kentucky, USA

2Department of Physiology & Division of Cardiovascular Medicine, University of Kentucky, Lexington, Kentucky, USA

3Department of Surgery, University of Kentucky, Lexington, Kentucky, USA

**\* Correspondence:**Kenneth S. Campbell  
k.s.campbell@uky.edu

Keywords: Multiscale modeling, Myocardial growth, Baroreflex, Valvular disease, Concentric growth, Eccentric growth (Min.5-Max. 8)

Abstract

Multiscale models of the cardiovascular system are becoming effective tools for investigating the mechanisms that drive ventricular growth and biological remodeling. Some of these models can also predict how perturbations to molecular-level mechanisms impact organ-level function. This type of research might yield insights that lead to improved patient care. PyMyoVent is a multiscale computer model that bridges from molecular to organ-level function and simulates a left ventricle pumping blood around a systemic circulation. In previous work, we implemented baroreflex control of arterial pressure by using feedback to regulate heart rate, intracellular Ca2+ dynamics, the molecular-level function of both the thick and the thin myofilaments, and vascular tone. In this paper, we extend PyMyoVent with concentric growth (wall thickening / thinning) and eccentric growth (chamber dilation / constriction) driven by cell-level signals. Specifically, concentric growth is controlled by the energy used by the myocytes for contraction (expressed as myosin ATPase normalized to myofibrillar volume) while eccentric growth responds to intracellular passive stress. The new framework reproduced clinical measures of left ventricular growth in three types of valvular disease, namely aortic stenosis, aortic insufficiency, and mitral insufficiency. Furthermore, simulations of each valvular disorder reversed growth, returning the ventricle to its default size, when the disease-mimicking perturbation was removed. In conclusion, these simulations suggest that myosin ATPase normalized to myofibrillar volume and intracellular passive stress can be used to drive concentric and eccentric growth in simulations of valve disease.

# Introduction

The heart adapts to its environment and changes its shape in response to hemodynamic loads, including pathological conditions associated with valvular disease. Throughout this work, the changes in shape will be referred to as cardiac growth. The inherent structure of the myocardium can also change, a process that is described as remodeling [1, 2].

The heart can grow in two modes. Concentric growth is defined by wall thickening and an increase in ventricular mass, due to the deposition of sarcomeres in parallel, with little or no change in the internal size of the ventricular chambers [3]. Eccentric growth reflects the addition of sarcomeres in series, which dilates the chamber and increases wall mass with minimal change in wall thickness [3]. In valvular disease, cardiac growth initiates as an early adaptive response that can progress to remodeling and subsequent heart failure if the valvular dysfunction persists [3-5].

Computer models are providing new insights into cardiac growth. Most of the simulations performed to date have used myocardial stress [6, 7], myocardial strain [8-10], or some combination of stress and strain [11, 12] to drive growth. Building on these ideas, Rondanina and Bovendeerd [13] compared simulations driven by different combinations of stress and strain. They concluded that growth responses simulated using stress-based laws were more realistic than growth patterns driven by strain. Mojumder et al. [14] reached similar conclusions after simulating LV growth following pressure overload.

Mechanical loads are clearly important for growth but models driven solely by these signals cannot reproduce the cardiac growth that follows changes to hormone levels, metabolic function, and/or the status of biochemical signaling pathways. Accordingly, researchers have also begun to develop models that are sensitive to molecular and cellular-level events [15]. Yoshida et al. [16] used one of these systems to compare how volume overload and hormone surges affected cardiac growth during pregnancy. They concluded that the rise in progesterone (a biological signal) was more important for cardiac growth than volume overload (a mechanical signal). In related work, Estrada et al. [17] demonstrated that hormonal changes were also the dominant driving signal for cardiac growth in pressure overload.

Although it is possible to separate mechanical and biochemical signals in a computer model, doing so in vivo is much more difficult. This is because changes to the intracellular environment will alter the way that the heart contracts and thus the mechanical signals that it experiences. Mechanics and biochemistry are inter-twined. In pioneering work, Davis et al. [18] incorporated this behavior in an innovative model that integrated mechanics and molecular signaling. They postulated that the aspect ratio of myocytes responded to MEK1-ERK signaling with myocytes becoming wider with increasing values of the contractile force-time integral. They also suggested that ventricular mass was regulated by calcineurin signaling, and increased if the force-time integral deviated (in either direction) from a homeostatic setpoint. These elegant assumptions allowed Davis et al.’s model to reproduce the different magnitudes of concentric and eccentric growth measured in several strains of genetically-modified mice.

Very recently, Bischof et al. [19] inactivated a subunit of ATP synthase in mice and demonstrated that this reduced cell-level concentrations of ATP. Intriguingly, the intervention also induced cardiomyocyte hypertrophy. One interpretation of this result is that it reflects a completely new pathway for cardiac growth. Alternatively, it could be related to the same mechanisms that Davis et al. described.

Specifically, Bischof et al. demonstrated that hearts undergo concentric hypertrophy when the supply of ATP is restricted. Davis et al., on the other hand, showed that concentric hypertrophy is associated with an increased force-time integral. As the latter authors pointed out, the integral reflects the mechanical work performed by the heart, and thus its demand for ATP. It may therefore be possible to explain the observations of both Davis et al. and Bischof et al. using a single mechanism in which concentric hypertrophy responds to changes in the availability of ATP. Put simply, the heart hypertrophies when the supply of ATP is compromised (as investigated by Bischof et al.) and also if the demand for ATP increases (as studied by Davis et al.).

The present study was developed based on this general hypothesis. An additional research goal was to investigate pathophysiological conditions that are directly relevant to clinical care. Accordingly, the first step was to extend an multiscale model of the systemic circulation named PyMyoVent [20] so that it grew in response to both biochemical and mechanical signals. Concentric growth responded to the myosin ATPase associated with contraction while eccentric growth was driven by passive intracellular stress. Multiple simulations were then performed to investigate how the ventricle responded to changes in hemodynamic load associated with different types of valvular disease. These tests showed that the new framework reproduced clinical changes in left ventricular size measured during aortic stenosis, aortic insufficiency, and mitral insufficiency. The results reinforce the potential importance of cellular ATP concentrations as a driving signal for concentric hypertrophy and lay a foundation for future studies integrating cell-level signaling, hemodynamic loads, and cardiac growth.

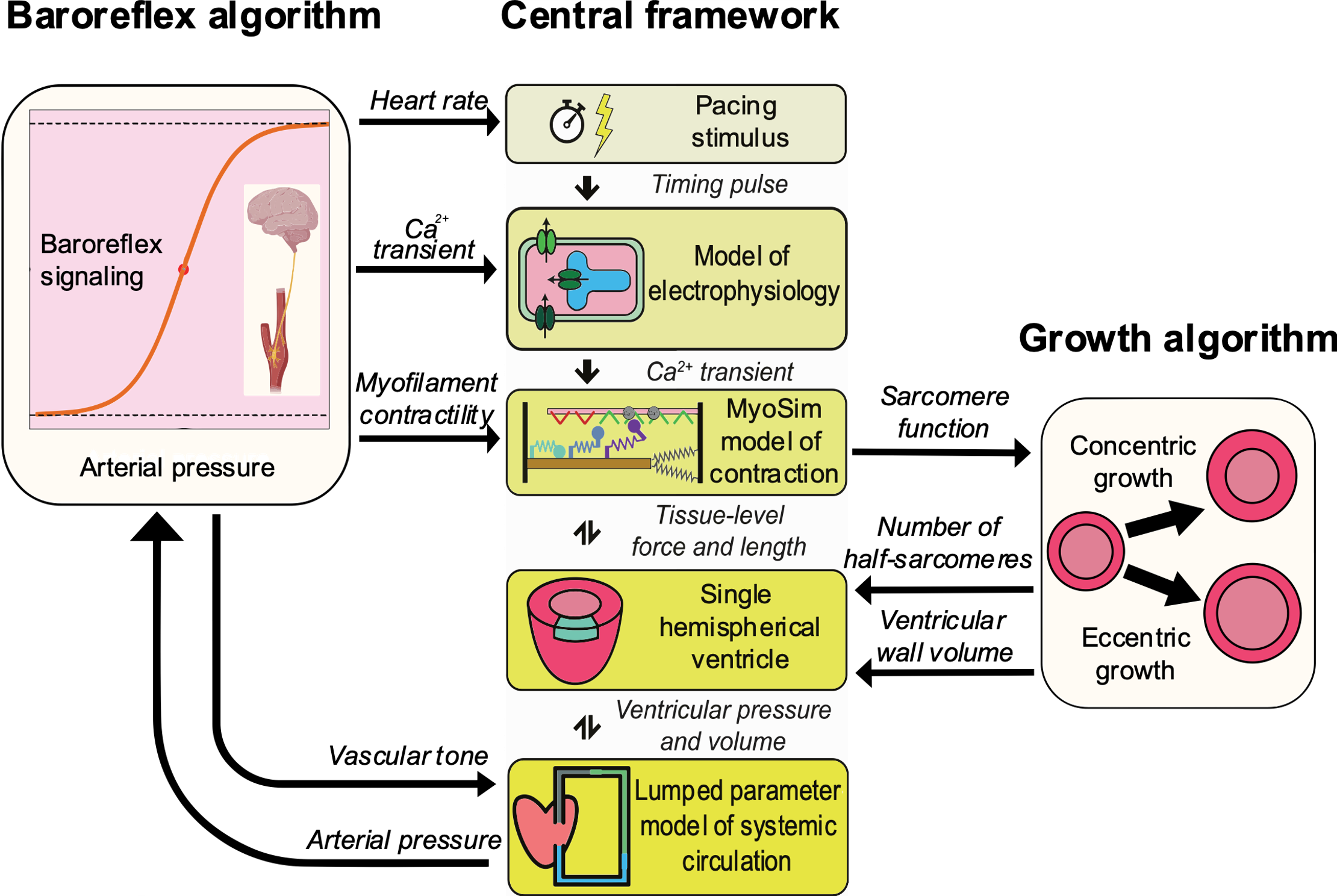
# Materials and Methods

## Overview

Fig 1 illustrates the PyMyoVent model. As originally described by Campbell et al. [21], the central framework consists of a pacing stimulus that drives an electrophysiological model which predicts a Ca2+ transient. A contraction model called MyoSim [22, 23] then uses the calculated Ca2+ transient to predict ventricular wall stress, which is then transformed into ventricular pressure via *Laplace’s Law*. Finally, a single hemispherical model of the LV pumps blood into a lumped parameter model of systemic circulation based on *Ohm’s law*.

The baroreflex algorithm was described by Sharifi et al. [24] and drives arterial pressure towards a user-defined setpoint by by modulating the heart rate, intracellular Ca2+ transient, molecular-level function of both the thick and the thin myofilaments, and vascular tone.

The growth algorithm was developed for this manuscript and is described below.



**Figure** **1.** **Overview of the PyMyoVent framework.** The baroreflex algorithm regulates the arterial pressure towards a user-defined setpoint by modulating heart rate, intracellular Ca2+ transients, myofilament contractility, and vascular tone. The growth algorithm drives concentric growth (wall thickening / thinning) using myosin ATPase normalized by myofibrillar volume. Whereas the eccentric growth (chamber dilation / constriction) is driven using intracellular passive stress. Adapted from Campbell et al. [21] and Sharifi et al. [24].

## Baroreflex module

In our previous work [24] we extended PyMyoVent [21] by incorporating a module of the baroreflex feedback loop (Figure 1) to drive arterial pressure towards a user-defined setpoint. This was accomplished by modulating the heart rate, intracellular Ca2+ transient, molecular-level function of both the thick and the thin myofilaments, and vascular tone. It was shown that the baroreflex algorithm was able to regulate arterial pressure towards setpoints ranging between ~30 mmHg to ~150 mmHg, as well as maintaining the arterial pressure under perturbed ventricular loading, such as acute blood loss or aortic stenosis. More details on the baroreflex module can be found in the previous work [24].

## Growth module

The growth module algorithm was inspired by the underlying biology. *In vivo*, growth stimuli signals trigger a complex pathological downstream signaling pathway that promotes cell growth and ventricular enlargement. In the current model, a growth stimulus signal (Si) transduces into a normalized growth signal Ga,i that represents the net result of triggered upstream signals within the cell. The rate of change in Ga,i is defined as



where i represents the growth type (i.e. concentric or eccentric), ka,i is a rate constant and sets the speed at which Ga,i responds to a change in Si. Si,set is the homeostatic level (setpoint) for the stimulus signal Si. During positive feedback, Ga,i tends towards one when Si is greater than Si,set and towards zero when Si is less than Si,set. *In vivo*, these bounds mimic the saturated levels of phosphorylation and dephosphorylation of underlying proteins by protein kinase.

The control signal Gc,i reflects the net results of downstream signals and governs how the effector parameters (i.e. wall volume or the number of half-sarcomeres) should respond to the normalized growth signal Ga,i. The rate of change in Gc,i is defined as



where γgrowth,i and γanti growth,i are rate constants that set the speed at which the effector parameters would grow or shrink according to Ga,i. Finally, the growth module links the control signals Gc,i to effector parameters as described in the following sections.

### Eccentric growth

In the current model, eccentric growth was implemented by changing the number of serial half-sarcomeres (nhs) assumed to be around the circumference of the left ventricle. The intracellular passive stress in the half-sarcomeres, *τ*passive, was considered as the stimulus signal (Secc) for eccentric growth. The intracellular passive stress was modeled as



where xhs is the current length of the half-sarcomere, Lslack is the half-sarcomere length at which the passive stress is zero, L sets the curvature of the relationship, and is the scaling factor. The rate of change in the number of half-sarcomeres, nhs, is governed via equation , where Gc,ecc is the control signal for eccentric growth. According to equations - , the number of half-sarcomeres (nhs) increases when Secc > Secc,set, but decreases when Secc < Secc,set.



### Concentric growth

Concentric growth was modeled by changing the left ventricular wall volume (Vwall) to mimic the parallel deposition of half-sarcomeres. Myosin ATPase normalized to myofibrillar volume (ATPase/Vmyofibrillar) was used as the stimulus signal for concentric growth (Scon). The myosin ATPase normalized to myofibrillar volume is expressed as



where N0 is the number of myosin heads in a hypothetical half-sarcomere with a cross section of 1 m2, ∆G is the free energy produced by ATP hydrolysis (70 kJ mol-1), L0 is the reference length of a half-sarcomere (1.1 μm), NA is Avogadro’s number (6.02 × 1023 mol-1), J4 is the detachment flux (s-1) of myosin heads from the force generating state (MFG) to the disordered relaxed state (MDRX), and x is the potential positions of myosin heads relative to the no-load position, which varies from -10 to 10 nm.

The rate of change in Vwall is defined via equation , which consists of two components. The first component, Gc,con, responds to the corresponding change in Scon, whereas the second component, Gc,ecc, incorporates the proportional change due to the eccentric growth [2].



## Implementation and computer code

The code was written in Python using Numpy [25], Scipy [26], and pandas [27] libraries. The source code and instructions on how to reproduce all figures shown in this manuscript are available at <https://campbell-muscle-lab.github.io/PyMyoVent/>.

Equations , , , and were discretized and implemented as a system of ordinary differential equations in PyMyoVent. Both nhs and Vwall were updated at each time-step. For simplicity, identical values were used for ka,ecc and ka,con. According to a preliminary sensitivity study (Figure S1), the γgrowth,i and γanti growth,i rate constants only governed the speed at which the growth module reaches steady state, not the magnitude of growth. Thus, their values were chosen to obtain the steady state LV growth in less than a thousand heartbeats. The setpoints for both the concentric (Scon, set) and eccentric (Secc, set) growth laws were chosen to match the average value of the stimuli signals at steady state using the default parameters described below.

## Simulations

### Baseline

As described in previous works with PyMyoVent [21, 24] no data fitting was performed to optimize the model parameters. Instead, default parameters were selected to mimic the cardiovascular function of a healthy adult reported in the literature [28, 29]. All simulations shown in this manuscript started with the same assumptions using default model parameters. For example, total blood volume of the systemic circulation system was set to 4.5 liters and all simulations were initiated by placing all the stressed blood volume into the veins. Similarly, in all simulations, the baroreflex algorithm was activated at 20 s to maintain arterial pressure at a setpoint of 90 mmHg when the simulation was at steady state using default parameters (Figure S2).

Throughout the manuscript there are figures showing simulation results that include several hundred heartbeats. Therefore, pulsatile variables that vary remarkably during a cardiac cycle are shown with the envelope of the extreme values over the cycle.

### Valvular disorders

Three types of valvular disorders, namely aortic stenosis, aortic insufficiency, and mitral insufficiency were simulated by applying the relevant perturbations to the baseline simulation.

According to the *Poiseuille* equation, the aortic valve cross-sectional area is inversely proportional to the resistance across the valve. Hence, the stenotic aortic valve was modeled by increasing the resistance, Raorta, in equation , which regulates the blood flow from the left ventricle to the aorta. In this study, three levels of severity for aortic stenosis were modeled to represent the different stages of the disease according to American Heart Association (AHA) guidelines [30]. For instance, a ~60 % reduction in the aortic valve area, from a mean value of 2.5 cm2 for healthy adults [31-33] to a mean value of 1 cm2 for patients with aortic stenosis [34, 35], was mimicked by a 500 % increase in the aortic resistance. All simulated cases for aortic stenosis are summarized in Table 1.



|  |  |  |
| --- | --- | --- |
| **Table** **1.** **Simulated levels of severity for aortic stenosis.** AS: Aortic Stenosis | | |
| % Increase in the aortic resistance | Equivalent % reduction in aortic valve area | Represented stage of disease according to AHA guidelines [30] |
| 250 % | 46.55  (From 2.50 cm2 to 1.33 cm2) | At risk of AS / Progressive AS |
| 500 % | 60  (From 2.50 cm2 to 1.00 cm2) | Asymptomatic severe AS |
| 750 % | 65  (From 2.50 cm2 to 0.86 cm2) | Symptomatic severe AS |

Aortic insufficiency was modeled by assigning a non-zero value to Gaorta in equation , which is equivalent to the conductance (reciprocal of resistance) of the aortic valve. This allows a portion of the blood volume in the aorta to move backward to the left ventricle during diastole. The american Heart Association (AHA) guidelines [30] categorize three levels of severity for aortic insufficiency based on the regurgitant volume, namely: mild (regurgitant volume < 30 ml beat-1), moderate (30 ml beat-1 < regurgitant volume < 59 ml beat-1), and severe (regurgitant volume > 60 ml beat-1). These levels of severity were simulated using the values for Gaorta shown in Table 2.

|  |  |  |
| --- | --- | --- |
| **Table** **2.** **Simulated different levels severity for aortic insufficiency.** | | |
| Gaorta | Equivalent regurgitant volume (ml beat-1) | Represented stage of disease according to AHA guidelines [30] |
| 5e-4 | 20 | Mild aortic insufficiency |
| 1e-3 | 40 | Moderate aortic insufficiency |
| 2e-3 | 70 | Severe aortic insufficiency |

Similarly, mitral insufficiency was simulated by giving a non-zero value to Gmitral in equation , which governs the blood flow between the veins and left ventricle. Three levels of severity were selected and simulated according to the regurgitant volume of 60 (ml beat-1) reported by the American Heart Association guidelines [30]. The simulations for various stages of the disease are summarized in Table 3.



|  |  |  |
| --- | --- | --- |
| **Table** **3.** **Simulated different levels of severity for mitral insufficiency.** | | |
| Gmitral | Equivalent regurgitant volume (ml beat-1) | Represented stage of disease according to AHA guidelines [30] |
| 1e-3 | 30 | At risk of / Progressive mitral insufficiency |
| 2e-3 | 60 | Asymptomatic severe mitral insufficiency |
| 3e-3 | 80 | Symptomatic severe mitral insufficiency |

# Results

## Concentric growth in response to induced aortic stenosis

Figure 2 depicts a simulation of aortic stenosis in the PyMyoVent framework. The initial transition in the model response is due to the regulation of arterial pressure towards the setpoint of 90 mmHg by the baroreflex module (Figure S2). At 50 s (first vertical dashed line from the left in all panels) the growth module was activated and then between the time points of 300 and 400 s (second and third vertical dashed lines) Raorta in equation was gradually increased by 500% from 20 to 120 (mmHg L-1 s) to mimic a 60% reduction in the aortic valve area according to Table 2.

At the cellular-level, elevated aortic resistance initially increased the energy consumption required for contraction (myosin ATPase normalized to myofibrillar volume, Scon), which led to an increase in Ga,con and Gc,con. The intracellular passive stress Secc, however, had only a subtle change and thus Ga,ecc and Gc,ecc did not alter much. At the organ-level, the change in LV size was demonstrated by a ~30% increase in the ventricular wall volume (Vwall), ~8% reduction in the LV cavity volume at end-diastole, and almost no change in the LV cavity volume at end-systole. Ultimately, these changes together led to thickening of the wall by ~21% and ~29% at end-systole and end-diastole, respectively, suggesting the occurrence of concentric growth. After growth reached steady state, all cell-level signals (Ga,con, Gc,con, Ga,ecc, and Gc,ecc) normalized back to their homeostatic range as the LV geometry adapted to the stenosis condition.

Throughout the progression of growth, the baroreflex module maintained the arterial pressure at the setpoint of 90 mmHg (middle column in Figure 2) by increasing the heart rate from ~63 to ~68 bpm, intracellular Ca2+ dynamics (by increasing kact and kSERCA), myofilament function (by increasing k1 and k3 and decreasing kon), and vascular tone (by increasing Rarteriolar and decreasing Cveins). Although the peak value of the stimulus signal for concentric growth Scon (myosin ATPase normalized to myofibrillar volume) appears higher at growth steady state than at baseline steady state, due to changes in heart rate and systolic duration caused by the baroreflex, the averaged value reaches the setpoint level for concentric growth (Figures S-S).

Diagram, schematic

Description automatically generated

**Figure** **2.** **Predicted concentric growth in response to aortic stenosis**. The left-hand column shows the responses of the central framework in PyMyoVent [21] shown in Figure 1. The thin filament panel shows the fraction of actin binding sites in Noff and Non states. The thick filament panel shows the fraction of myosin heads in super-relaxed (MSRX), disordered relaxed (MDRX), and force-generating (MFG) states. The middle column shows the baroreflex control of arterial pressure at setpoint of 90 mmHg. kact and kSERCA handle the intracellular Ca2+ dynamics, while k1, k3, and kon handle the myofilament function, and Rarteriolar and Cveins handle the vascular tone. The right-hand column shows the properties relevant to the growth module. Scon, Scon,set, Ga,con and Gc,con refer to the stimulus signal, setpoint, normalized growth signal, and control signal for concentric growth, respectively. Secc, Secc,set, Ga,ecc and Gc,ecc refer to the stimulus signal, setpoint, normalized growth signal, and control signal for eccentric growth, respectively. The initial transition in all panels is due to baroreflex control of arterial pressure towards the setpoint of 90 mmHg (Figure S1). The growth module was activated at 50 s (first dashed vertical line from left on all panels) when the system was at steady state using default parameters. The system was gradually perturbed from 300 s to 400 s (second and third vertical dashed lines) by increasing Raorta (top panel in the right-hand column) by 500%.

## Concentric and eccentric growth in response to aortic insufficiency

Figure 3 shows an example of the results for the aortic insufficiency condition. The simulation was performed similar to the one shown in Figure 2, but instead of changing Raorta, Gaorta in equation was increased from 0 to 1e-3 ([mmHg s]-1 L) to develop an insufficient aortic valve with a regurgitant volume of ~40 (ml beat-1) (Table 3).

In response to the induced insufficiency in the aortic valve, the initial rise in stimuli signals (Scon and Secc) at the cell-level drove the normalized growth signals (Ga,con and Ga,ecc) to increase, and hence elevated the control signals (Gc,con and Gc,ecc). The control signals were then recovered by increasing the ventricular wall volume and number of serial half-sarcomeres by ~45% and ~12%, respectively. At the organ-level, these changes resulted in the dilation of the LV cavity (~38% at end-diastole and ~37% and at end-systole) and wall hypertrophy (~16% at both end-systole and end-diastole). Although the baroreflex module maintained the arterial pressure setpoint at 90 mm Hg, arterial pressure became more pulsatile and changed from ~116/61 mmHg to ~128/46 mmHg.

Diagram, engineering drawing, schematic

Description automatically generated

**Figure** **3. Predicted concentric and eccentric growth in response to aortic insufficiency.** The panels are arranged similarly to those in Figure 2, except that aortic regurgitant volume is shown in place of aortic resistance in the right-hand column. The simulation shown in this figure was perturbed gradually (second and third vertical dashed lines) by increasing Gaorta in equation from 0 to 1e-3 ([mmHg s]-1 L) to induce an aortic regurgitant volume of ~40 ml (Table 3).

## Eccentric growth in response to mitral insufficiency

Figure 4 summarizes the model response to an example of mitral insufficiency. The simulation started with the same setting described in Figures 2 and 3. However, instead of changing Raorta or Gaorta, Gmitral in equation was increased from 0 to 2e-3 ([mmHg s]-1 L) to induce a regurgitant volume of ~60 (ml beat-1) through the mitral valve (Table 3).

At the cell-level, the insufficient mitral valve increased both stimuli signals for concentric (Scon) and eccentric (Secc) growth and, consequently, increased the relevant downstream control signals. The elevated control signals Gc,con and Gc,ecc were then re-normalized by driving the ventricular wall volume and number of serial half-sarcomeres to increase by ~50% and 17%, respectively. At the organ-level, these changes were manifested by dilation of the LV cavity (~57% at end-diastole and ~68% at end-systole) and mild thickening of the LV wall (~12% at end-diastole and 10% at end-systole).

Due to baroreflex control of arterial pressure, there was a subtle increase in Ca2+ dynamics (via increasing kact and kSERCA), myofilament function (via increasing k1 and k3, and decreasing kon), and vascular tone (via increasing Rarteriolar and decreasing Cveins). Additionally the heart rate elevated from ~63 to ~66 bpm. Although the peak value of intracellular passive stress appears to be different when growth is at steady state, compared to the baseline steady state, due to changes in heart rate and diastolic duration, the averaged value reaches the setpoint level for eccentric growth (Figures S5-S).

Diagram, schematic

Description automatically generated

**Figure** **4**. **Predicted eccentric growth in response to mitral insufficiency.** The panels are arranged similarly to those in Figure 2, except that mitral regurgitant volume is shown in place of aortic resistance in the right-hand column. The simulation shown in this figure was perturbed gradually (second and third vertical dashed lines) by increasing Gmitral in equation from 0 to 2e-3 ([mmHg s]-1 L) to induce a mitral regurgitant volume of ~60 ml (Table 3).

## Left ventricular pressure-volume loop relationship

Figure 5 illustrates the pressure-volume (PV) loops for the various valvular disorders with different severities. For the aortic stenosis case (top panel in Figure 5), intensifying the severity of the disease resulted in a higher peak systolic pressure. However, end-systolic LV volume remained unchanged and end-diastolic LV volume had a subtle decrease, which in turn led to a subtle reduction in stroke volume and ejection fraction. Also, the higher the aortic resistance in the model (Raorta in equation ), the larger the stroke work done by the LV (the enclosed area of the PV loop).

For the aortic insufficiency case (middle panel in Figure 5), by increasing the level of insufficiency, the PV loop shifted to the right, which indicates more dilation in the LV cavity. A higher regurgitant volume also resulted in a larger stroke volume and higher end-systolic pressure, and thus larger stroke work done by the LV. In addition, increasing the severity of the disease resulted in further disturbance to the relaxation phase of the PV loop, which angled down to the right.

Finally, increasing the level of mitral insufficiency led to more dilation of the LV cavity by shifting the PV loop to the right (bottom panel in Figure 5). Increasing the severity of the disease caused the stroke volume, and thus the stroke work, to increase. Additionally, the relaxation phase of the PV loop was disrupted, angling down to the left as the severity increased. The peak systolic pressure, however, remained nearly unchanged.

Diagram

Description automatically generated

**Figure** **5**. **Simulated** **left ventricular pressure-volume (PV) loop relationship for three types of valvular dysfunction with different levels of severity.** Baseline loop refers to the steady state response before applying any disease-mimicking perturbation. The other loops refer to final steady state solution after applying the relevant perturbation. Note that RV means regurgitant volume.

## LV recovery after removal of the overloading condition

The model was also tested by removing the disease-mimicking perturbations after the LV growth had reached steady state. Figure 6 depicts the reversal of LV growth when the underlying perturbations in Figures 2-4 were removed. All three cases were started and perturbed exactly as shown in the original Figures. At 900 s (forth vertical line on all panels) the underlying perturbations were gradually lifted. For instance, aortic resistance was reduced from 120 to the default value of 20 (mm Hg L-1 s) for the aortic stenosis case. In all cases, LV dimensions (Figure 6) and function (Figures S7-S9) were fully regained to their homeostatic range once the underlying perturbation was eliminated.

Diagram

Description automatically generated

**Figure** **6. Reversal of LV growth in response to removal of valvular diseases.** The left-hand column shows the removal of aortic stenosis, the middle column shows aortic insufficiency, and the right-hand column shows mitral insufficiency.In all panels, the first vertical line reflects the activation of the growth module. The second and third vertical lines demonstrate when the disease-mimicking perturbations were applied. The fourth and fifth vertical lines show when the underlying perturbations were removed.

## Importance of baroreflex control of arterial pressure

The effect of baroreflex control on the evolution of growth was evaluated by redoing the simulations in Figures -, but with the baroreflex algorithm deactivated. Simulations started with the same initial conditions, as shown in Figures -, except the baroreflex algorithm was deactivated at 200s. Figure demonstrates the effects of baroreflex control on a selected group of model variables that were achieved after growth reached steady state.

For the aortic stenosis case, arterial pressure dropped from ~113/64 mmHg, under the control of baroreflex, to ~98/53 mmHg with no reflex control. LV end-systolic pressure also reduced from ~172 to ~146 mmHg. Consequently, due to the altered hemodynamics, the growth algorithm predicted a reduction in the LV size by ~11%, ~20%, and ~24% for the LV end-diastolic volume, LV end-systolic volume, and LV wall volume, respectively, when compared to the LV size with the baroreflex activated. For the insufficient aortic valve simulation, the retrograde aortic blood flow did not change the arterial pressure in comparison to the case with baroreflex control, and thus the prediction from the growth algorithm for LV size remained nearly unchanged. The simulation of mitral valve insufficiency resulted in a drop in arterial pressure from ~119/62 mmHg to ~109/54 mmHg, as well as a reduction in LV end-systolic pressure from ~124 to ~114 mmHg, when the baroreflex was deactivated. Additionally, the predictions of LV cavity volume at end-diastole and end-systole, along with the LV wall volume, were reduced by ~7%, ~14% and ~17%, respectively. Ultimately, the absence of the baroreflex algorithm prolonged the time that was required for the growth module to reach the final steady state, resulting in longer simulations times. More information regarding the full simulations is shown in Figures S-S.

Chart

Description automatically generated

**Figure** **7. Effects of the baroreflex control of arterial pressure on simulated hemodynamics and growth module predictions.** Green bars reflect the results for growth steady state under control of baroreflex. Orange bars represent the variables at growth steady state without the control of baroreflex.

## Comparison of simulation results with clinical data

To validate our model, the simulated results were compared with clinical data from the literature, which was acquired by cardiac magnetic resonance imaging (Table S1). Clinical data were categorized into four groups labeled control, patients with aortic stenosis, patients with aortic insufficiency, and patients with mitral insufficiency. For each category, measured data were collected from eight different studies, as shown in Table S1.

Ventricular dimensions were quantified with the LV end-diastolic volume index, LV end-systolic volume index, and LV mass index. Simulation results were normalized using an average body surface area of 1.9 m2 [36, 37] to match the units of reported values in the literature. Statistical differences between the model predictions and clinical data for the diseased states were determined using two-sided equal variances t-tests.

Figure 8 shows model validation for predicting LV size with respect to the clinical data compiled from the literature (Table S1). For the aortic stenosis case (left-hand column in Figure 8), as the severity of the disease increased, the model predicted an increase in the LV mass index. However, the LV volume index at both end-diastole and end-systole remained nearly unchanged. For the other two cases (insufficient aortic and mitral valves), all LV size parameters predicted by the model increased as the severity of insufficiency increased. The results of the statistical tests suggest that the model predictions for nearly all LV size parameters in all cases, except the LV mass index in response to mitral insufficiency, were not significantly different than the clinical data.

## Diagram, schematic Description automatically generated

**Figure** **8. Model validation for LV size in comparison to clinical data from the literature (Table S1).** Each column summarizes the model validation for a particular valvular disease (left, aortic stenosis; middle, aortic insufficiency; right, mitral insufficiency).In all panels, interquartile ranges for clinical data are shown with box plots in two groups of Control and Patient, whereas simulation results are shown with circle markers in two groups of Baseline (Sim) and Patient (Sim). LV end-diastolic volume index: LV end-diastolic volume normalized by the body surface area, LV end- systolic volume index: LV end-systolic volume normalized by the body surface area, LV mass index: LV myocardium mass normalized by the body surface area. Note that RV means regurgitant volume. ns (not significant), \*: 1.00e-02 < p ≤ 5.00e-02

Systolic function was assessed with the LV stroke volume index and ejection fraction. Clinical data for systolic function was compiled similarly to LV size parameters. For studies (Table S1) where the LV stroke volume index was not reported, the absolute difference between the reported LV volume index at end-diastole and end-systole was used instead.

Figure 9 summarizes the model validation for LV systolic function. According to Figure 9, by increasing the severity of aortic stenosis, the model predicted a slight reduction in both the LV stroke volume index and ejection fraction. For the insufficient aortic valve, as the severity of the disease increased, the predicted LV stroke volume index increased as well, but ejection fraction remained unchanged. For the mitral insufficiency condition, an increase in the regurgitant volume (RVmitral) resulted in a higher predicted LV stroke volume index, but reduced ejection fraction. All predicted values for systolic function, except for the ejection fraction in response to mitral insufficiency, were not significantly different than the reported clinical data.

Diagram

Description automatically generated

**Figure** **9. Model validation for LV systolic function in comparison to collected clinical data from the literature (Table S1.)** Figure panels are arranged like Figure 8. In all panels, interquartile ranges for clinical data are shown with box plots in two groups of Control and Patient, whereas simulation results are shown with circle markers in two groups of Baseline (Sim) and Patient (Sim). LV stroke volume index: LV stroke volume normalized by the body surface area. Note that RV means regurgitant volume. ns (not significant), \*: 1.00e-02 < p ≤ 5.00e-02

# Discussion

This study extends an existing multiscale model of cardiovascular function by incorporating a growth module that simulates both concentric growth (wall thickening / thinning) and eccentric growth (chamber dilation / constriction). The simulation results showed that the new framework could predict the correct form of LV growth in response to three forms of valvular disease, namely, aortic stenosis, aortic insufficiency, and mitral insufficiency. Model results were then validated with clinical data from the literature. Furthermore, simulations for each valvular disorder regained LV size and function (reversal of growth) when the disease-mimicking perturbation was removed.

## Role of myosin ATPase in driving concentric growth

In patients with chronic aortic stenosis, concentric growth is induced by the pressure overload experienced by the heart. Pressure overloading is a mechanical condition that is characterized by an increase in the resistance of blood flow through the aortic valve during LV systole. This condition reduces the shortening velocity of sarcomeres and thus increases the contractile force that is generated. It has been suggested that increases in the magnitude of myofilament force over time correlates with concentric growth [18] and reflects the total work performed by the LV. Therefore, the increased metabolic demand of cells, to meet such an elevated demand for performing adequate work in response to aortic stenosis, could be the potential driver of concentric growth (cardiac hypertrophy). Additionally, Davis et al. [18] investigated the effects of Ca2+ related parameters on heart remodeling and did not find a strong correlation, suggesting these parameters produce a weak driving signal for cardiac hypertrophy.

Mitochondria are the main source of energy in eukaryotic cells and are abundant in high-energy-demand organs like the heart. In healthy cardiomyocytes, the primary function of mitochondria is to meet the energy demand of the beating heart by producing ATP through oxidative phosphorylation. This makes up roughly 95% of the ATP production in the cardiomyocytes, with cross-bridge cycling of myosin heads consuming nearly 70% of ATP in the cell [38]. Considering the close relationship between workload and energy generation demand, concentric growth (cardiac hypertrophy) will inevitably lead to alterations in mitochondrial function, including mitochondrial dysfunction [39, 40]

The increase in ATPase rate and increased ATP demand results in cardiomyocytes continuously synthesizing mitochondria to compensate for changes in energy demands and to remove damaged organelles, the process of which involves fusion and fission of existing mitochondria and separation of damaged ones for degradation [41]. Too much mitophagy results in depletion of the mitochondrial population, while insufficient mitophagy will lead to the accumulation of damaged mitochondria [41], and an unviable shift in cardiac metabolism (Figure ). It has been established that increased glucose utilization in hypertrophied hearts is a compensatory response to the energy deficit caused by reduced fatty acid oxidation at a time of high energy demand for cardiac contraction [42-45]. Additionally, increased glycolysis has been strongly linked to cardiac hypertrophy (concentric growth), as well as an increased flux into ancillary pathways [46]. However, preventing the switch of energy substrates in cardiomyocytes, during pathological stimulation, can attenuate the influx of glucose into anabolic precursors and reduces hypertrophic growth [47]. Therefore, the metabolic requirements of cells to meet the demand for performing work would increase in the presence of pressure overloading, which makes myosin ATPase an appropriate marker/driver of concentric growth (Figure ).

The metabolic switch from fatty acids to glucose is associated with an increase in anabolic metabolism, which provides glucose-derived aspartate for cellular hypertrophy [44, 47]. Lin28a is a major regulator of pathological cardiac hypertrophy, which directly binds to Pck2 mRNA to facilitate this metabolic repatterning in response to cardiac stress [48]. This reveals a critical role of substrate switch for cell growth independent of energy demand. Lin28a enhances glucose uptake, via an increase in insulin-PI3K-mTOR signaling [49]. Specifically, Lin28a increases IGF1 receptor, p-IRS-1, p-Akt, p-mTOR and p-p70s6k expression levels in cardiomyocytes [50] (Figure ). With the shift in metabolism, enhanced glucose uptake, and increased IGF receptor expression (via Lin28a), the downstream signaling for stimulating pathological cardiac hypertrophy initiates.

It has been well established that increased IGF receptor expression activates PI3K [51], which in turn can chronically activate Akt1 signaling. Chronic activation of the PI3K/AKT pathway occurs in cardiomyopathy. In vitro, the chronic activation of Akt1 gene expression can induce adaptive cardiac hypertrophy [52] by mTOR (Figure ). The mammalian target of rapamycin (mTOR) pathway has been shown to be involved in the development of hypertrophic cardiomyopathy and is considered a therapeutic target for this disease [53]. The Akt/mTOR pathway contributes significantly to the activation of mTORC1 during the development of cardiac hypertrophy [54]. Collectively, this links the increased metabolic state (myosin ATPase activity), fuel utilization shift (glucose utilization), and signaling for pathological hypertrophy (insulin-PI3K-Akt-mTOR signaling) (Figure ).

In the framework presented in section 3, myosin ATPase has a direct relationship with the detachment flux of myosin heads (J4), which is dependent on the population of myosin heads in the force-generating state (MFG). During pressure overloading, the reduced shortening velocity of sarcomeres increases the number of bound myosin heads in the MFG state by causing less myosin heads to be pulled off due to strain-dependent detachment. This elevates the myosin ATPase, reflecting higher energy demand for cells to produce enough contraction. In response to the increased stimulus signal for concentric growth (Scon), the growth algorithm increases the concentric growth signal Ga,con that reflects the net result of upstream signals. Elevated Ga,con, subsequently, drives the kinetics of the control signal Gc,con reflecting the net result of downstream signals at the cellular level, which modulates the parallel deposition of half-sarcomeres (concentric growth).

Diagram

Description automatically generated

**Figure** **10. Role of energy demand (myosin ATPase normalized to myofibrillar volume) and intracellular passive stress (titin domains) in driving cardiac growth.**

Myosin ATPase and titin-domain architecture (N2A/N2BA-isoform of human cardiac muscle) laid out in a half-sarcomere for cardiac growth based signaling. Akt, protein serine/threonine kinase; ADP, adenosine diphosphate; ATP, adenosine triphosphate; CARP, cardiac-ankyrin-repeat-protein; DARP, diabetes-related ankyrin-repeat protein; ERK2, extracellular signal-regulated kinase-2; FHL2, four-and-a-half-LIM-domain protein; MAPK, mitogen-activated protein kinase; MAPK, mitogen-activated protein kinases; MARPs, muscle-ankyrin-repeat proteins; MEK1/2, MAP-ERK-kinase-1 and -2; MLP, muscle LIM protein; mTOR, mammalian target of rapamycin; MURF2, muscle-specific RING finger proteins(-2); Nbr1, neighbor of BRCA1 gene-1; NFAT, nuclear factor of activated T cells; p62, sequestosome 1/p62; P70s6K, p70 S6 kinase; PDK1, phosphoinositide-dependent kinase-1; PI3K, phosphatidyl inositol-3-OH-kinase.

## Role of intracellular sarcomeric passive stress in driving eccentric growth

In patients with valvular diseases such as chronic mitral/aortic insufficiency, eccentric growth is induced by volume overload. Such a condition initially results in excessive diastolic filling of the LV and thus overstretching of sarcomeres before any remodeling occurs. Emerging evidence has linked titin to fundamental signaling pathways, such as those regulating protein quality control, hypertrophic gene expression, and stress sensing. Titin can thus be viewed as a crucial integrating element at the intersection of myocyte signaling. The mechanical and mechano-signaling functions of the titin springs are variably tuned in health and disease, particularly in the heart by altering passive stiffness through titin-isoform switching, protein phosphorylation, and hypertrophic signaling.

In heart muscle, titin is expressed in two main isoforms: the N2B-isoform, which contains a short, stiff spring segment, and (variable) N2BA-isoforms, which contain longer springs and thus are more compliant (Figure ) [55]. Titin is a long protein that spans from the Z disk to M line with an elastic structure within the I band. This elastic behavior of titin within the I-band plays an essential role in generating passive stiffness of the sarcomere, which store strain-energy during diastolic filling and recoil during systole.

Cardiac titin has some unique properties that arise from the co-expression of N2BA and N2B isoforms in the half-sarcomere, as well as the presence of the N2-A domain in the middle of the spring segment. The N2-Bus is an additional extensible element in the cardiac titin spring, next to the Ig regions and the PEVK segment [56], but it is also involved in protein-protein interactions (Figure ). PEVK knockouts have been shown to trigger diastolic dysfunction through cardiac hypertrophy, presumably by increasing the binding of FHL1 to the N2-Bus, thereby activating the N2-Bus-associated stress sensor [57]. The N2-Bus binds two isoforms of the four-and-a-half-LIM-domain protein, FHL1 [58] and FHL2 [59]. Both FHL1 and FHL2 are transcriptional co-activators and interact with effector mitogen-activated protein kinases (MAPKs). FHL1 bound to the N2-Bus associates with ERK2 and MEK1/2, as well as Raf1, which is activated via stretch and increase passive stress [58] and may suppress ERK2 and MEK1/2. Decreased or absent ERK1/2 signaling induces myocyte lengthening and eccentric growth [60]. Thus, FHL1 is a component of the stretch sensor at the I band that acts to sense stretch to restrict or lock the range at which physiological sarcomere length can extend following stretch to scaffold stress-induced interactions of MAPK components at titin in order to mediate ensuing hypertrophic signaling, which can lead to pathological cardiac hypertrophy.

A unique sequence of M-band titin is linked to regulatory pathways of muscle growth through binding to FHL2. FHL2 has been shown to sense cardiac stress, which is part of the M band signaling complex with Nbr1 and p62 [61]. This protein has numerous other interaction partners, including metabolic enzymes [59], and appears to be a transcriptional co-activator. M band titin has links to additional pathways of muscle-growth regulation, particularly through the interaction with MURFs proteins that can shuttle to the nucleus to alter muscle gene expression. The titin kinase domain controls muscle gene expression and protein turnover via association with the neighbor-of-BRCA1 gene-1 (nbr1) protein, which in turn signals to MURF2 via binding to p62 (Figure 10). MURF2 activates hypertrophic genes in the nucleus, such as serum response factor [62].

Hypertrophic signaling mechanisms are also located at the Z disk titin domain (Figure 10). Binding of the extreme NH2-terminal titin Ig domains, Z1/Z2, to telethonin [63] also recruits a telethonin-ligand, muscle LIM protein (MLP), to the Z disk [64, 65]. MLP has also been detected in the I band [66], at costameres, and abundantly in the cytosol, as well as in the nucleus. Shuttling of MLP to the nucleus [67] can activate transcriptional regulators and may enhance protein expression. MLP also binds to calcineurin, a protein phosphatase dephosphorylating nuclear factor of activated T cells (NFAT), which can thus translocate to the nucleus and induce a hypertrophic gene program [68]. This hypertrophic pathway is thought to be activated by stress or strain imposed onto the Z disk, but the exact mechanism of action and the role of titin’s NH2 terminus in it remain obscure.

Lastly, Ig domains at titin’s N2-A-domain interact with the three homologous muscle-ankyrin-repeat proteins (MARPs), cardiac-ankyrin-repeat protein (CARP), diabetes-related ankyrin-repeat protein (DARP), and ankyrin-repeat-domain protein-2 (Ankrd2) [69, 70], which in turn bind to myopalladin [71], an important actin-regulating protein [72] (Figure ). Since members of the MARP family also associate with transcription factors kojic [73], a role for MARPs as nuclear regulators of transcription is likely. Thus, via MARP-binding, the N2-A-domain of titin could be involved in hypertrophic signaling mechanisms.

Overall, mechanical stimuli in the form of passive stresses are sensed by sarcomeric titin domains that trigger a cascade of downstream signals, which ultimately lead to the upregulating of protein synthesis, sarcomere addition, and myocardium growth.

In our model, intracellular passive stress has a nonlinear relationship with the half-sarcomere length (equation ). As a result, volume overloading that initially increases the diastolic filling of the LV, thus overstretching the half-sarcomeres, leads to an increase in the intracellular passive stress. In response to this elevated mechanical stimuli, the growth algorithm increases the eccentric growth signal Ga,ecc, which in turn drives the kinetics of the control signal Gc,ecc (Figure ). Ultimately, through the addition of half-sarcomeres in series, the half-sarcomere length and associated passive stress, along with Ga,ecc and Gc,ecc, re-normalize back to their homeostatic range.

## Comparison with existing models of LV growth

Although many other computational models have been developed and shed light on the underlying mechanics of LV growth, there are still limitations that need to be addressed [15]. Some of these limitations are related to the assumptions used for the duration of the cardiac cycle and the representation of systolic function. For instance, some models [7, 12, 74] have only simulated LV growth during diastolic loading and neglected systolic behavior of myocardium during ejection. Other models [9, 75, 76] investigated the mechanics of LV growth, which were performed under a full cardiac cycle, but the contractile function was simulated using phenomenological Hill-type models. Another group of works [10, 17] have used a time-varying elastance model of the ventricle to simulate a full cardiac cycle. Rondanina and Bovendeerd [13, 77] recently investigated different combinations of mechanical growth stimuli where they used a one-fiber model of cardiac function. This model related the mechanics of the LV at the organ level, expressed in terms of LV pressure and volume, to mechanics at the tissue level, expressed as sarcomere stress and length [78].

However, the framework presented in the current study simulates LV growth under a full cardiac cycle in which the contractile behavior of the LV is driven by a mechanistic model of half-sarcomeres that simulates the sliding of myofilaments based on the Huxley crossbridge formation [79] at the molecular level. By modeling the mechanics of half-sarcomeres, we are able to study the effects of pathological processes at the molecular level and how they affect disease development at the organ level. Additionally, this framework could potentially be used to study the effects of various pharmaceutical interventions for treating cardiac diseases.

The absence of a baroreflex feedback loop is another limitation of existing models [15]. In general, most existing models are performed under constant heart rate with no mechanism to control the arterial pressure. Kerckhoffs et al. [9] observed that the absence of hemodynamic feedback was the potential cause of mismatch between calculated peak LV pressure in their model and experimentally measured values. Rondanina and Bovendeerd [77] showed that by implementing a model of hemodynamic feedback into their growth model, they could address the observed reduction in mean arterial pressure and cardiac output found in their prior work investigating valvular disorders [13]. Our framework uses a baroreflex feedback loop to maintain arterial pressure by modulating heart rate, intracellular Ca2+ transient, function of both myofilaments, and vascular tone. As shown in the current results (Figure ), deactivating the baroreflex control when applying disease-mimicking perturbations (e.g. aortic stenosis or mitral insufficiency) can change the arterial pressure and LV hemodynamics. Altered hemodynamics, on the other hand, varies the LV loading and thus results into different outcomes of the growth algorithm. Furthermore, the absence of the baroreflex feedback loop prolonged the required simulation time took by the growth module to reach to the steady state. For instance, simulating aortic stenosis condition without the baroreflex control, the growth algorithm did not completely reach to steady state even after doubling the amount of simulation time (Figure S).

The reversal of cardiac growth is a favorable outcome of clinical interventions for dysfunctional valves, i.e., when the ventricle returns to a normal size and shape. Although existing computational models have shown success in predicting the development of growth, many of them are challenged when trying to predict the reversal of growth [15, 80]. For example, Yoshida et al. [81] investigated the regression of growth due to the removal of pressure overloading, while using the growth law developed by [9]. Although this growth law performed the best in capturing the development of LV growth, in comparison to seven other growth laws [82], it could not predict the reversal of growth. Yoshida et al. [81] further suggested that using an evolving setpoint could potentially address the inability of existing models to predict the reversal of growth. Of the few works that have studied the reversal of growth, Lee et al. [74] modified a previously developed eccentric growth law [12] and were able to capture the reversal of growth for a realistic LV geometry under certain types of loading. Arumugam et al. [75] extended their previous work [74] and investigated the development of anisotropic growth in a biventricular model of the heart in response to mechanical dyssynchrony. Using maximum elastic myofiber stretch over a cardiac cycle as the sole stimulus signal of their growth law, their model demonstrated growth in the left ventricular chamber size and septal wall, but reversal of growth for the right ventricular chamber size and LV free wall.

Our model, however, completely regained the LV size and function once the underlying perturbation for each valvular disorder was lifted. There are two potential explanations for this result. Firstly, the PyMyoVent framework uses a mechanistic model of a half-sarcomere to simulate the contractile behavior of myocardium, which captures length-dependent activation, cooperativity between thick and thin filaments, and the strain-dependent behavior of cross-bridges [22, 23]. Such a model can account for the effects of altered ventricular loading on the force generation of half-sarcomere that other models may be unable to capture. For instance, Yoshida et al. [81] had to manually adjust the muscle contractility in their model to mimic the lower force production of myocardium due to the removal of pressure overloading. In contrast, removal of the aortic stenosis condition in our model led to lower hemodynamic resistance during LV systole, which in turn increased the shortening velocity of half-sarcomeres due to higher strain in the myosin heads. This event reduces the number of bound myosin heads in the force-generating state (MFG) and thus lowers the associated force that is generated in the half-sarcomere, such that it matches with the altered hemodynamic loading. Secondly, the current framework shows additional benefits from being coupled with the baroreflex feedback loop. Specifically, there is no need to manually adjust the circulatory parameters when the overloading is removed to match with realistic hemodynamics as Yoshida et al. [81] did in their work. Instead, such a feedback loop controls the arterial pressure by modulating heart rate, intracellular Ca2+ transient, function of both myofilaments, and vascular tone. To the best of the authors’ knowledge, the current study is the first time that LV growth has been simulated with molecular-level sarcomere mechanics while the arterial pressure is being controlled by a baroreflex feedback loop.

## Limitations

The limitations discussed in the previous works with PyMyoVent [21, 24] are still applicable to the current framework. However, the following limitations are specifically related to the growth module added in this work. Firstly, the current model can only capture uniform changes in the ventricular size and dimensions. This is due to the simplified 1-D hemispherical geometry of the LV, which does not account for the complex torsional motion of the heart [83], longitudinal and transmural variation of contractile properties [84], or the variation in myofibers orientations [85].

Secondly, the current framework can only quantify the cardiac growth (i.e. change in the ventricular size and dimension), but not the myofiber remodeling. Alterations in mechanical loading [2, 86] can be accompanied by myofiber disarray and remodeling. However, the PyMyoVent framework assumes the half-sarcomeres, and thus the myofibers, are uniformly placed around the circumference of LV at base and their orientation remains unchanged during LV growth. Thirdly, the current study does not include the effect of fibrosis that is commonly observed in patient with aortic stenosis [87].

# Conclusions

This work extends a multiscale model of cardiovascular function by incorporating a growth module that simulates both concentric (wall thickening / thinning) and eccentric (chamber dilation / constriction) growth. The new framework reproduced clinical measures of LV growth in three types of valvular disease, namely aortic stenosis, aortic insufficiency, and mitral insufficiency. Additionally, the new framework could fully regain the LV size and function (reversal of growth) when the disease-mimicking perturbation was removed. In conclusion, the results of this study suggest that myosin ATPase normalized to myofibrillar volume and intracellular passive stress can be used to drive concentric and eccentric growth in simulations of valve disease.

**Acknowledgements**

# Supported by NIH HL133359 to KSC and JFW, NIH 148785 and TR0001998 to KSC, and AHA TP135689 to KSC.

**Author contributions**

SH drafted the manuscript, wrote prototype versions of the code, ran the final simulations, created the figures, helped develop the website and GitHub repository, and ran prototype simulations. CKM helped with planning the structure of the manuscript and edited the manuscript. AGWH helped with his knowledge in cell signaling by drafting sections 4.1 and 4.2. JFW helped develop the model framework and edited the manuscript. KSC planned the overall project, developed the growth algorithm, wrote the final version of the code, and edited the manuscript.

# References

1. Frey N, Olson EN. Cardiac hypertrophy: the good, the bad, and the ugly. Annu Rev Physiol. 2003;65:45-79. Epub 2003/01/14. doi: 10.1146/annurev.physiol.65.092101.142243. PubMed PMID: 12524460.

2. Pitoulis FG, Terracciano CM. Heart Plasticity in Response to Pressure- and Volume-Overload: A Review of Findings in Compensated and Decompensated Phenotypes. Front Physiol. 2020;11:92. Epub 2020/03/03. doi: 10.3389/fphys.2020.00092. PubMed PMID: 32116796; PubMed Central PMCID: PMCPMC7031419.

3. Hill JA, Olson EN. Cardiac plasticity. N Engl J Med. 2008;358(13):1370-80. Epub 2008/03/28. doi: 10.1056/NEJMra072139. PubMed PMID: 18367740.

4. Shimizu I, Minamino T. Physiological and pathological cardiac hypertrophy. J Mol Cell Cardiol. 2016;97:245-62. Epub 2016/06/06. doi: 10.1016/j.yjmcc.2016.06.001. PubMed PMID: 27262674.

5. Nakamura M, Sadoshima J. Mechanisms of physiological and pathological cardiac hypertrophy. Nat Rev Cardiol. 2018;15(7):387-407. Epub 2018/04/21. doi: 10.1038/s41569-018-0007-y. PubMed PMID: 29674714.

6. Rausch MK, Dam A, Goktepe S, Abilez OJ, Kuhl E. Computational modeling of growth: systemic and pulmonary hypertension in the heart. Biomech Model Mechanobiol. 2011;10(6):799-811. Epub 2010/12/29. doi: 10.1007/s10237-010-0275-x. PubMed PMID: 21188611; PubMed Central PMCID: PMCPMC3235798.

7. Klepach D, Lee LC, Wenk JF, Ratcliffe MB, Zohdi TI, Navia JA, et al. Growth and remodeling of the left ventricle: A case study of myocardial infarction and surgical ventricular restoration. Mech Res Commun. 2012;42:134-41. doi: 10.1016/j.mechrescom.2012.03.005. PubMed PMID: 22778489; PubMed Central PMCID: PMCPMC3390946.

8. Guterl KA, Haggart CR, Janssen PM, Holmes JW. Isometric contraction induces rapid myocyte remodeling in cultured rat right ventricular papillary muscles. Am J Physiol Heart Circ Physiol. 2007;293(6):H3707-12. Epub 2007/10/09. doi: 10.1152/ajpheart.00296.2007. PubMed PMID: 17921334.

9. Kerckhoffs RC, Omens J, McCulloch AD. A single strain-based growth law predicts concentric and eccentric cardiac growth during pressure and volume overload. Mech Res Commun. 2012;42:40-50. Epub 2012/05/29. doi: 10.1016/j.mechrescom.2011.11.004. PubMed PMID: 22639476; PubMed Central PMCID: PMCPMC3358801.

10. Witzenburg CM, Holmes JW. Predicting the Time Course of Ventricular Dilation and Thickening Using a Rapid Compartmental Model. J Cardiovasc Transl Res. 2018;11(2):109-22. Epub 2018/03/20. doi: 10.1007/s12265-018-9793-1. PubMed PMID: 29550925; PubMed Central PMCID: PMCPMC6546110.

11. Arts T, Lumens J, Kroon W, Delhaas T. Control of whole heart geometry by intramyocardial mechano-feedback: a model study. PLoS Comput Biol. 2012;8(2):e1002369. Epub 2012/02/22. doi: 10.1371/journal.pcbi.1002369. PubMed PMID: 22346742; PubMed Central PMCID: PMCPMC3276542.

12. Goktepe S, Abilez OJ, Parker KK, Kuhl E. A multiscale model for eccentric and concentric cardiac growth through sarcomerogenesis. J Theor Biol. 2010;265(3):433-42. Epub 2010/05/08. doi: 10.1016/j.jtbi.2010.04.023. PubMed PMID: 20447409.

13. Rondanina E, Bovendeerd PHM. Evaluation of stimulus-effect relations in left ventricular growth using a simple multiscale model. Biomech Model Mechanobiol. 2020;19(1):263-73. Epub 2019/08/08. doi: 10.1007/s10237-019-01209-2. PubMed PMID: 31388869; PubMed Central PMCID: PMCPMC7005098.

14. Mojumder J, Choy JS, Leng S, Zhong L, Kassab GS, Lee LC. Mechanical stimuli for left ventricular growth during pressure overload. Exp Mech. 2021;61(1):131-46. Epub 2021/03/23. doi: 10.1007/s11340-020-00643-z. PubMed PMID: 33746236; PubMed Central PMCID: PMCPMC7968380.

15. Sharifi H, Mann CK, Rockward AL, al. e. Multiscale simulations of left ventricular growth and remodeling. Biophys Rev. 2021. doi: <https://doi.org/10.1007/s12551-021-00826-5>. PubMed Central PMCID: PMCPMC8555068.

16. Yoshida K, Saucerman JJ, Holmes JW. Multiscale model of heart growth during pregnancy: Integrating mechanical and hormonal signaling. bioRxiv. 2020. doi: <https://doi.org/10.1101/2020.09.18.302067>.

17. Estrada AC, Yoshida K, Saucerman JJ, Holmes JW. A multiscale model of cardiac concentric hypertrophy incorporating both mechanical and hormonal drivers of growth. Biomech Model Mechanobiol. 2021;20(1):293-307. Epub 2020/09/25. doi: 10.1007/s10237-020-01385-6. PubMed PMID: 32970240; PubMed Central PMCID: PMCPMC7897221.

18. Davis J, Davis LC, Correll RN, Makarewich CA, Schwanekamp JA, Moussavi-Harami F, et al. A Tension-Based Model Distinguishes Hypertrophic versus Dilated Cardiomyopathy. Cell. 2016;165(5):1147-59. Epub 2016/04/27. doi: 10.1016/j.cell.2016.04.002. PubMed PMID: 27114035; PubMed Central PMCID: PMCPMC4874838.

19. Bischof C, Mirtschink P, Yuan T, Wu M, Zhu C, Kaur J, et al. Mitochondrial-cell cycle cross-talk drives endoreplication in heart disease. Sci Transl Med. 2021;13(623):eabi7964. Epub 2021/12/09. doi: 10.1126/scitranslmed.abi7964. PubMed PMID: 34878823.

20. Campbell KS. PyMyoVent. 2021.

21. Campbell KS, Chrisman BS, Campbell SG. Multiscale Modeling of Cardiovascular Function Predicts That the End-Systolic Pressure Volume Relationship Can Be Targeted via Multiple Therapeutic Strategies. Frontiers in physiology. 2020;11:1043. doi: 10.3389/fphys.2020.01043. PubMed PMID: 32973561; PubMed Central PMCID: PMCPMC7466769.

22. Campbell KS. Dynamic coupling of regulated binding sites and cycling myosin heads in striated muscle. J Gen Physiol. 2014;143(3):387-99. doi: 10.1085/jgp.201311078. PubMed PMID: 24516189; PubMed Central PMCID: PMCPMC3933939.

23. Campbell KS, Janssen PML, Campbell SG. Force-Dependent Recruitment from the Myosin Off State Contributes to Length-Dependent Activation. Biophys J. 2018;115(3):543-53. Epub 2018/07/29. doi: 10.1016/j.bpj.2018.07.006. PubMed PMID: 30054031; PubMed Central PMCID: PMCPMC6084639.

24. Sharifi H, Mann CK, Wenk JF, al. e. A multiscale model of the cardiovascular system that incorporates baroreflex control of chronotropism, cell-level contractility, and vascular tone. bioRxiv. 2021. doi: <https://doi.org/10.1101/2021.10.21.465366>.

25. Van der Walt S, Colbert SC, Varoquaux G. The NumPy array: a structure for efficient numerical computation. arXiv. 2011. doi: 10.1109/MCSE.2011.37.

26. Virtanen P, Gommers R, Oliphant TE, Haberland M, Reddy T, Cournapeau D, et al. SciPy 1.0: fundamental algorithms for scientific computing in Python. Nat Methods. 2020;17(3):261-72. Epub 2020/02/06. doi: 10.1038/s41592-019-0686-2. PubMed PMID: 32015543; PubMed Central PMCID: PMCPMC7056644.

27. Reback J, jbrockmendel., McKinney W, al. e. pandas-dev/pandas: Pandas 1.3.2. . 2021.

28. Maceira AM, Prasad SK, Khan M, Pennell DJ. Normalized left ventricular systolic and diastolic function by steady state free precession cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2006;8(3):417-26. Epub 2006/06/08. doi: 10.1080/10976640600572889. PubMed PMID: 16755827.

29. Petersen SE, Aung N, Sanghvi MM, Zemrak F, Fung K, Paiva JM, et al. Reference ranges for cardiac structure and function using cardiovascular magnetic resonance (CMR) in Caucasians from the UK Biobank population cohort. J Cardiovasc Magn Reson. 2017;19(1):18. Epub 2017/02/10. doi: 10.1186/s12968-017-0327-9. PubMed PMID: 28178995; PubMed Central PMCID: PMCPMC5304550.

30. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, 3rd, Gentile F, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021;143(5):e72-e227. Epub 2020/12/18. doi: 10.1161/CIR.0000000000000923. PubMed PMID: 33332150.

31. Chin CW, Khaw HJ, Luo E, Tan S, White AC, Newby DE, et al. Echocardiography underestimates stroke volume and aortic valve area: implications for patients with small-area low-gradient aortic stenosis. Can J Cardiol. 2014;30(9):1064-72. Epub 2014/08/26. doi: 10.1016/j.cjca.2014.04.021. PubMed PMID: 25151288; PubMed Central PMCID: PMCPMC4161727.

32. Chin CWL, Everett RJ, Kwiecinski J, Vesey AT, Yeung E, Esson G, et al. Myocardial Fibrosis and Cardiac Decompensation in Aortic Stenosis. JACC Cardiovasc Imaging. 2017;10(11):1320-33. Epub 2016/12/27. doi: 10.1016/j.jcmg.2016.10.007. PubMed PMID: 28017384; PubMed Central PMCID: PMCPMC5683736.

33. Luszczak J, Olszowska M, Drapisz S, Plazak W, Karch I, Komar M, et al. Assessment of left ventricle function in patients with symptomatic and asymptomatic aortic stenosis by 2-dimensional speckle-tracking imaging. Med Sci Monit. 2012;18(12):MT91-6. Epub 2012/12/01. doi: 10.12659/msm.883587. PubMed PMID: 23197243; PubMed Central PMCID: PMCPMC3560794.

34. Everett RJ, Treibel TA, Fukui M, Lee H, Rigolli M, Singh A, et al. Extracellular Myocardial Volume in Patients With Aortic Stenosis. J Am Coll Cardiol. 2020;75(3):304-16. Epub 2020/01/25. doi: 10.1016/j.jacc.2019.11.032. PubMed PMID: 31976869; PubMed Central PMCID: PMCPMC6985897.

35. Spath NB, Gomez M, Everett RJ, Semple S, Chin CWL, White AC, et al. Global Longitudinal Strain Analysis Using Cardiac MRI in Aortic Stenosis: Comparison with Left Ventricular Remodeling, Myocardial Fibrosis, and 2-year Clinical Outcomes. Radiol Cardiothorac Imaging. 2019;1(4):e190027. Epub 2019/10/31. doi: 10.1148/ryct.2019190027. PubMed PMID: 33778518; PubMed Central PMCID: PMCPMC7977929 M.G. disclosed no relevant relationships. R.J.E. disclosed no relevant relationships. S.S. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: author was a paid consultant for GlaxoSmithKline; institution received grant from GlaxoSmithKline. Other relationships: disclosed no relevant relationships. C.W.L.C. disclosed no relevant relationships. A.C.W. disclosed no relevant relationships. A.G.J. disclosed no relevant relationships. D.E.N. Activities related to the present article: institution receives grant from British Heart Foundation. Activities not related to the present article: disclosed no relevant relationships. Other relationships: disclosed no relevant relationships. M.R.D. Activities related to the present article: institution receives grant from British Heart Foundation. Activities not related to the present article: disclosed no relevant relationships. Other relationships: disclosed no relevant relationships.

36. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1):1-39 e14. Epub 2015/01/07. doi: 10.1016/j.echo.2014.10.003. PubMed PMID: 25559473.

37. Verbraecken J, Van de Heyning P, De Backer W, Van Gaal L. Body surface area in normal-weight, overweight, and obese adults. A comparison study. Metabolism. 2006;55(4):515-24. Epub 2006/03/21. doi: 10.1016/j.metabol.2005.11.004. PubMed PMID: 16546483.

38. Watkins H, Ashrafian H, Redwood C. Inherited cardiomyopathies. N Engl J Med. 2011;364(17):1643-56. doi: 10.1056/NEJMra0902923. PubMed PMID: 21524215.

39. Green DR, Galluzzi L, Kroemer G. Mitochondria and the autophagy-inflammation-cell death axis in organismal aging. Science. 2011;333(6046):1109-12. Epub 2011/08/27. doi: 10.1126/science.1201940. PubMed PMID: 21868666; PubMed Central PMCID: PMCPMC3405151.

40. Puddu P, Puddu GM, Cravero E, De Pascalis S, Muscari A. The putative role of mitochondrial dysfunction in hypertension. Clin Exp Hypertens. 2007;29(7):427-34. Epub 2007/11/13. doi: 10.1080/10641960701613852. PubMed PMID: 17994352.

41. Iglewski M, Hill JA, Lavandero S, Rothermel BA. Mitochondrial fission and autophagy in the normal and diseased heart. Curr Hypertens Rep. 2010;12(6):418-25. Epub 2010/09/25. doi: 10.1007/s11906-010-0147-x. PubMed PMID: 20865352; PubMed Central PMCID: PMCPMC3032809.

42. Luptak I, Balschi JA, Xing Y, Leone TC, Kelly DP, Tian R. Decreased contractile and metabolic reserve in peroxisome proliferator-activated receptor-alpha-null hearts can be rescued by increasing glucose transport and utilization. Circulation. 2005;112(15):2339-46. Epub 2005/10/06. doi: 10.1161/CIRCULATIONAHA.105.534594. PubMed PMID: 16203912.

43. Neubauer S. The failing heart--an engine out of fuel. N Engl J Med. 2007;356(11):1140-51. Epub 2007/03/16. doi: 10.1056/NEJMra063052. PubMed PMID: 17360992.

44. Ritterhoff J, Tian R. Metabolism in cardiomyopathy: every substrate matters. Cardiovasc Res. 2017;113(4):411-21. Epub 2017/04/11. doi: 10.1093/cvr/cvx017. PubMed PMID: 28395011; PubMed Central PMCID: PMCPMC5852620.

45. Tian R, Musi N, D'Agostino J, Hirshman MF, Goodyear LJ. Increased adenosine monophosphate-activated protein kinase activity in rat hearts with pressure-overload hypertrophy. Circulation. 2001;104(14):1664-9. Epub 2001/10/03. doi: 10.1161/hc4001.097183. PubMed PMID: 11581146.

46. Meerson FZ, Spiritchev VB, Pshennikova MG, Djachkova LV. The role of the pentose-phosphate pathway in adjustment of the heart to a high load and the development of myocardial hypertrophy. Experientia. 1967;23(7):530-2. Epub 1967/07/15. doi: 10.1007/BF02137950. PubMed PMID: 4228586.

47. Ritterhoff J, Young S, Villet O, Shao D, Neto FC, Bettcher LF, et al. Metabolic Remodeling Promotes Cardiac Hypertrophy by Directing Glucose to Aspartate Biosynthesis. Circ Res. 2020;126(2):182-96. Epub 2019/11/12. doi: 10.1161/CIRCRESAHA.119.315483. PubMed PMID: 31709908; PubMed Central PMCID: PMCPMC8448129.

48. Ma H, Yu S, Liu X, Zhang Y, Fakadej T, Liu Z, et al. Lin28a Regulates Pathological Cardiac Hypertrophic Growth Through Pck2-Mediated Enhancement of Anabolic Synthesis. Circulation. 2019;139(14):1725-40. Epub 2019/01/15. doi: 10.1161/CIRCULATIONAHA.118.037803. PubMed PMID: 30636447; PubMed Central PMCID: PMCPMC6443464.

49. Zhang M, Niu X, Hu J, Yuan Y, Sun S, Wang J, et al. Lin28a protects against hypoxia/reoxygenation induced cardiomyocytes apoptosis by alleviating mitochondrial dysfunction under high glucose/high fat conditions. PLoS One. 2014;9(10):e110580. Epub 2014/10/15. doi: 10.1371/journal.pone.0110580. PubMed PMID: 25313561; PubMed Central PMCID: PMCPMC4196990.

50. Zhu H, Shyh-Chang N, Segre AV, Shinoda G, Shah SP, Einhorn WS, et al. The Lin28/let-7 axis regulates glucose metabolism. Cell. 2011;147(1):81-94. Epub 2011/10/04. doi: 10.1016/j.cell.2011.08.033. PubMed PMID: 21962509; PubMed Central PMCID: PMCPMC3353524.

51. McMullen JR, Shioi T, Huang WY, Zhang L, Tarnavski O, Bisping E, et al. The insulin-like growth factor 1 receptor induces physiological heart growth via the phosphoinositide 3-kinase(p110alpha) pathway. J Biol Chem. 2004;279(6):4782-93. Epub 2003/11/05. doi: 10.1074/jbc.M310405200. PubMed PMID: 14597618.

52. Shiojima I, Sato K, Izumiya Y, Schiekofer S, Ito M, Liao R, et al. Disruption of coordinated cardiac hypertrophy and angiogenesis contributes to the transition to heart failure. J Clin Invest. 2005;115(8):2108-18. Epub 2005/08/03. doi: 10.1172/JCI24682. PubMed PMID: 16075055; PubMed Central PMCID: PMCPMC1180541.

53. Lavandero S, Foncea R, Perez V, Sapag-Hagar M. Effect of inhibitors of signal transduction on IGF-1-induced protein synthesis associated with hypertrophy in cultured neonatal rat ventricular myocytes. FEBS Lett. 1998;422(2):193-6. Epub 1998/03/07. doi: 10.1016/s0014-5793(98)00008-8. PubMed PMID: 9490004.

54. Volkers M, Toko H, Doroudgar S, Din S, Quijada P, Joyo AY, et al. Pathological hypertrophy amelioration by PRAS40-mediated inhibition of mTORC1. Proc Natl Acad Sci U S A. 2013;110(31):12661-6. Epub 2013/07/12. doi: 10.1073/pnas.1301455110. PubMed PMID: 23842089; PubMed Central PMCID: PMCPMC3732982.

55. Freiburg A, Trombitas K, Hell W, Cazorla O, Fougerousse F, Centner T, et al. Series of exon-skipping events in the elastic spring region of titin as the structural basis for myofibrillar elastic diversity. Circ Res. 2000;86(11):1114-21. Epub 2000/06/13. doi: 10.1161/01.res.86.11.1114. PubMed PMID: 10850961.

56. Linke WA, Rudy DE, Centner T, Gautel M, Witt C, Labeit S, et al. I-band titin in cardiac muscle is a three-element molecular spring and is critical for maintaining thin filament structure. J Cell Biol. 1999;146(3):631-44. Epub 1999/08/12. doi: 10.1083/jcb.146.3.631. PubMed PMID: 10444071; PubMed Central PMCID: PMCPMC2150553.

57. Granzier HL, Radke MH, Peng J, Westermann D, Nelson OL, Rost K, et al. Truncation of titin's elastic PEVK region leads to cardiomyopathy with diastolic dysfunction. Circ Res. 2009;105(6):557-64. Epub 2009/08/15. doi: 10.1161/CIRCRESAHA.109.200964. PubMed PMID: 19679835; PubMed Central PMCID: PMCPMC2785004.

58. Sheikh F, Raskin A, Chu PH, Lange S, Domenighetti AA, Zheng M, et al. An FHL1-containing complex within the cardiomyocyte sarcomere mediates hypertrophic biomechanical stress responses in mice. J Clin Invest. 2008;118(12):3870-80. Epub 2008/11/27. doi: 10.1172/JCI34472. PubMed PMID: 19033658; PubMed Central PMCID: PMCPMC2575833.

59. Lange S, Auerbach D, McLoughlin P, Perriard E, Schafer BW, Perriard JC, et al. Subcellular targeting of metabolic enzymes to titin in heart muscle may be mediated by DRAL/FHL-2. J Cell Sci. 2002;115(Pt 24):4925-36. Epub 2002/11/15. doi: 10.1242/jcs.00181. PubMed PMID: 12432079.

60. Kehat I, Davis J, Tiburcy M, Accornero F, Saba-El-Leil MK, Maillet M, et al. Extracellular signal-regulated kinases 1 and 2 regulate the balance between eccentric and concentric cardiac growth. Circ Res. 2011;108(2):176-83. Epub 2010/12/04. doi: 10.1161/CIRCRESAHA.110.231514. PubMed PMID: 21127295; PubMed Central PMCID: PMCPMC3032171.

61. Radke MH, Polack C, Methawasin M, Fink C, Granzier HL, Gotthardt M. Deleting Full Length Titin Versus the Titin M-Band Region Leads to Differential Mechanosignaling and Cardiac Phenotypes. Circulation. 2019;139(15):1813-27. Epub 2019/02/01. doi: 10.1161/CIRCULATIONAHA.118.037588. PubMed PMID: 30700140; PubMed Central PMCID: PMCPMC6453709.

62. Lange S, Xiang F, Yakovenko A, Vihola A, Hackman P, Rostkova E, et al. The kinase domain of titin controls muscle gene expression and protein turnover. Science. 2005;308(5728):1599-603. PubMed PMID: 15802564.

63. Zou P, Pinotsis N, Lange S, Song YH, Popov A, Mavridis I, et al. Palindromic assembly of the giant muscle protein titin in the sarcomeric Z-disk. Nature. 2006;439(7073):229-33. Epub 2006/01/13. doi: 10.1038/nature04343. PubMed PMID: 16407954.

64. Knoll R, Hoshijima M, Hoffman HM, Person V, Lorenzen-Schmidt I, Bang ML, et al. The cardiac mechanical stretch sensor machinery involves a Z disc complex that is defective in a subset of human dilated cardiomyopathy. Cell. 2002;111(7):943-55. Epub 2003/01/01. doi: 10.1016/s0092-8674(02)01226-6. PubMed PMID: 12507422.

65. Knoll R, Kostin S, Klede S, Savvatis K, Klinge L, Stehle I, et al. A common MLP (muscle LIM protein) variant is associated with cardiomyopathy. Circ Res. 2010;106(4):695-704. Epub 2010/01/02. doi: 10.1161/CIRCRESAHA.109.206243. PubMed PMID: 20044516.

66. Arber S, Hunter JJ, Ross J, Jr., Hongo M, Sansig G, Borg J, et al. MLP-deficient mice exhibit a disruption of cardiac cytoarchitectural organization, dilated cardiomyopathy, and heart failure. Cell. 1997;88(3):393-403. Epub 1997/02/07. doi: 10.1016/s0092-8674(00)81878-4. PubMed PMID: 9039266.

67. Boateng SY, Senyo SE, Qi L, Goldspink PH, Russell B. Myocyte remodeling in response to hypertrophic stimuli requires nucleocytoplasmic shuttling of muscle LIM protein. J Mol Cell Cardiol. 2009;47(4):426-35. Epub 2009/04/21. doi: 10.1016/j.yjmcc.2009.04.006. PubMed PMID: 19376126; PubMed Central PMCID: PMCPMC2739242.

68. Samarel AM. PICOT: a multidomain scaffolding inhibitor of hypertrophic signal transduction. Circ Res. 2008;102(6):625-7. Epub 2008/03/29. doi: 10.1161/CIRCRESAHA.108.173807. PubMed PMID: 18369159.

69. Witt SH, Labeit D, Granzier H, Labeit S, Witt CC. Dimerization of the cardiac ankyrin protein CARP: implications for MARP titin-based signaling. J Muscle Res Cell Motil. 2005;26(6-8):401-8. Epub 2006/02/02. doi: 10.1007/s10974-005-9022-9. PubMed PMID: 16450059.

70. Mayans O, van der Ven PF, Wilm M, Mues A, Young P, Furst DO, et al. Structural basis for activation of the titin kinase domain during myofibrillogenesis. Nature. 1998;395(6705):863-9. Epub 1998/11/06. doi: 10.1038/27603. PubMed PMID: 9804419.

71. Bang ML, Mudry RE, McElhinny AS, Trombitas K, Geach AJ, Yamasaki R, et al. Myopalladin, a novel 145-kilodalton sarcomeric protein with multiple roles in Z-disc and I-band protein assemblies. J Cell Biol. 2001;153(2):413-27. Epub 2001/04/20. doi: 10.1083/jcb.153.2.413. PubMed PMID: 11309420; PubMed Central PMCID: PMCPMC2169455.

72. Otey CA, Rachlin A, Moza M, Arneman D, Carpen O. The palladin/myotilin/myopalladin family of actin-associated scaffolds. Int Rev Cytol. 2005;246:31-58. Epub 2005/09/17. doi: 10.1016/S0074-7696(05)46002-7. PubMed PMID: 16164966.

73. Kojic S, Medeot E, Guccione E, Krmac H, Zara I, Martinelli V, et al. The Ankrd2 protein, a link between the sarcomere and the nucleus in skeletal muscle. J Mol Biol. 2004;339(2):313-25. Epub 2004/05/12. doi: 10.1016/j.jmb.2004.03.071. PubMed PMID: 15136035.

74. Lee LC, Genet M, Acevedo-Bolton G, Ordovas K, Guccione JM, Kuhl E. A computational model that predicts reverse growth in response to mechanical unloading. Biomech Model Mechanobiol. 2015;14(2):217-29. doi: 10.1007/s10237-014-0598-0. PubMed PMID: 24888270; PubMed Central PMCID: PMCPMC4254895.

75. Arumugam J, Mojumder J, Kassab G, Lee LC. Model of Anisotropic Reverse Cardiac Growth in Mechanical Dyssynchrony. Sci Rep. 2019;9(1):12670. Epub 2019/09/05. doi: 10.1038/s41598-019-48670-8. PubMed PMID: 31481725; PubMed Central PMCID: PMCPMC6722088.

76. Lee LC, Sundnes J, Genet M, Wenk JF, Wall ST. An integrated electromechanical-growth heart model for simulating cardiac therapies. Biomech Model Mechanobiol. 2016;15(4):791-803. doi: 10.1007/s10237-015-0723-8. PubMed PMID: 26376641.

77. Rondanina E, Bovendeerd PHM. Stimulus-effect relations for left ventricular growth obtained with a simple multi-scale model: the influence of hemodynamic feedback. Biomech Model Mechanobiol. 2020;19(6):2111-26. Epub 2020/05/03. doi: 10.1007/s10237-020-01327-2. PubMed PMID: 32358671; PubMed Central PMCID: PMCPMC7603455.

78. Bovendeerd PH, Borsje P, Arts T, van De Vosse FN. Dependence of intramyocardial pressure and coronary flow on ventricular loading and contractility: a model study. Ann Biomed Eng. 2006;34(12):1833-45. Epub 2006/10/19. doi: 10.1007/s10439-006-9189-2. PubMed PMID: 17048105; PubMed Central PMCID: PMCPMC1705493.

79. Huxley AF. Muscle structure and theories of contraction. Prog Biophys Biophys Chem. 1957;7:255-318. Epub 1957/01/01. PubMed PMID: 13485191.

80. Yoshida K, Holmes JW. Computational models of cardiac hypertrophy. Prog Biophys Mol Biol. 2021;159:75-85. Epub 2020/07/24. doi: 10.1016/j.pbiomolbio.2020.07.001. PubMed PMID: 32702352; PubMed Central PMCID: PMCPMC7855157.

81. Yoshida K, McCulloch AD, Omens JH, Holmes JW. Predictions of hypertrophy and its regression in response to pressure overload. Biomech Model Mechanobiol. 2020;19(3):1079-89. Epub 2019/12/10. doi: 10.1007/s10237-019-01271-w. PubMed PMID: 31813071; PubMed Central PMCID: PMCPMC8071348.

82. Witzenburg CM, Holmes JW. A Comparison of Phenomenologic Growth Laws for Myocardial Hypertrophy. J Elast. 2017;129(1-2):257-81. Epub 2018/04/11. doi: 10.1007/s10659-017-9631-8. PubMed PMID: 29632418; PubMed Central PMCID: PMCPMC5889094.

83. Russel IK, Gotte MJ, Bronzwaer JG, Knaapen P, Paulus WJ, van Rossum AC. Left ventricular torsion: an expanding role in the analysis of myocardial dysfunction. JACC Cardiovascular imaging. 2009;2(5):648-55. doi: 10.1016/j.jcmg.2009.03.001. PubMed PMID: 19442954.

84. Sharma S, Razeghi P, Shakir A, Keneson BJ, 2nd, Clubb F, Taegtmeyer H. Regional heterogeneity in gene expression profiles: a transcript analysis in human and rat heart. Cardiology. 2003;100(2):73-9. doi: 10.1159/000073042. PubMed PMID: 14557693.

85. Rodriguez-Cantano R, Sundnes J, Rognes ME. Uncertainty in cardiac myofiber orientation and stiffnesses dominate the variability of left ventricle deformation response. Int J Numer Method Biomed Eng. 2019;35(5):e3178. Epub 2019/01/12. doi: 10.1002/cnm.3178. PubMed PMID: 30632711; PubMed Central PMCID: PMCPMC6618163.

86. Washio T, Sugiura S, Okada JI, Hisada T. Using Systolic Local Mechanical Load to Predict Fiber Orientation in Ventricles. Frontiers in physiology. 2020;11:467. Epub 2020/06/26. doi: 10.3389/fphys.2020.00467. PubMed PMID: 32581822; PubMed Central PMCID: PMCPMC7295989.

87. Treibel TA, Kozor R, Schofield R, Benedetti G, Fontana M, Bhuva AN, et al. Reverse Myocardial Remodeling Following Valve Replacement in Patients With Aortic Stenosis. J Am Coll Cardiol. 2018;71(8):860-71. Epub 2018/02/24. doi: 10.1016/j.jacc.2017.12.035. PubMed PMID: 29471937; PubMed Central PMCID: PMCPMC5821681.

88. Lee HJ, Lee H, Kim SM, Park JB, Kim EK, Chang SA, et al. Diffuse Myocardial Fibrosis and Diastolic Function in Aortic Stenosis. JACC Cardiovasc Imaging. 2020;13(12):2561-72. Epub 2020/08/24. doi: 10.1016/j.jcmg.2020.07.007. PubMed PMID: 32828787.

89. Liu B, Neil DAH, Premchand M, Bhabra M, Patel R, Barker T, et al. Myocardial fibrosis in asymptomatic and symptomatic chronic severe primary mitral regurgitation and relationship to tissue characterisation and left ventricular function on cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2020;22(1):86. Epub 2020/12/15. doi: 10.1186/s12968-020-00674-4. PubMed PMID: 33308240; PubMed Central PMCID: PMCPMC7734760.

90. Malahfji M, Senapati A, Tayal B, Nguyen DT, Graviss EA, Nagueh SF, et al. Myocardial Scar and Mortality in Chronic Aortic Regurgitation. J Am Heart Assoc. 2020;9(23):e018731. Epub 2020/11/27. doi: 10.1161/JAHA.120.018731. PubMed PMID: 33241753; PubMed Central PMCID: PMCPMC7763777.

91. Seldrum S, de Meester C, Pierard S, Pasquet A, Lazam S, Boulif J, et al. Assessment of Left Ventricular Reverse Remodeling by Cardiac MRI in Patients Undergoing Repair Surgery for Severe Aortic or Mitral Regurgitation. J Cardiothorac Vasc Anesth. 2019;33(7):1901-11. Epub 2018/12/26. doi: 10.1053/j.jvca.2018.11.013. PubMed PMID: 30583928.

92. Bakkestrom R, Banke A, Pecini R, Irmukhamedov A, Nielsen SK, Andersen MJ, et al. Cardiac remodelling and haemodynamic characteristics in primary mitral valve regurgitation. Open Heart. 2018;5(2):e000919. Epub 2019/01/08. doi: 10.1136/openhrt-2018-000919. PubMed PMID: 30613416; PubMed Central PMCID: PMCPMC6307562.

93. Geiger J, Rahsepar AA, Suwa K, Powell A, Ghasemiesfe A, Barker AJ, et al. 4D flow MRI, cardiac function, and T1 -mapping: Association of valve-mediated changes in aortic hemodynamics with left ventricular remodeling. J Magn Reson Imaging. 2018;48(1):121-31. Epub 2017/12/06. doi: 10.1002/jmri.25916. PubMed PMID: 29206322; PubMed Central PMCID: PMCPMC5988917.

94. Lee SP, Lee W, Lee JM, Park EA, Kim HK, Kim YJ, et al. Assessment of diffuse myocardial fibrosis by using MR imaging in asymptomatic patients with aortic stenosis. Radiology. 2015;274(2):359-69. Epub 2014/09/25. doi: 10.1148/radiol.14141120. PubMed PMID: 25251584.

95. Singh A, Chan DCS, Greenwood JP, Dawson DK, Sonecki P, Hogrefe K, et al. Symptom Onset in Aortic Stenosis: Relation to Sex Differences in Left Ventricular Remodeling. JACC Cardiovasc Imaging. 2019;12(1):96-105. Epub 2017/12/19. doi: 10.1016/j.jcmg.2017.09.019. PubMed PMID: 29248646.

96. Polte CL, Gao SA, Johnsson AA, Lagerstrand KM, Bech-Hanssen O. Characterization of Chronic Aortic and Mitral Regurgitation Undergoing Valve Surgery Using Cardiovascular Magnetic Resonance. Am J Cardiol. 2017;119(12):2061-8. Epub 2017/04/30. doi: 10.1016/j.amjcard.2017.03.041. PubMed PMID: 28450039.

97. Edwards NC, Moody WE, Yuan M, Weale P, Neal D, Townend JN, et al. Quantification of left ventricular interstitial fibrosis in asymptomatic chronic primary degenerative mitral regurgitation. Circ Cardiovasc Imaging. 2014;7(6):946-53. Epub 2014/08/21. doi: 10.1161/CIRCIMAGING.114.002397. PubMed PMID: 25140067.

98. Everett RJ, Tastet L, Clavel MA, Chin CWL, Capoulade R, Vassiliou VS, et al. Progression of Hypertrophy and Myocardial Fibrosis in Aortic Stenosis: A Multicenter Cardiac Magnetic Resonance Study. Circ Cardiovasc Imaging. 2018;11(6):e007451. Epub 2018/06/20. doi: 10.1161/CIRCIMAGING.117.007451. PubMed PMID: 29914867; PubMed Central PMCID: PMCPMC6023592.

99. Myerson SG, d'Arcy J, Christiansen JP, Dobson LE, Mohiaddin R, Francis JM, et al. Determination of Clinical Outcome in Mitral Regurgitation With Cardiovascular Magnetic Resonance Quantification. Circulation. 2016;133(23):2287-96. Epub 2016/05/18. doi: 10.1161/CIRCULATIONAHA.115.017888. PubMed PMID: 27189033.

100. Fairbairn TA, Steadman CD, Mather AN, Motwani M, Blackman DJ, Plein S, et al. Assessment of valve haemodynamics, reverse ventricular remodelling and myocardial fibrosis following transcatheter aortic valve implantation compared to surgical aortic valve replacement: a cardiovascular magnetic resonance study. Heart. 2013;99(16):1185-91. Epub 2013/06/12. doi: 10.1136/heartjnl-2013-303927. PubMed PMID: 23749779.

101. Myerson SG, d'Arcy J, Mohiaddin R, Greenwood JP, Karamitsos TD, Francis JM, et al. Aortic regurgitation quantification using cardiovascular magnetic resonance: association with clinical outcome. Circulation. 2012;126(12):1452-60. Epub 2012/08/11. doi: 10.1161/CIRCULATIONAHA.111.083600. PubMed PMID: 22879371.

102. Barone-Rochette G, Pierard S, Seldrum S, de Meester de Ravenstein C, Melchior J, Maes F, et al. Aortic valve area, stroke volume, left ventricular hypertrophy, remodeling, and fibrosis in aortic stenosis assessed by cardiac magnetic resonance imaging: comparison between high and low gradient and normal and low flow aortic stenosis. Circ Cardiovasc Imaging. 2013;6(6):1009-17. Epub 2013/10/09. doi: 10.1161/CIRCIMAGING.113.000515. PubMed PMID: 24100045.

103. Schiros CG, Dell'Italia LJ, Gladden JD, Clark D, 3rd, Aban I, Gupta H, et al. Magnetic resonance imaging with 3-dimensional analysis of left ventricular remodeling in isolated mitral regurgitation: implications beyond dimensions. Circulation. 2012;125(19):2334-42. Epub 2012/04/13. doi: 10.1161/CIRCULATIONAHA.111.073239. PubMed PMID: 22496130; PubMed Central PMCID: PMCPMC3939018.

104. Uretsky S, Supariwala A, Nidadovolu P, Khokhar SS, Comeau C, Shubayev O, et al. Quantification of left ventricular remodeling in response to isolated aortic or mitral regurgitation. J Cardiovasc Magn Reson. 2010;12:32. Epub 2010/05/26. doi: 10.1186/1532-429X-12-32. PubMed PMID: 20497540; PubMed Central PMCID: PMCPMC2893171.

105. Steadman CD, Jerosch-Herold M, Grundy B, Rafelt S, Ng LL, Squire IB, et al. Determinants and functional significance of myocardial perfusion reserve in severe aortic stenosis. JACC Cardiovasc Imaging. 2012;5(2):182-9. Epub 2012/02/22. doi: 10.1016/j.jcmg.2011.09.022. PubMed PMID: 22340825.

106. Grotenhuis HB, Ottenkamp J, Westenberg JJM, Bax JJ, Kroft LJM, de Roos A. Reduced aortic elasticity and dilatation are associated with aortic regurgitation and left ventricular hypertrophy in nonstenotic bicuspid aortic valve patients. J Am Coll Cardiol. 2007;49(15):1660-5. Epub 2007/04/17. doi: 10.1016/j.jacc.2006.12.044. PubMed PMID: 17433959.

# Supplementary material

Multiscale modeling of cardiac valve disease using cell-level signals to drive myocardial growth

Hossein Sharifi 1, Austin G. Wellette-Hunsucker 2, Charles K. Mann 1, Jonathan F. Wenk 1,3, Kenneth S. Campbell 2

1Department of Mechanical Engineering, University of Kentucky, Lexington, Kentucky, USA

2Department of Physiology & Division of Cardiovascular Medicine, University of Kentucky, Lexington, Kentucky, USA

3Department of Surgery, University of Kentucky, Lexington, Kentucky, USA

**\* Correspondence:**Kenneth S. Campbell  
k.s.campbell@uky.edu

Keywords: Multiscale modeling, Myocardial growth, Baroreflex, Concentric growth, Eccentric growth (Min.5-Max. 8)

## Supplementary tables

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table S****1.** List of studies with quantified clinical data for LV dimensions and systolic function acquired by cardiac magnetic resonance imaging. | | | | | | | | | | | |
| **Control volunteers** | | | **Patients with Aortic stenosis** | | | **Patients with Mitral insufficiency** | | | **Patients with Aortic insufficiency** | | |
| Study | Year | n | Study | Year | n | Study | Year | n | Study | Year | n |
| Lee et al. [88] | 2020 | 30 | Lee et al. [88] | 2020 | 191 | Liu et al. [89] | 2020 | 104 | Malahfji et al. [90] | 2021 | 392 |
| Spath et al. [35] | 2019 | 41 | Everett et al. [34] | 2020 | 440 | Seldrum et al. [91] | 2019 | 59 | Seldrum et al. [91] | 2019 | 29 |
| Seldrum et al. [91] | 2019 | 30 | Spath et al. [35] | 2019 | 159 | Bakkesstrom et al. [92] | 2018 | 46 | Geiger et al. [93] | 2017 | 16 |
| Lee et al. [94] | 2015 | 15 | Singh et al. [95] | 2019 | 174 | Polte et al. [96] | 2017 | 40 | Polte et al. [96] | 2017 | 38 |
| Edwards et al. [97] | 2014 | 35 | Everett et al. [98] | 2018 | 61 | Myerson et al. [99] | 2016 | 152 | Fairbairn et al. [100] | 2013 | 50 |
| Chin et al. [31] | 2014 | 33 | Chin et al. [31] | 2014 | 133 | Edwards et al. [97] | 2014 | 35 | Myerson et al. [101] | 2012 | 158 |
| Barone-Rochette et al. [102] | 2013 | 20 | Barone-Rochette et al. [102] | 2013 | 128 | Schiros et al. [103] | 2012 | 94 | Uretsky et al. [104] | 2010 | 34 |
| Schiros et al. [103] | 2012 | 51 | Steadman et al. [105] | 2012 | 41 | Uretsky et al. [104] | 2010 | 23 | Grotenhuis et al.[106] | 2007 | 20 |
| Data were reported as mean ± standard deviation (SD) or median (interquartile range). | | | | | | | | | | | |

## Supplementary figures

**Diagram

Description automatically generated**

**Figure S****1. Sensitivity of growth module to rate constants of control signals γgrowth,con and γgrowth,ecc.** For simplicity, γanti growth,i were chosen to have similar magnitudes as γgrowth,i but in the opposite directions, where i reflects the growth type. γ0,con and γ0,ecc are the rate constants values that were used in all simulations of this study. The growth module was activated at 50 s (first dashed vertical line from left on all panels) when the system was at steady state using default parameters. The system was gradually perturbed from 300 s to 400 s (second and third vertical dashed lines) by applying the underlying valvular disorders.

Chart, bar chart

Description automatically generated

**Figure S****2.** **Baseline steady state using default parameters under control of baroreflex feedback loop.** Left hand column shows the response of central framework in PyMyoVent [21]. Right hand column shows the response of baroreflex algorithm. Simulation started with using default parameters. At 20 s, baroreflex algorithm was activated to move arterial pressure towards the setpoint of 90 mmHg by modulating heart rate, intracellular Ca2+ dynamics (kact and kSERCA), myofilament function (k1, k3, and kon), and vascular tone (Rarteriolar and Cveins). Non and Noff refer to status of actin binding sites. MSRX, MDRX, and MFG represent the status of myosin heads on thick filament in the super-realxed, disordered-relaxed, and force generating states, respectively. Parteries and Pset refer to the actual arterial pressure and setpoint for the arterial pressure, respectively.

Diagram

Description automatically generated

**Figure S****3. Alteration in the averaged myosin ATPase normalized by myofibrillar volume (Mean Scon) with respect to the concentric growth setpoint (Scon,set).** Results are replicated from Figure 2. Scon is stimulus signal for concentric growth law. Ga,con and Gc,con are, normalized growth and control signals for concentric growth, respectively

Chart

Description automatically generated

**Figure S****4. Comparison in myosin ATPase normalized by myofibrillar volume profile over a cardiac cycle at baseline and growth states.**

**Diagram, schematic

Description automatically generated**

**Figure S****5. Alteration in the averaged intracellular passive stress (Mean Secc) with respect to the eccentric growth setpoint (Secc,set).** Results are replicated from Figure 4. Secc is stimulus signal for concentric growth law. Ga,ecc and Gc,ecc are, normalized growth and control signals for eccentric growth, respectively

Chart

Description automatically generated

**Figure S****6. Comparison in intracellular passive stress profile over a cardiac cycle at baseline and growth states.**

Diagram, engineering drawing, schematic

Description automatically generated

**Figure S****7. Predicted recovery of LV size and function in response to removed pressure overloading.** Similar arrangement for panels as in Figure 2. Growth module activated at 50 s when the simulation was at initial steady state. On all panels, first vertical line shows when the growth module is activated. Second and third vertical line demonstrate the onset and ending of the applied pressure overloading. Fourth and fifth vertical lines shows the onset and ending of the removed pressure overloading.

Diagram, engineering drawing

Description automatically generated

**Figure S****8. Predicted recovery of LV size and function in response to removed aortic insufficiency.** Similar arrangement for panels as in Figure 2. Growth module activated at 50 s when the simulation was at initial steady state. On all panels, first vertical line shows when the growth module is activated. Second and third vertical line demonstrate the onset and ending of the applied aortic insufficiency. Fourth and fifth vertical lines shows the onset and ending of the removed aortic insufficiency.

Diagram, engineering drawing

Description automatically generated

**Figure S****9. Predicted recovery of LV size and function in response to removed volume overloading.** Similar arrangement for panels as in Figure 2. Growth module activated at 50 s when the simulation was at initial steady state. On all panels, first vertical line shows when the growth module is activated. Second and third vertical line demonstrate the onset and ending of the applied volume overloading. Fourth and fifth vertical lines shows the onset and ending of the removed volume overloading.

Diagram, schematic

Description automatically generated

**Figure S****10. Simulated aortic stenosis without the baroreflex control of arterial pressure.** The panels are arranged similarly to those in Figure 2. The simulation was gradually perturbed from 300 s to 400 s (second and third vertical dashed lines) by increasing Raorta (top panel in the right-hand column) in equation by 500%. The baroreflex module was deactivated at 200 s (vertical red dashed line).

Diagram, schematic

Description automatically generated

**Figure S****11. Simulated aortic insufficiency without the baroreflex control of arterial pressure.** The panels are arranged similarly to those in Figure 2, except that aortic regurgitant volume is shown in place of aortic resistance in the right-hand column. The simulation shown in this figure was perturbed gradually (second and third vertical dashed lines) by increasing Gaorta in equation from 0 to 1e-3 ([mmHg s]-1 L) to induce a regurgitant volume of ~40 ml (Table 3). The baroreflex module was deactivated at 200 s (vertical red dashed line).

Diagram, schematic

Description automatically generated

**Figure S****12. Simulated mitral insufficiency without the baroreflex control of arterial pressure.** The panels are arranged similarly to those in Figure 2, except that mitral regurgitant volume is shown in place of aortic resistance in the right-hand column. The simulation shown in this figure was perturbed gradually (second and third vertical dashed lines) by increasing Gmitral in equation from 0 to 2e-3 ([mmHg s]-1 L) to induce a mitral regurgitant volume of ~60 ml (Table 3). The baroreflex module was deactivated at 200 s (vertical red dashed line).