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

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Abstract

Multi-scale models of the cardiovascular system are immerging as effective tools for investigating the mechanisms that drive ventricular growth and biological remodeling. Such models can be used to evaluate the effects of molecular-level mechanisms on organ-level function, such as modulating cross-bridge kinetics to alter pump function, which could provide new insights for improving patient care. PyMyoVent is a multi-scale computer model that simulates left ventricular (LV) function within a systemic circulation by bridging from molecular to organ-level mechanisms. In previous work, we implemented a module of the baroreflex feedback loop into PyMyoVent and showed that it could maintain arterial pressure at a setpoint level by regulating 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 and molecular-level signals. Specifically, concentric growth is controlled by the energy used by the cells for contraction (expressed as myosin ATPase normalized to myofibrillar mass) while eccentric growth responds to intracellular passive stress. The new framework reproduced clinical measures of LV growth in three types of valvular disease, namely aortic stenosis , mitral regurgitation, and aortic regurgitation. Furthermore, simulations for each valvular disorder regained LV size and function (reversal of growth) when the disease-mimicking perturbation was removed. In conclusion, the simulations suggest that myosin ATPase normalized to myofibrillar mass and intercellular passive stress can be used to drive concentric and eccentric growth in simulations of valve disease.

# Introduction

The heart is able to adapt its shape and size in response to pathological conditions, such as altered ventricular loading from valvular disease and/or mutations to sarcomeric proteins. This process is referred to as cardiac growth and remodeling (Frey and Olson, 2003; Watkins et al., 2011; Pitoulis and Terracciano, 2020). Based on the ventricular geometry, there are two conventional types of growth: (1) concentric growth that 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 ventricular chamber size (Hill and Olson, 2008) and (2) eccentric growth that is characterized by the addition of sarcomeres in series, which results in ventricular dilation and elevated ventricular mass with little or no change in the wall thickness (Hill and Olson, 2008). In general, cardiac growth initiates as an early adaptive response to abnormal volume or pressure loading in order to reestablish a homeostatic stress state. However, if the underlying cause is left unresolved it can lead to myocardial fibrosis, myocyte dysfunction, and ultimately heart failure (Hill and Olson, 2008; Shimizu and Minamino, 2016; Nakamura and Sadoshima, 2018).

Computer based models are providing new insights on the progression of cardiac growth and remodeling. Despite numerous studies that have developed mathematical formulations to represent these phenomena, the choice of driving stimulus for these growth laws is still up for debate. Conventionally, computational models of cardiac growth have utilized either myofiber stress (Rausch et al., 2011; Klepach et al., 2012), strain (Guterl et al., 2007; Kerckhoffs et al., 2012; Witzenburg and Holmes, 2018), or some combination of the two (Goktepe et al., 2010; Arts et al., 2012) as their driving signal. Rondnina and Bovendeerd (Rondanina and Bovendeerd, 2020a) tested four combinations of myofiber stress and strain driven laws, for both concentric and eccentric growth, and concluded that using at least one stress-driven law would predict more reliable growth. In another work, Mojumder et al. (Mojumder et al., 2021) showed that concentric growth of the LV, due to pressure overloading, correlates better with myofiber stress than stretch.

Though previous models have shown promising results, the underlying mechanisms that drive growth are more complex and are accompanied by perturbations at the molecular level (including signaling pathways, hormone levels, energy metabolism, etc.) that have not been thoroughly investigated. Therefore, the focus of computational modeling in cardiac growth is shifting from phenomenological models towards more realistic multi-scale mechanistic models that incorporate the effect of molecular/cellular events in order to drive growth (Sharifi et al., 2021a). For example, Yoshida et al. (Yoshida et al., 2020b) incorporated a network model of cellular level signaling pathways with a compartmental model of a rat heart to investigate cardiac growth in response to volume overloading and a surge in hormone levels during pregnancy. Their multi-scale model showed that most of the growth, especially during the first half of pregnancy, was due to a rise in progesterone (i.e. hormonal signal) and not from the volume overloading (i.e. mechanical signal). Estrada et al. (Estrada et al., 2021) incorporated the effects of hormonal and mechanical signals in a finite element model of the left ventricle (LV) to predict hypertrophy in response to transverse aortic constriction (TAC). They showed that the effect of hormonal inputs on the prediction of cardiac hypertrophy was larger than the mechanical stimulus.

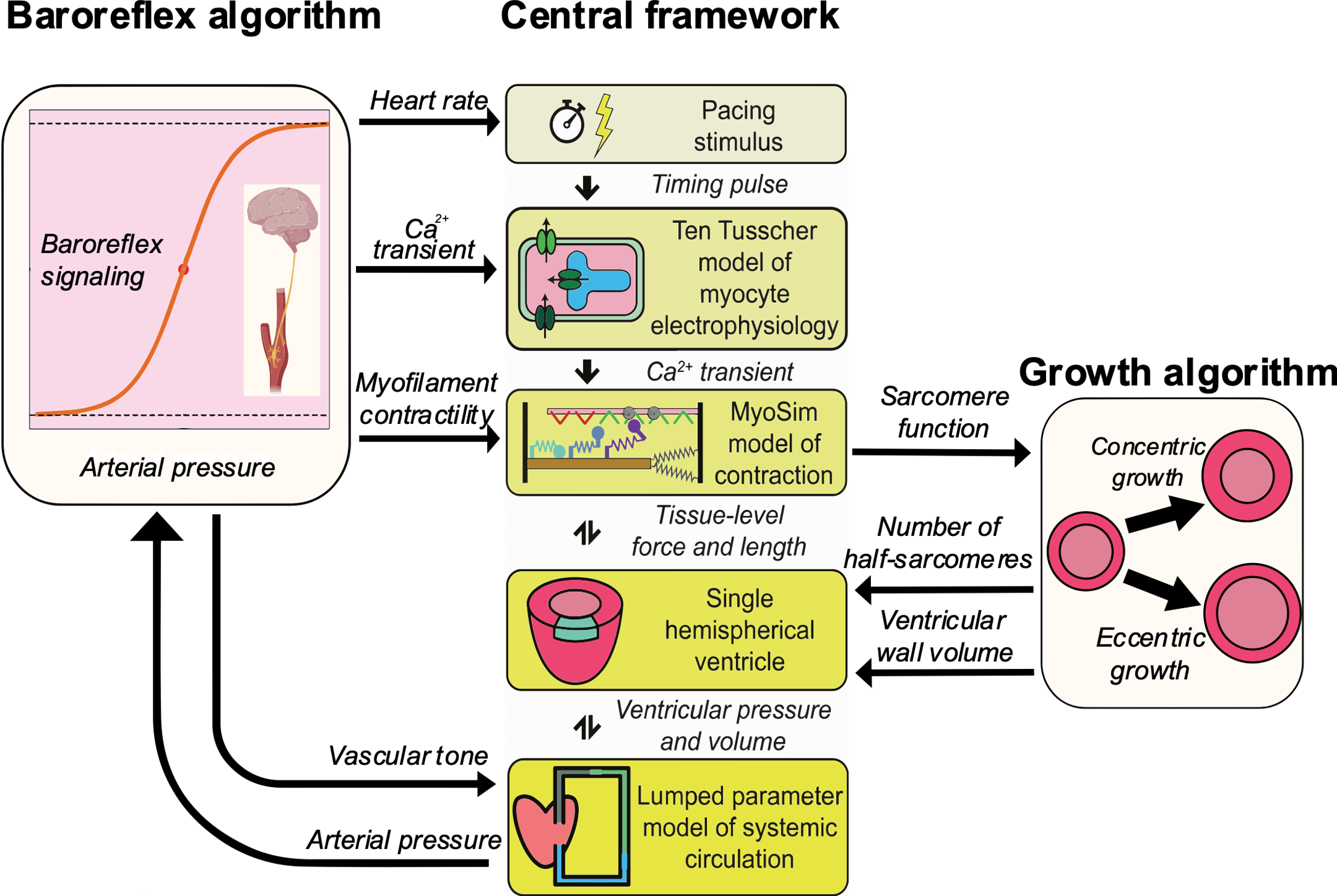
Myosin ATP phosphohydrolase (ATPase) activity is another molecular-level mechanism that has been reported to have a correlation with abnormal ventricular loading (Kozlovskis et al., 1987). Briefly, myosin ATPase hydrolyzes ATP to a complex of ADP and phosphate (Pi) molecules and a release of energy that is required for the binding of myosin heads during the cross-bridge cycle. It has been shown that abnormal LV loading, such as pressure overloading, can perturb myocardial metabolism and thus lead to a decrease in cardiac efficiency (Tuomainen and Tavi, 2017; Nakamura and Sadoshima, 2018). In a recent work, Lopez et al. (Lopez et al., 2020) studied the effects of energetic dysfunction on mechanical loading in failing rat hearts using a multi-scale model of cardiac mechanoenergetics. They found that elevated levels of inorganic phosphate kinetically impaired the myosin ATPase cross-bridge cycle in a TAC rat model of heart failure.

To further investigate the role of ATPase on cardiac growth, we incorporated a growth module into our existing multi-scale model of cardiovascular function, which is referred to as PyMyoVent (Campbell et al., 2020; Sharifi et al., 2021b). First, we implemented a growth law that uses myosin ATPase per myofibrillar volume and intracellular passive stress in the half-sarcomeres as the driving signals for concentric and eccentric growth, respectively. Secondly, we tested the ability of the model to capture different types of cardiac growth in response to three kinds of valvular disorders, namely 1) aortic stenosis (AS), 2) mitral regurgitation (MR), and 3) aortic regurgitation (AR). Thirdly, we investigated whether the new framework can recover normal LV size and function when the underlying overload was removed. Finally, we validated the model predictions for valvular disorders against clinical data that was compiled from the literature.

# Materials and Methods

## Overview

The current study extends our previous work (Sharifi et al., 2021b) by adding a module of LV growth to a multi-scale model of cardiovascular function named PyMyoVent. Figure 1 shows an overview of the PyMyoVent framework and illustrates how different modules communicate with each other. The original framework was published by Campbell et al. (Campbell et al., 2020), where they were able to show that a variation in model parameters (e.g. myosin rate constants) could change the system level parameters (e.g. end-systolic pressure-volume relationship). This original framework is essentially built on four main modules. First, a pacing stimulus is used to drive Ca2+ handling in the electrophysiology module. The contraction model called MyoSim (Campbell, 2014; Campbell et al., 2018) then uses calculated Ca2+ transient to predict the 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*. More details on these modules are provided in (Campbell et al., 2020).



**Figure** **1.** **Overview of the PyMyoVent framework.** Baroreflex feedback loop regulates the arterial pressure towards a setpoint by modulating heart rate, intracellular Ca2+ transients, myofilament contractility, and vascular tone. Growth algorithm uses myosin ATPase per myofibrillar volume and intracellular passive stress in half-sarcomeres to control the concentric growth (wall thickening) and eccentric growth (ventricular dilation), respectively.

## Baroreflex module

In our previous work (Sharifi et al., 2021b) we extended PyMyoVent (Campbell et al., 2020) by incorporating a module of the baroreflex feedback loop (Fig 1) to drive arterial pressure towards a setpoint level. The feedback algorithm was inspired by the underlying biology, where the afferent signal was driven by a sigmoidal relationship with arterial pressure and the efferent pathway signal was constrained between the maximum sympathetic and maximum parasympathetic drive. This module was used to regulate the heart rate, intracellular Ca2+ transient, contractility of both the thick and the thin filaments, and vascular tone. It was shown that the baroreflex feedback loop was able to regulate the system at setpoint levels for the arterial pressure between ~30 mm Hg to ~150 mm Hg, as well as maintaining the arterial pressure at the setpoint level under perturbed ventricular loading, such as acute blood loss or aortic stenosis. More details on the baroreflex feedback loop module can be found in the previous work (Sharifi et al., 2021b).

## Growth module

The growth module consists of two laws for concentric (wall thickening) and eccentric (ventricular dilation) growth, respectively. Each growth law is driven via a normalized growth signal Ga,i that can vary between 0 and 1 due to a deviation in the corresponding stimulus signal Si. The rate of change in Ga,i is defined as



where i represents the growth type (i.e. concentric or eccentric), kdrive is a constant rate factor and sets the speed at which Ga,i responds to a change in Si. Si,set is the homeostatic level (setpoint) for 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.

The normalized growth signal then transduces into a controller signal Gc,i that regulates how wall volume or the number of half-sarcomeres respond to a change in the corresponding normalized growth signal Ga,i. The rate of change in Gc,i is defined as



where γgrowth and γanti growth are gain factors for increasing and decreasing the controlled parameters. For the purpose of simplicity, both factors are chosen to have similar magnitudes but in opposite directions. Calculated controller signals then drive the change in wall volume or the number of half-sarcomeres as described in the following sections.

### Eccentric growth

Eccentric growth is controlled by the number of serial half-sarcomeres (nhs) around the circumference of LV in the cardiovascular model. The driving signal for eccentric growth (Secc) was assumed to be the intracellular passive stress in the half-sarcomeres, *τ*passive, which has a nonlinear relationship with the half-sarcomere length (equation ).



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 serial half-sarcomeres is controlled via equation , where Gc,ecc is the control signal for eccentric growth. According to equation , an increase in the driving signal (i.e. increase in intracellular half-sarcomere passive stress) would increase the number of serial half-sarcomeres to reduce the passive stress back to its homeostatic level (setpoint). A reduction in the driving signal, on the other hand, reduces the number of serial half-sarcomeres, which increases the passive stress towards the setpoint.



### Concentric growth

The concentric growth law controls LV wall volume (Vwall) to mimic the parallel deposition of half-sarcomeres. The ratio of myosin ATPase per myofibrillar volume (equation ) was assumed to be the stimulus signal for concentric growth (Scon), where N0 is the density of myosin heads over 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 half-sarcomere (1.1 μm), NA is Avogardo’s number (6.02 × 1023 mol-1), J4 is the detachment flux of myosin heads from the force generating state (MFG) to the disordered relaxed state (MDRX), and n is the number of bins that were used to evaluate the cross-bridge populations.



The rate of change in Vwall is defined via equation , which consists of two components. The first component Gc,con responds to a change in the stimulus signal for concentric growth (Scon), whereas the second component Gc,ecc incorporates the proportional change due to the eccentric growth (Pitoulis and Terracciano, 2020).



## Simulations

### Implementation and computer code

The code was written in Python using Numpy (S. et al., 2011), Scipy (Virtanen et al., 2020), and pandas (al., 2021) 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/>.

### Baseline

As described in previous works with PyMyoVent (Campbell et al., 2020; Sharifi et al., 2021b) no data fitting was performed to optimize the model parameters. Instead, parameters were tuned in a way to mimic the cardiovascular function of a healthy adult according to a normal range of characteristics reported in the literature (Maceira et al., 2006; Petersen et al., 2017). For example, total blood volume for the systemic circulation system was set to 4.5 liters. All simulations in this manuscript started by using default values for model parameters and assigning all stressed volume into the veins. At 20 s, when all compartmental blood volumes and pressures in the circulation system were at steady state, the baroreflex feedback module was activated to move the arterial pressure towards the setpoint of 90 mm Hg. The characteristics of baseline simulation are shown in Table 1.

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| **Table** **1** Simulated baseline cardiovascular function of a healthy adult. | |
| Heart rate (BPM) | ~63 |
| End-diastolic LV volume (ml) | ~146 |
| Pulse pressure (mm Hg) | ~117 / 61 |
| Stroke volume (ml) | ~94 |
| Ejection fraction (%) | ~64 |

### Valvular disorders

Three types of valvular disorders, namely aortic stenosis (AS), mitral regurgitation (MR), and aortic regurgitation (AR), were simulated by applying the relevant perturbations to the baseline simulation. AS is a valvular disease where the aortic valve becomes narrowed, opens poorly during systole, and induces pressure overloading of the LV. To mimic the aortic stenosis condition, aortic resistance in the systemic circulatory module was increased to induce LV pressure overload. According to the Poiseuille equation, resistance of a vessel has an inverted relation with the square of the cross-sectional area. For instance, a 500 % increase in the aortic resistance is equivalent to a ~60 % reduction in the aortic valve area, from a mean value of 2.5 cm2 for healthy adults (Luszczak et al., 2012; Chin et al., 2014; Chin et al., 2017) to a mean value of 1 cm2 for patients with aortic stenosis (Spath et al., 2019; Everett et al., 2020). In accordance with American Heart Association guidelines (Otto et al., 2021), the aortic valve area of 1 cm2 is one of the key thresholds for categorizing the severity of the disease. Therefore, three levels of AS mimicking different levels of severity were simulated as shown in Table 2.

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| --- | --- | --- |
| **Table** **2.** Simulated levels of AS severity | | |
| % Increase in the aortic resistance | Equivalent % reduction in aortic valve area | Represented level of severity according to AHA guidelines (Otto et al., 2021) |
| 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 |

MR is another type of valvular disorder wherein the mitral valve does not close properly during systole and allows retrograde blood flow to occur back into the left atria. The regurgitant blood volume leads to volume overloading and thus excessive diastolic filling of the LV (Carabello et al., 1992). In the current framework, the retrograde blood flow through the mitral valve was controlled via a model parameter named “leaking factor” (Gleak,mitral in equation ) that is zero for a proper valve (i.e. “baseline simulation”) and is nonzero for an insufficient valve.



The following values for “leaking factor” (Table 3) were used to simulate three levels of severity for patients with MR with respect to the threshold of 60 (ml beat-1) for regurgitant volume based on AHA guidelines (Otto et al., 2021).

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| **Table** **3.** Simulated different levels of MR severity | | |
| Gleak,mitral | Equivalent regurgitant volume (ml beat-1) | Represented level of severity according to AHA guidelines (Otto et al., 2021) |
| 1e-3 | 30 | At risk of MR / Progressive MR |
| 2e-3 | 60 | Asymptomatic severe  MR |
| 3e-3 | 80 | Symptomatic severe MR |

AR is another prevalent valvular disease which is characterized with backward diastolic flow of blood from the aorta into the LV. The regurgitant blood volume generates excess diastolic filling of the LV, but the initial ejection of the forward stroke volume impinging on the backward regurgitant volume causes a surge in the systolic pressure and hence leads to a wide pulse pressure and systolic hypertension (Bekeredjian and Grayburn, 2005). Therefore, AR imposes a combination of volume and pressure overload on the LV, which undergoes a combination of both types of eccentric and concentric growth (Carabello, 2002; Bekeredjian and Grayburn, 2005; Akinseye et al., 2018). The backward diastolic flux through the aortic valve was handled via a model parameters named Gleak,aorta (equation ) which is zero for a healthy valve (i.e. “baseline simulation”) and nonzero for a leaking aortic valve.



AHA guidelines (Otto et al., 2021) categorize three levels of severity for AR based on the regurgitant volume, namely: mild AR (regurgitant volume < 30 ml beat-1), moderate AR (30 ml beat-1 < regurgitant volume < 59 ml beat-1), and severe AR (regurgitant volume > 60 ml beat-1). These levels of AR were simulated by using values for Gleak,aorta shown in Table 4.

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| **Table** **4.** Simulated different levels of AR severity | | |
| Gleak,aorta | Equivalent regurgitant volume (ml beat-1) | Represented level of severity according to AHA guidelines (Otto et al., 2021) |
| 5e-4 | 20 | Mild AR |
| 1e-3 | 40 | Moderate AR |
| 2e-3 | 70 | Severe AR |

## Model validation

To validate our model, the simulated results were compared with clinical data from the literature, which was acquired by cardiac magnetic resonance imaging (Table 5). Clinical data were categorized into four cases named “control volunteers”, “patients with AS”, “patients with MR”, and “patients with AR”. For each category, measured data were collected from eight different studies. Ventricular dimensions were quantified with the LV end-diastolic volume index, LV end-systolic volume index, and LV mass index. Systolic function was assessed with the LV stroke volume index and ejection fraction. An averaged body surface area of 1.9 m2 (Verbraecken et al., 2006; Lang et al., 2015) was used to normalize the simulated results. Some studies in Table 5 did not report the measured LV stroke volume indexed, so the absolute difference between the reported end-diastolic and end-systolic LV volume indexed was used.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table** **5.** List of studies with quantified clinical data for LV dimensions and systolic function acquired by cardiac magnetic resonance imaging. | | | | | | | | | | | |
| **Control volunteers** | | | **Patients with AS** | | | **Patients with MR** | | | **Patients with AR** | | |
| Study | Year | n | Study | Year | n | Study | Year | n | Study | Year | n |
| Lee et al. (Lee et al., 2020) | 2020 | 30 | Lee et al. (Lee et al., 2020) | 2020 | 191 | Liu et al. (Liu et al., 2020) | 2020 | 104 | Malahfji et al. (Malahfji et al., 2020) | 2021 | 392 |
| Spath et al. (Spath et al., 2019) | 2019 | 41 | Everett et al. (Everett et al., 2020) | 2020 | 440 | Seldrum et al. (Seldrum et al., 2019) | 2019 | 59 | Seldrum et al. (Seldrum et al., 2019) | 2019 | 29 |
| Seldrum et al. (Seldrum et al., 2019) | 2019 | 30 | Spath et al. (Spath et al., 2019) | 2019 | 159 | Bakkesstrom et al. (Bakkestrom et al., 2018) | 2018 | 46 | Geiger et al. (Geiger et al., 2018) | 2017 | 16 |
| Lee et al. (Lee et al., 2015b) | 2015 | 15 | Singh et al. (Singh et al., 2019) | 2019 | 174 | Polte et al. (Polte et al., 2017) | 2017 | 40 | Polte et al. (Polte et al., 2017) | 2017 | 38 |
| Edwards et al. (Edwards et al., 2014) | 2014 | 35 | Everett et al. (Everett et al., 2018b) | 2018 | 61 | Myerson et al. (Myerson et al., 2016) | 2016 | 152 | Fairbairn et al. (Fairbairn et al., 2013) | 2013 | 50 |
| Chin et al. (Chin et al., 2014) | 2014 | 33 | Chin et al. (Chin et al., 2014) | 2014 | 133 | Edwards et al. (Edwards et al., 2014) | 2014 | 35 | Myerson et al. (Myerson et al., 2012) | 2012 | 158 |
| Barone-Rochette et al. (Barone-Rochette et al., 2013) | 2013 | 20 | Barone-Rochette et al. (Barone-Rochette et al., 2013) | 2013 | 128 | Schiros et al. (Schiros et al., 2012) | 2012 | 94 | Uretsky et al. (Uretsky et al., 2010) | 2010 | 34 |
| Schiros et al. (Schiros et al., 2012) | 2012 | 51 | Steadman et al. (Steadman et al., 2012) | 2012 | 41 | Uretsky et al. (Uretsky et al., 2010) | 2010 | 23 | Grotenhuis et al.(Grotenhuis et al., 2007) | 2007 | 20 |
| Data were reported as mean ± standard deviation (SD) or median (interquartile range). | | | | | | | | | | | |

# Results

## Concentric growth in response to induced aortic stenosis (pressure overloading)

Figure 2 depicts the response of the PyMyoVent framework to an example of pressure overloading, mimicking aortic stenosis. Once the simulation reached initial steady state at 50 s, representing the “baseline” simulation, the growth module was activated (first vertical dashed line from the left in all panels). The setpoints for both the concentric and eccentric growth laws were assigned to match the average value of the driving signals during the initial steady state. At 300 s (second vertical dashed line), when the simulation was at steady state while the growth module was activated, the aortic resistance gradually increased (over 100 s between the second and third vertical lines) by 500% from 20 to 120 (mm Hg L-1 s) to mimic a 60% reduction in aortic valve area according to Table 2. In response to the induced pressure overloading, the growth module increased LV wall volume (Vwall) by ~30% whereas the number of serial half-sarcomeres around the circumference of LV remained nearly unchanged. Due to these changes, the LV wall thickness increased by ~21% and ~29% at end-systole and end-diastole, respectively, while the LV cavity (chamber) volume shrunk by ~8% at end-diastole but remined unchanged at end-systole. These responses capture the characteristic features of concentric growth. The baroreflex feedback loop maintained arterial pressure at a setpoint of 90 mm Hg (middle column in Fig 2) via increasing heart rate, contractility of both thick and thin myofilaments, and vascular tone.

Diagram, schematic

Description automatically generated

**Figure** **2.** **Predicted concentric growth due to pressure overloading (aortic stenosis**). The left hand column shows the response of the PyMyoVent (Campbell et al., 2020) framework at multi-scale levels. 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 continued modulation of the baroreflex module over reflex-sensitive parameters to maintain the arterial pressure at a setpoint level of 90 mm Hg. The right hand column shows the properties relevant to the growth module and metrics relevant to LV systolic function. The growth module was activated at 50 s (first dashed vertical line from left on all panels) when the system was at initial steady state. When the growth module was activated and the simulation was at steady state, the aortic resistance gradually increased by 500% between the second and third vertical lines from left on all panels (from time point of 300 s to 400 s). For pulsatile parameters (for example, ventricular pressure), an envelope of the extreme values is shown.

## Eccentric growth in response to induced mitral regurgitation (volume overloading)

Fig 3 shows the model response to an example of volume overloading, which simulates an insufficient mitral valve. As before, the simulation started with default model parameters representing the “baseline” simulation, and was run to steady state until the growth module was activated at 50 s. It should be noted that the same setpoints were used for all of the valvular disease simulations. Between the time-points of 300 s and 400 s, the factor Gleak, mitral (equation ) was gradually increased from 0 to 2e-3 to induce a regurgitant volume of ~60 ml (Table 3). In response to the volume overloading, the growth module increased the number of serial half-sarcomeres by ~17%, which resulted in LV cavity dilation of ~57% and ~68% at end-diastole and end-systole, respectively. LV wall volume (Vwall) was also increased by ~50% and thus slightly increased LV wall thickness by ~10% and ~12% at end-systole and end-diastole, respectively. Due to the excessive increase in LV cavity volume compared to wall thickness, the model correctly captured the characteristics of eccentric growth in response to volume overloading. Once again, the baroreflex module maintained the arterial pressure setpoint level at 90 mm Hg via up-regulation of the heart rate, myofilaments contractility, and vascular tone.

Diagram, schematic

Description automatically generated

**Figure** **3**. **Predicted eccentric growth in response to volume overloading (mitral regurgitation).** The panels are arranged similarly to those in Fig 2, except that mitral regurgitant volume is shown in place of aortic resistance in the right hand column. The growth module activated at 50 s when the simulation was at initial steady state. The volume overloading condition was simulated (between the second and third vertical lines on all panels) by gradually increasing Gleak,mitral in equation from 0 to 2e-3 to induce a mitral regurgitant volume of ~60 ml (Table 3). For pulsatile parameters (for example, ventricular pressure), an envelope of the extreme values is shown.

## Concentric and eccentric growth in response to aortic regurgitation (combination of pressure and volume overloading)

In the final case, Fig 4 shows the response of PyMyoVent to a combination of both pressure and volume overloading by mimicking aortic regurgitation. The simulation started with the same initial configuration as in Figs 2 and 3, except the LV was overloaded with backward blood flow from the aorta to the LV during diastole. At 300 s (second vertical line on all panels) Gleak, aorta in equation was gradually increased from 0 to 1e-3 to induce a regurgitant volume of ~40 ml (Table 4). The number of serial half-sarcomeres grew by ~12% and thus increased the LV cavity volume by ~37% and ~38% at end-systole and end-diastole, respectively. Furthermore, due to pressure overloading, the LV wall volume (Vwall) increased by ~45%, which led to an increase in LV wall thickness of ~16% at both end-diastole and end-systole. Although the baroreflex module maintained the arterial pressure setpoint at 90 mm Hg, arterial pressure became more pulsatile and changed from ~116/61 mm Hg to ~128/46 mm Hg.

Diagram, schematic

Description automatically generated

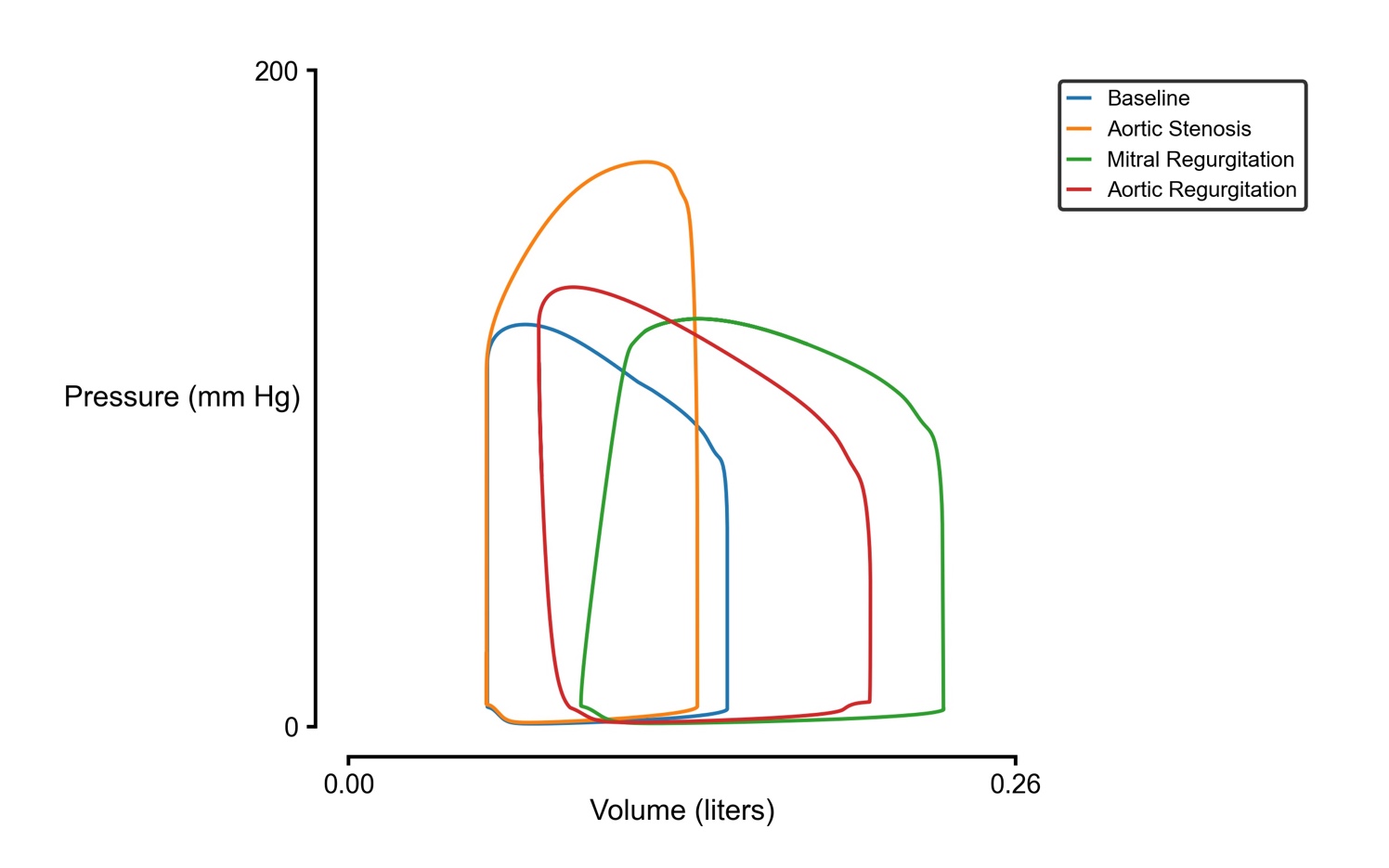
**Figure** **4. Predicted concentric and eccentric growth in response to combined pressure and volume overloading (aortic regurgitation).** The panels are arranged similarly to those in Fig 2, except that aortic regurgitant volume is shown in place of aortic resistance in the right hand column. The growth module activated at 50 s when the simulation was at initial steady state. The insufficiency in the aortic valve was induced by gradually (during 100 s between the second and third vertical lines on all panels) increasing Gleak, aorta in equation from 0 to 1e-3 to make a regurgitant volume of ~40 ml (Table 4). For pulsatile parameters (for example, ventricular pressure), an envelope of the extreme values is shown.

## Left ventricular Pressure-volume loop relationship

Fig 5 shows the pressure-volume (PV) loops for simulated baseline (healthy) function and three types of valvular dysfunction (overloaded LV). Relative to baseline, the AS condition caused the end-systolic LV pressure to rise by ~40%, end-diastolic LV volume reduced by ~8%, but end-systolic LV volume remained unchanged, and thus, the stroke volume reduced by ~12%. The area enclosed by the PV loop, representing the stroke work done by LV, increased by ~17%.

For the MR case, end-systolic LV pressure remained nearly unchanged, however, LV volume increased significantly and shifted the entire loop to the right. Stroke volume increased by ~51% and consequently increased the enclosed area and LV stroke work by ~50%. Due to the insufficient mitral valve, the relaxation phase was no longer isovolumic and LV volume continued to decrease.

In the AR case, end-systolic LV pressure elevated slightly by ~9% and LV cavity volume dilated at both end-systole and end-diastole. Stroke volume and stroke work were increased by ~38% and ~41%, respectively. Similar to the MR case, the relaxation phase was no longer isovolumic and thus the LV volume increased due to the retrograde flow from the aorta.



**Figure** **5**. **Left ventricular pressure-volume (PV) loop relationship for baseline (healthy) and three types of valvular dysfunction (overloaded LV).** The baseline loop was generated using the time range of (298 s – 299 s) in Figs 2-4 before applying any overloads. The other three loops were generated using the time range of (780 s – 781 s) from the relevant simulations shown in Figs 2-4.

## LV recovery after removal of the overloading condition

Fig 6 depicts the reversal of LV growth when the abnormal loading conditions were removed. Each column represents a simulated valvular dysfunction shown in Figs 2-4. All three cases started and overloaded exactly as shown in Figs 2-4. At 900 s (forth vertical line on all panels) the overloading were gradually removed, for instance, aortic resistance was reduced from 120 to 20 (mm Hg L-1 s) for the AS case. In all cases, LV dimensions (Fig 6) and cardiovascular function (Figs S1-3) were fully recovered to their homeostatic range once the overloading was removed.

Diagram

Description automatically generated

**Fig** **6. Reversal of LV growth in response to removal of overloading.** Left-hand column shows reversal of concentric growth due to removal of the AS condition. Middle column shows reversal of eccentric growth in response to removal of the insufficient mitral valve. Right-hand column shows reversal of LV growth due to removal of an insufficient aortic valve. On all panels, the first vertical line shows when the growth module is activated. Second and third vertical line demonstrate the onset and ending of the applied relevant overloading. Fourth and fifth vertical lines show the onset and ending of removing the relevant overloading.

## Predicted LV size agreed with collected clinical data

Fig 7 shows model validation for predicting LV size with respect to the clinical data compiled from the literature (Table 5). For the baseline case, all indices were within the range of clinical data. For aortic stenosis, model perditions were in line with clinical data such that as the level of valve narrowing increased, LV end-diastolic volume index slightly reduced, LV end-systolic volume index remained nearly unchanged, but LV mass index increased notably. For mitral regurgitation, model predictions were within the range of clinical data and followed the same trend, such that as the regurgitant volume increased the LV end-diastolic volume index, LV end-systolic volume index, and LV mass index all increased. Finally, the LV size parameters predicted for aortic regurgitation were also within the range of clinical data and demonstrated the same trend, such that as the severity of the insufficient valve increased both LV volume indices and LV mass index increased.

## Diagram, schematic Description automatically generated

**Fig** **7. Model validation for LV size in comparison to collected clinical data from the literature (Table 5).** Left hand column shows model validation for aortic stenosis. Middle column shows model validation for mitral regurgitation. Right hand column shows model validation for aortic regurgitation. In all panels, clinical data are shown with circle markers in two groups of CD and PD. Model predictions are shown with star markers in two groups of CS and PS. For each valvular disease case, three levels of severity for model simulations are shown in accordance with Tables 2-4. Model results are indexed by an average body surface area of 1.9 m2 (Verbraecken et al., 2006; Lang et al., 2015). CD stands for “control data”, PD for “patients data”, CS for “control simulation”, and PS for “patients simulation”.

## Predicted LV systolic function versus clinical data

Fig 8 depicts model validation for predicting systolic function in comparison to clinical data compiled from the literature (Table 5). For aortic stenosis, increasing the level of valve stenosis decreased the systolic function of the LV, as both LV stroke volume index and ejection fraction reduced. For mitral regurgitation, the LV stroke volume index increased as the severity of the regurgitation increased, which matches the trend in the clinical data. However, the LV ejection fraction decreased as the severity of mitral regurgitation increased. For aortic regurgitation, increased valve insufficiency did not change the ejection fraction, but caused in increasing trend in the LV stroke volume index, as seen in the clinical data. In all cases, model predictions were within the range of the clinical data, except for the ejection fraction of mitral regurgitation.

Diagram, schematic

Description automatically generated

**Fig** **8. Model validation for LV systolic function in comparison to collected clinical data from the literature (Table 5.)** Figure panels are arranged similar to Fig 7. In all panels, clinical data are shown with circle markers in two groups of CD and PD. Model predictions are shown with star markers in two groups of CS and PS. For each valvular disease case, three levels of severity for model simulations are shown in accordance with Tables 2-4. Model predictions for stroke volume are indexed by an average body surface area of 1.9 m2 (Verbraecken et al., 2006; Lang et al., 2015). CD stands for “control data”, PD for “patients data”, CS for “control simulation”, and PS for “patients simulation”.

# Discussion

This study extends an existing multi-scale model of cardiovascular function by incorporating a growth module that simulates both concentric growth (wall thickening) and eccentric growth (chamber dilation). 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, mitral regurgitation, and aortic regurgitation, which were then validated with clinical data from the literature. Furthermore, the model simulations could also capture the reversal of growth when the overloading condition was removed.

## Role of myosin ATPase in driving concentric growth

Pressure-overload induced LV growth is accompanied by numerous changes in molecular-level events, including cardiac energy metabolism (Sankaralingam and Lopaschuk, 2015). The underlying perturbations in cardiomyocytes can increase the ATP demand for myosin ATPase, which reduces the amount of ATP available for other processes within the cell. If ATP production is also perturbed, and cannot match demand (Ingwall, 2009), this will compromise other ATP consuming mechanisms such as sarcoendoplasmic reticulum Ca2+ ATPase (SERCA) uptake. Eventually, the metabolic dysfunction can result in ATP depletion and heart failure (Ashrafian et al., 2007; Lopez et al., 2020; Pitoulis and Terracciano, 2020).

PyMyoVent uses myosin ATPase per myofibrillar volume to drive the concentric growth by modulating the LV myocardial volume. Increased afterload due to aortic stenosis causes myocardium to shorten more slowly, since it needs to pump blood against an elevated resistance. Due to less shortening of half-sarcomeres during systole (Fig 9), the fraction of actin binding sites available for myosin heads (Noverlap), and hence, the fraction of bound binding sites (Nbound) increases. This, in turn, increases the number of myosin heads in MFG and consequently the detachment rate of myosin heads (J4). Based on equation , elevated detachment flux (J4) surges the demand for ATP consumption (myosin ATPase). Increased myosin ATPase per volume of myofibrils drives the concentric growth law to increase the ventricle wall volume and thus thickening the wall. According to *Laplace’s law*, the thickened wall normalizes stress in the LV. At the molecular-level, this is manifested in the half-sarcomeres by reducing myosin heads in MFG, which in turn re-normalizes the detachment flux (J4) and myosin ATPase (Fig 9). Although the peak value of myosin ATPase per myofibrillar volume appears higher at growth steady state than at baseline steady state (Fig 9), due to changes in heart rate and systolic duration caused by the baroreflex, the average value reaches the setpoint level for concentric growth (Fig S4).

Chart, bar chart

Description automatically generated

**Fig** **9. Effects of pressure overloading on myosin ATPase and development of concentric growth**. The simulated results are taken from Fig 2 and enlarged for clarity. Pulsatile parameters such as half-sarcomere length, are shown with an envelope of the response. Nbound is the fraction of bound actin binding sites. Noverlap is the fraction of accessible binding sites for myosin heads. Scon is the driving/stimulus signal for concentric growth. Sset is the setpoint level for concentric growth law.

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

Evidence suggests that certain complexes within the sarcomeric Z-disk, as well as within the I band, may act as mechanical sensors, which can drive downstream events related to mechanotransduction, such as gene expression and protein synthesis (Lyon et al., 2015). Excessive diastolic filling of the LV, due to either an insufficient aortic or mitral valve, causes overstretching of the sarcomeres and thus increases the end-diastolic wall stress (preload). The overstretched sarcomeres trigger these mechanotransduction pathways that initiate the serial addition of sarcomeres within the cell (Grossman, 1980), which then leads to eccentric growth at the organ level (Sahli Costabal et al., 2019). This results in ventricular dilation, which is the characteristic outcome of volume overloading.

In our model, intracellular passive stress has a nonlinear relationship with the change in half-sarcomere length (equation ), which means that overstretching can lead to significant increases in passive stress. Fig 10 summarizes how a volume overloading condition changes the number of half-sarcomeres in series within the model. Essentially, increased diastolic filling resulted in overstretching of half-sarcomeres, which increased the passive stress. The deviation in intracellular passive stress from its homeostatic level (setpoint) drove the eccentric growth law to increase the number of half-sarcomeres in series (Fig 10). This increase in the number of half-sarcomeres then re-normalized the half-sarcomere length and associated passive stress back to the normal range. Fig S5 confirms that the mean intracellular passive stress reaches the setpoint level at final steady state.

Chart, box and whisker chart

Description automatically generated

**Fig** **10. Effects of volume overloading on intracellular passive stress and development of eccentric growth.** The simulated results are taken from Fig 3. Pulsatile parameters such as half-sarcomere length, are shown with an envelope of the response. Secc is the driving/stimulus signal for eccentric growth. Sset is the setpoint level for the eccentric growth law.

## Comparison with existing models of LV growth

In recent decades, many other computational models of LV growth have been developed. Although these models have shed light on the underlying mechanics of LV growth, there are still limitations (Sharifi et al., 2021a). 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 (Goktepe et al., 2010; Klepach et al., 2012; Lee et al., 2015a) have only simulated LV growth during diastolic loading and neglected systolic behavior of myocardium during ejection. Other models (Arts et al., 2005; Kerckhoffs et al., 2012; Lee et al., 2016) investigated the mechanics of LV growth, performed under a full cardiac cycle, where the contractile function was simulated using phenomenological Hill-type models. Another group of works (Witzenburg and Holmes, 2018; Estrada et al., 2021) have used a time-varying elastance model of the ventricle to simulate full cardiac cycles. Rondanina and Bovendeerd (Rondanina and Bovendeerd, 2020a; b) recently investigated different combinations of mechanical growth stimuli where they used a one-fiber model of cardiac function to relate the mechanics of the LV at the organ level to mechanics at the tissue level.

The current framework presented here, however, simulates LV growth under the full cardiac cycle in which the contractile behavior of the LV is driven by a mechanistic model of half-sarcomeres, which simulates the sliding of myofilaments based on the Huxley crossbridge formation (Huxley, 1974) 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 pharmaceutical interventions for treating cardiac diseases.

The absence of a baroreflex feedback loop is another limitation of existing models (Sharifi et al., 2021a). Although valvular diseases impose abnormal loading on the heart, the arterial pressure remains unchanged (Everett et al., 2018a; Gotzmann et al., 2019). In general, existing models of LV growth are performed under constant heart rate with no mechanism to maintain the arterial pressure via modulating the contractility of myocardium and vascular tone. Kerckhoffs et al. (Kerckhoffs et al., 2012) 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 (Rondanina and Bovendeerd, 2020b) 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 (Rondanina and Bovendeerd, 2020a). As shown in the current results, the addition of a baroreflex module allows our model to maintain arterial pressure by modulating heart rate, intracellular Ca2+ transient, contractility of both the thick and the thin filaments, and vascular tone

The reversal of cardiac growth is a favorable outcome of clinical interventions for dysfunctional valves, i.e., 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 (Sharifi et al., 2021a; Yoshida and Holmes, 2021). For example, Yoshida et al. (Yoshida et al., 2020a) investigated the regression of growth due to the removal of pressure overloading, while using the growth law developed by (Kerckhoffs et al., 2012). Although this growth law performed the best in capturing the development of LV growth, in comparison to seven other growth laws (Witzenburg and Holmes, 2017), it could not predict the reversal of growth. Of the few works that have studied the reversal of growth, Lee et al. (Lee et al., 2015a) modified a previously developed eccentric growth law (Goktepe et al., 2010) and were able to capture the reversal of growth for a realistic LV geometry under certain types of loading. The growth law presented in the current study, which utilizes ATPase per myofibrillar volume and intracellular passive stress, was able to simulate the full reversal of growth after the overloading conditions were removed.

## Limitations and future perspectives

The limitations discussed in the previous works with PyMyoVent (Campbell et al., 2020; Sharifi et al., 2021b) are still applicable to the current framework. However, the following limitations are particularly 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 mainly due to the simplified 1-D hemispherical geometry of the LV, which does not account for the complex torsional motion of the heart (Russel et al., 2009), longitudinal and transmural variation of contractile properties (Sharma et al., 2003), or the variation in myofibers orientations (Rodriguez-Cantano et al., 2019).

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 (Pitoulis and Terracciano, 2020; Washio et al., 2020), as well as mutant sarcomeres in familial cardiomyopathy (Watkins et al., 2011), 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.

While not modeled/tested in this study, we believe our ATPase driven concentric growth law could be used to simulate hypertrophic cardiomyopathy (HCM). Though there are numerous mutations leading to HCM--including the myosin heavy chain (*MYH7*) and myosin binding protein C (*MYBPC3*), which are among the most prevalent (Maron and Maron, 2013; Toepfer et al., 2019)--such mutations essentially increase the magnitude of myofilament tension developed over time (Davis et al., 2016) and result into hypercontractile sarcomeres. A review by Spudich (Spudich, 2019) elegantly showed that hypercontractility could be induced by an increased number of accessible myosin heads for binding and myosin ATPase activity. This means our newly developed ATPase driven growth law is well positioned to investigate such phenomena.

# Conclusions

# This work extends a multiscale model of cardiovascular function by incorporating a growth module that simulates both wall thickening (concentric growth) and LV dilation (eccentric growth). In conclusion, the results of this study suggest that myosin ATPase per myofibrillar volume and intercellular passive stress in half-sarcomeres can be used as the driving signals for concentric and eccentric growth, in response to pressure and volume overload. Additionally, the new framework could fully recover the LV size and function (reversal of growth), which is currently lacking in many of the existing computational growth laws.

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# Supplementary material

Diagram, engineering drawing

Description automatically generated

**Fig S****1. Predicted recovery of LV size and function in response to removed pressure overloading.** Similar arrangement for panels as in Fig 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, schematic

Description automatically generated

**Fig S****2. Predicted recovery of LV size and function in response to removed volume overloading.** Similar arrangement for panels as in Fig 3. 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, engineering drawing, schematic

Description automatically generated

**Fig S****3. Predicted recovery of LV size and function in response to removed aortic regurgitation.** Similar arrangement for panels as in Fig 3. 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 regurgitation. Fourth and fifth vertical lines shows the onset and ending of the removed aortic regurgitation.

**Chart

Description automatically generated**

**Fig S****4. Comparison of mean myosin ATPase per myofibrillar volume with setpoint level for concentric growth law.**

**Chart, diagram

Description automatically generated**

**Fig S****5. Comparison of mean half-sarcomere (intracellular) passive stress with setpoint level for eccentric growth law.**