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Computational Analysis of the effect of Mitral Regurgitation on Left Ventricular Mechanics

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Abstract

Mitral Regurgitation (MR) results in a backflow of blood during systole, which imposes a volume load on the ventricle, resulting in a sequence of adaptations and modifications in the left ventricle. Recently, Finite Element (FE) models have been used to investigate the biomechanical features of the mitral valve due to MR and to understand its effect on the left ventricle. In this study, a realistic 3D FE model of the Left Ventricle (LV) was coupled to a closed–loop lumped parameter circulatory model in which backflow owing to MR was incorporated. To examine the biomechanical behavior of the left ventricle, simulations were executed on both a model of a healthy heart and a model of a heart with progressively severe mitral regurgitation. The overall LV mechanics for different simulation cases were assessed by quantifying the LV pressure-volume loop, ejection fraction (EF), circumferential and longitudinal strain variations. For the pressure-volume loop, as the MR severity grew, the peak LV pressure dropped and the LV stroke volume increased, which in turn increased the ejection fraction. Circumferential strain likewise increased, whereas longitudinal strain remained unaffected. Simulations were also run for severe MR cases with increased LV wall thickness to investigate the effect of both MR and LV hypertrophy on overall LV mechanics. The PV loop significantly shrunk down as the LV wall thickness was increased. In addition, for severe MR cases simulations were also performed by varying LV preload and afterload to assess the effect of LV loading conditions on EF. This study demonstrates that FE modelling is a valuable means to apprehend the biomechanics of the regurgitated left ventricle, which may be utilized to simulate different parameters impacting the regurgitated heart and assist medical professionals in making more informed judgments.

Keywords
Mitral regurgitation, Left Ventricle, Finite Element Modelling and Myocardial Strain.

1.Introduction
Valvular heart disease (VHD) is a major contributor to loss of physical function, quality of life and longevity. The complicated Mitral valve controls blood flow between the left atrium and left ventricle in the forward direction. The dysfunction of the mitral valve continues to be a major global health issue and causes morbidity and early death. Understanding the biomechanics of the human mitral valve through computational modeling might result in the creation of novel therapies, preventative measures, and diagnostic tools for mitral valve illnesses.

The mitral valve consists of two leaflets (anterior and posterior) sitting within the annulus. The posterior mitral leaflet originates from the left atrial (LA) endocardium. A sub valvular apparatus, comprising of 2 papillary muscles (anterolateral and posteromedial), arise from the LV myocardium and the chordae tendineae, supporting the leaflets. A dysfunction between these leaflets causes a heart disease called Mitral regurgitation (MR).

MR is caused by the retrograde flow of blood from the left ventricle (LV) into the left atrium (LA) through the mitral valve (MV), causing a systolic murmur heard best at the apex of the heart with radiation to the left axilla. Mitral regurgitation is one of the most common forms of valvular heart disease. Mitral regurgitation (MR) is the most frequent valve disease in the general population, with valvular regurgitation abnormalities ranking first. The Framingham Heart Study found that 19.0 percent of men and 19.1 percent of women had MR of a severity equivalent to or greater than mild. The prevalence of MR of a severity equal to or more than mild was reported in The Framingham Heart Study as 19.0% in men and 19.1% in women. MR is the most common valvular abnormality worldwide, affecting over 2% of the total population and has a prevalence that increases with age. Mitral regurgitation occurs when the mitral valve

does not shut completely during the contraction of the left ventricle, allowing blood to escape from the ventricle into the atrium. It can be caused by mitral valve prolapse, rheumatic fever or valve infection, or injury to the muscle connected to the heart valve caused by a heart attack. Enlargement of the left ventricle, which causes the ring of the mitral valve to extend and the leaflets to close insufficiently, is a rather common cause of regurgitation. Years of untreated high blood pressure or alcohol misuse can induce this hypertrophy; it can also be caused by prolonged mitral valve leaking. Mitral regurgitation (MR) burdens the left ventricle with a volume load that leads to a series of left ventricular (LV) compensatory adaptations and adjustments that vary considerably during the prolonged clinical course of MR. MR has three stages of severity which depends on the regurgitant fraction, the stages are compensated stage, transitional stage and decompensated stage.

The study has been conducted on the mitral regurgitation type of diseased heart by increasing and decreasing the wall thickness to determine the characteristics of this type of hearts' which can provide some helpful information about different conditions of disease. Also the afterload and preload condition of the diseased heart also been simulated which could provide a change in ejection fraction. The originality of this work is that the model is over human heart and we simulated a different perpectives.

1.1. Objectives

This study aims to introduce a model of heart which consists of a 3D electromechanical representation of ventricle coupling with a closed loop lumped parameter circulatory model of valvular regurgitation. It has been intended to develop the mixed finite element model of left ventricle of cardiovascular model and also to solve the mathematical model numerically using finite element method. In this study it analyzes the mechanical properties of regurgitated heart with increasing wall thickness. The results should bring the healthy heart and regurgitated heart into a comparison with their severity.

2.Literature Review

It has been discovered that valve regurgitation, or the back-ward flow in the heart that occurs when a cardiac valve does not entirely close shut, significantly affects cardiac function (Staier et al. 2012). Among the heart's valves are the mitral and tricuspid valves, which connect the atria to the ventricles, as well as the aorta to the ventricles (the aortic and pulmonary aortic valves) (Staier et al. 2012). In a heart that regurgitates, the cardiac output is dependent on the volume of the regurgitant fluid, which is a measure of how severe the condition is (Kim at al. 2016). Medical imaging has been used to study how much regurgitant volume there is, but the effect of regurgitant volume on ventricular mechanical function has not been studied before (Irvine et al. 2001).

A thorough understanding of how valvular regurgitation affects ventricular wall dynamics is critical because it will help researchers gain a better understanding of how heart failure progresses in terms of ventricular remodeling and remodeling (HF) (Lim et al. 2015). The amount of the regurgitant leak which is also known as the regurgitant volume and the progression of the regurgitation over time are two factors that influence the clinical effect of mitral regurgitation (MR). When more than 50% of the total stroke volume is redirected to the regurgitant flow, a diagnosis of severe MR, also known as the Decompensated stage, is made. When this percentage is between 30% and 50%, a condition known as moderate MR, also known as the transitional stage, is considered to be present. On the other hand, a diagnosis of compensated stage MR is given when the regurgitant fraction is less than 30% (Scognamiglio et al. 1990). Although a significant amount of research has been done to determine the volume of regurgitation using medical imaging techniques and also to predict the effects of regurgitant volume on ventricular mechanical function, no study has been done to predict the effects of regurgitation severity in specific valvular regurgitation on LVAD (left ventricular assist device) function in the failed ventricle following LVAD therapy. This is because no study has focused on predicting the effects of regurgitation severity in specific valvular regurgitation (Staier et al. 2012). The simulation research of mitral regurgitation was carried out here for patients with varying degrees of severity of this condition.

3.Methods:

3.1. Computational Model Framework:

The hemodynamics and ventricular mechanics of the LV were modeled using a computer modeling framework that consisted of a connected left ventricle (LV) and a closed-loop circulatory system (Figure 1) (Gaasch et al. 2008).

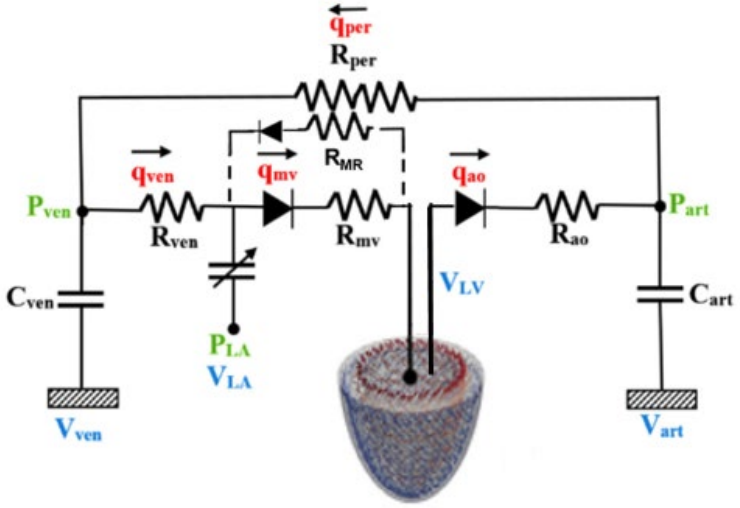


Figure 1. Windkessel model employed in the simulations. Elements on the dotted line were not used in healthy scenario modelling but were added during disease modelling to simulate MR. C is capacitance, and R is resistance.

The Windkessel model, which depicts hemodynamic flow resistance and blood wall elasticity, served as the basis for developing the framework model (Shavik et al. 2019). Here two element Windkessel Circuit is used here. It is assumed that the ratio of pressure to volume is stable, and that the amount of fluid that exits the Windkessel is proportional to the pressure of the fluid. The volume that is held in the capacitive element and the volume lost through the resistive element must be equal to the volume gained by volumetric input. The Windkessel-type circuits used in CVS models are generally designed using either electrical circuit analogies or a hydraulic representation. An active stress formulation was used to characterize the LV's mechanical behavior (Suga et al. 1974). To account for the muscle fiber's length dependence, a modified time-varying elastance model was used to compute the active force, while a Fung-type transversely isotropic hyperelastic constitutive model was used to explain the passive mechanical behavior (Shavik et al. 2021). A circulatory closed-loop model with lumped parameters was coupled to the LV finite element model. Within the context of this model, an atrial contraction was modeled with the help of a time-varying elastance function. Based on a prior experimental measurement, the myofiber orientation was changed transmurally across the LV wall in thermal condition. This change resulted in a linear variation that ranged from 60° at the endocardium to 60° below at the epicardium. (Guccione et al. 1993). This type of model is a quadratic tetrahedral element. The time constant for relaxation was established at 25 milliseconds, which is within the typical parameters (Streeter et al. 1969). Once more, this strain energy function adheres to these four boundary conditions: the LaGrange multiplier in compression, the LaGrange volume constraint, zero translation, and zero rotation. The formation that results from mixing these four components is known as FE mixed formation.

$$Q_{a,o} = \begin{cases} \frac{P_{LV} - P_{art}}{R_{ao}} & ; P_{LV} > P_{art} \\ 0 & ; P_{LV} \leq P_{art} \end{cases} \quad (1)$$

$$Q_{per} = \frac{P_{art} - P_{ven}}{R_{per}} \quad (2)$$

$$Q_{ven} = \frac{P_{ven} - P_{LA}}{R_{ven}} \quad (3)$$

$$Q_{ad} = \frac{P_{ad} - P_{ven}}{R_{ad}} \quad (4)$$

$$Q_{LA} = \begin{cases} \frac{P_{LA} - P_{LV}}{R_{mv}} ; P_{LV} < P_{LA} \\ 0 \quad ; P_{LV} \geq P_{LA} \end{cases} \quad (5)$$

$$V\_art = V_{art} + dt \times (Q_{per} - Q_{ao}) \quad (6)$$

$$V\_ven = V\_ven + dt \times (Q_{ad} - Q_{ven}) \quad (7)$$

$$V\_ad = V\_ad + dt \times (Q_{per} - Q_{ad}) \quad (8)$$

3.2. Regurgitated Heart:
To model, the mitral regurgitation model one additional branch was added to the CVS lumped parameter model. That additional branch had a backward diode to represent the backflow/ leakage flow. The dynamic flow parameter is represented by the following equations:

$$Q_{mr} = \frac{P_{LV} - P_{LA}}{R_{mr}} ; P_{LV} \geq P_{LA} \quad (9)$$

$$V\_cav = V_{cav} + dt \times (Q_{LA} - Q_{ao} - Q_{mr}) \quad (10)$$

$$V\_LA = V\_LA + dt \times (Q_{ven} - Q_{la} + Q_{mr}) \quad (11)$$

Here from equation 1 to 5 and 9 are flow rates of different segments which depends on its different loading condition (Resistance) and the pressure difference between the compartments. And from equations 6 to 8 and 10 and 11 are the volumes of five compartments which depends on the flow rate of the segments here. Where the subscripts denote left ventricle as (LV), aortic valve (a,o), peripheral (per), venous (ven), aortic (art), mitral regurgitation (MR), mitral valve (mv), distal arterial (ad)and left atrium (LA), respectively.

4. Results and Discussion

In this study, the effect of valvular regurgitation on ventricular mechanics was examined using a computational model of the heart consisting of a 3D electromechanical representation of the ventricle coupled with a lumped parameter of valvular regurgitation. Simulations were conducted to analyze the behavior of a healthy heart with several degrees of regurgitated heart severity.

A. Validation of Healthy Heart Model

First, a healthy case was simulated, and the results show that the model's predictions for the normal case accord well with the clinical measures. End diastolic volume (EDV) = 111.2 ml and ejection fraction (EF) = 60% are specific values that are within the range of a typical heart case. Specifically, the LV end-diastolic volume (EDV) (109ml), ejection fraction (EF) (60%), and LV wall thickness at end-diastole (EDWT) (0.8cm) are all within the normal range found in healthy humans (Maurer et al. 2007).

Diastolic Peak Pressure is 120 mmHg, the peak value of Circumferential strain (Ecc) is 23.2%, Radial Strain (Err) is 25%, and Longitudinal Strain (Ell) is 21%. All these values are in alignment with the clinical

measurements of the control in a study on HFpEF patients (Shavik et al. 2021) (EF: 61 ± 3%; DBP: 74 (68, 84) mmHg; SBP: 130 (118, 138) mmHg; Ecc: 27.1 ± 3.1%; Ell:20 ± 2.1%). In Fig-2 all these values are graphically displayed.

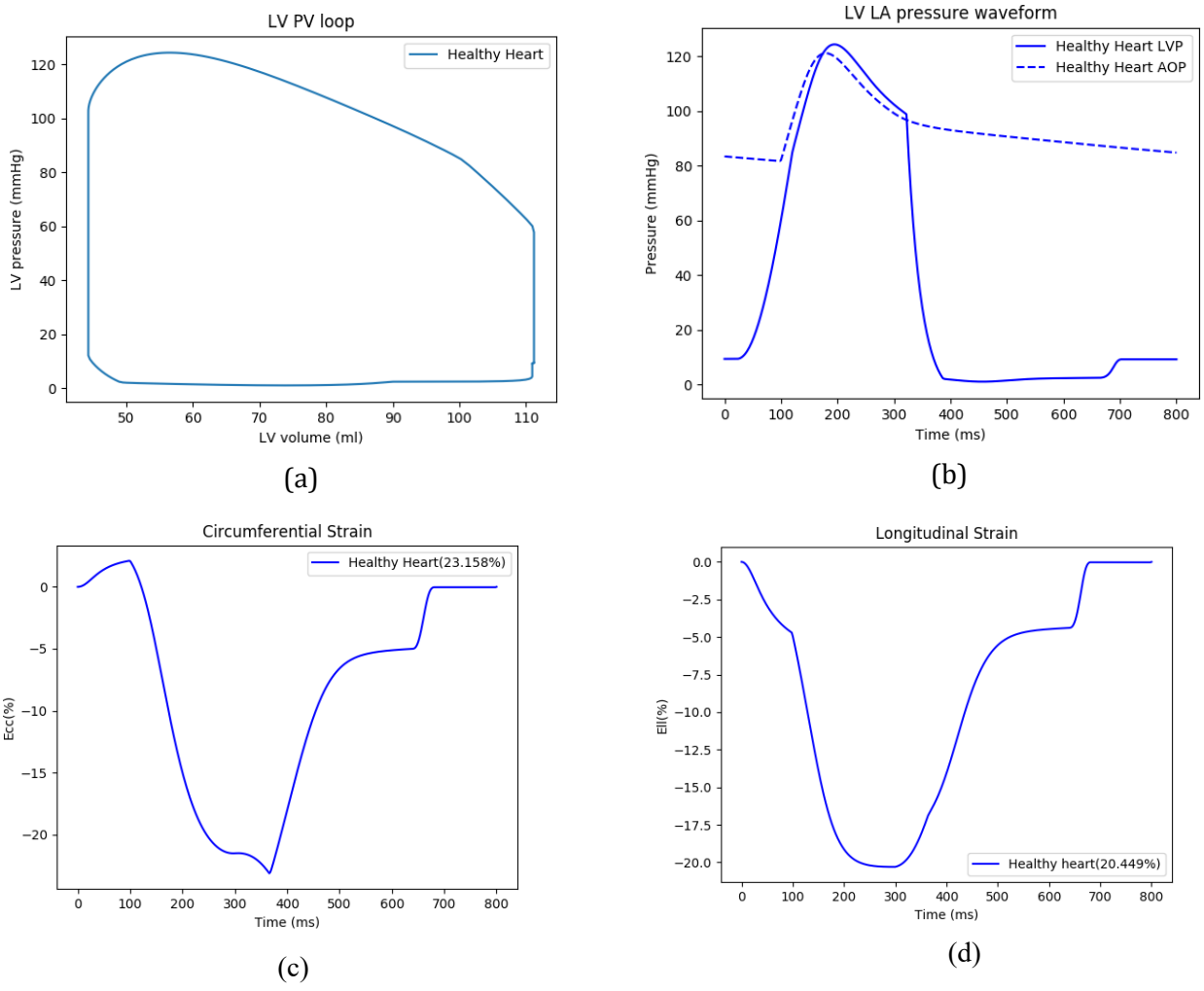


Figure 2. (a) PV loop, (b) ventricular pressure and aortic pressure vs time, (c) Circumferential Strain vs Time, (d) Longitudinal Strain vs Time of a healthy heart

B. Regurgitated Heart

In this investigation, three different stages of mitral regurgitation e.g., i) Mild MR (<30% backflow), ii) Moderate MR (30-50% backflow), and iii) Severe MR (>50% backflow) have been analyzed. By introducing an additional backflow path with resistance Rmr, regurgitation in the mitral valve has been captured successfully.

In Figure 3 the relation between the pressure and volume of a normal heart and regurgitated heart with varying severity is depicted. Increased MR severity resulted in a minor discrepancy between systolic and diastolic blood pressure values. End-diastolic volume (EDV) grew substantially, but the end-systolic volume (ESV) declined somewhat, resulting in the formation of a horizontally expanded pressure-volume loop. The raised EDV results from the increasing severity of mitral regurgitation because the ventricle anatomically dilates (remodels), increasing ventricular compliance. Since there has been leaking of blood (backflow), the ventricle cannot raise the pressure as before in a healthy heart, decreasing pressure with increasing MR severity. The variation in LV pressure over time is shown in Figure 4, where the pressure in the ventricle diminishes during diastole due to the backflow.

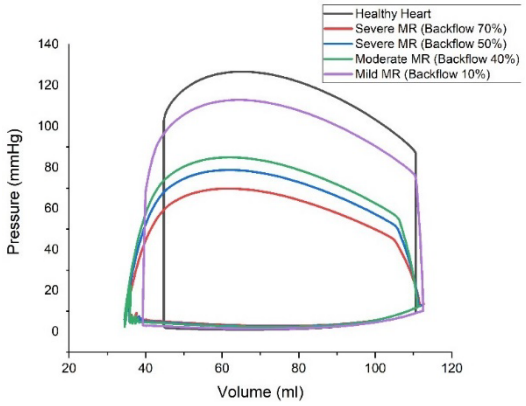


Figure 3. Comparison of PV loop of a healthy heart and several degrees of MR

Table 1 analyzes the increasing severity of the regurgitated heart's ejection fraction (EF) As the severity increases, the EF slightly increases and remains well above 55%, which corresponds to the clinical outcome. (Gaasch et al. 2008).

Mitral Regurgitation Severity	**Ejection Fraction**
Healthy Heart	60%
Mild MR (10% backflow)	65.4%
Moderate MR (30% backflow)	69.1%
Severe MR (50% backflow)	69.2%
Severe MR (70% backflow)	69.3%

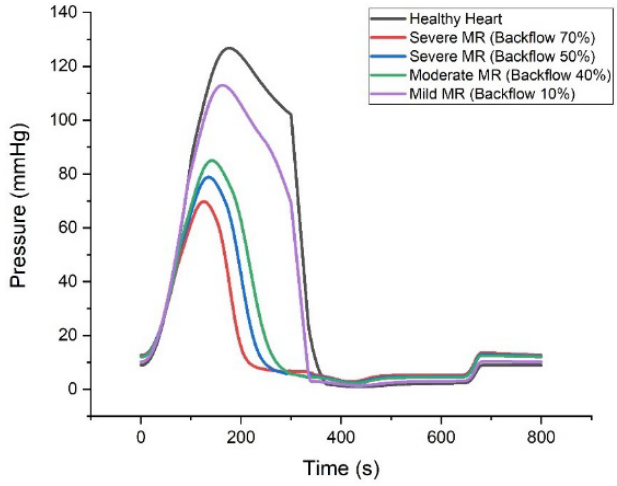


Figure 4. LV pressure Vs time of healthy heart and several degrees of MR.

The circumferential strain Ecc in Figure 5 exhibits a minor upward trend with increasing MR severity. While afterload is minimal and late systolic volume is lowered, acute MR; these parameters eventually rise as the ventricle grows and adjusts to the chronic volume overload.

Subsequently, particularly in decompensated MR, afterload exceeds normal resulting in an increasing Ecc. Increasing circumferential stress and strain with increasing severity resembles with clinical values (Roy et al. 2021). Whereas in Figure 6 it is apparent that longitudinal strain Err is relatively unaffected by the increasing severity of MR.

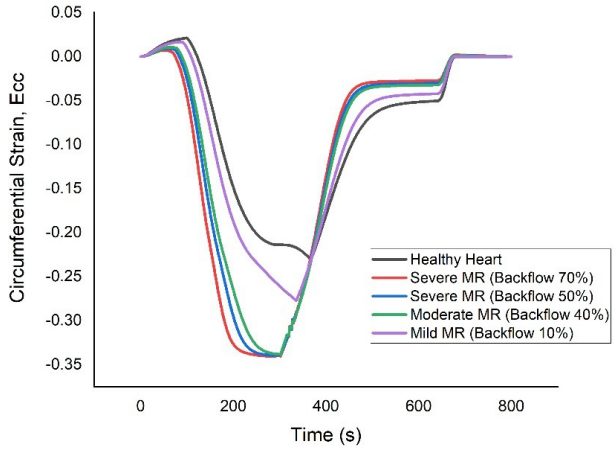


Figure 5. Comparison of the circumferential strain of a healthy heart and several degrees of MR.

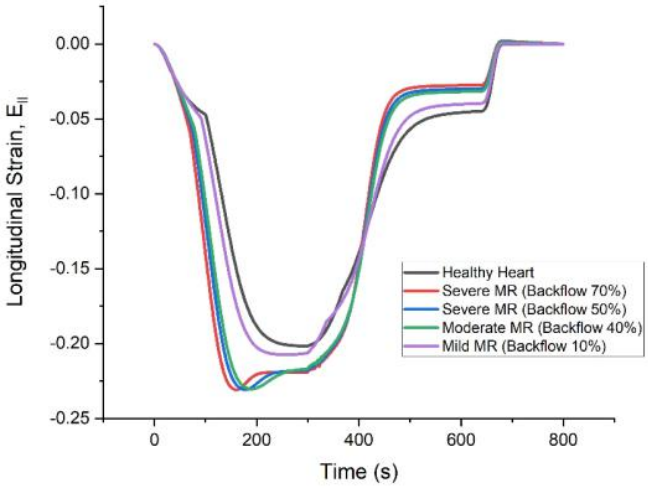


Figure 6. Comparison of the longitudinal strain of a healthy heart and several degrees of MR.

For a particular percentage of regurgitation, simulations were performed with different heart thicknesses to understand the effect of thickness of ventricular mechanics. Here we considered a severe regurgitated heart of 70% backflow and thickness of 0.9 and 1.4 cm. The PV loop is represented in Figure 7 at various thicknesses and the PV loop is shrinking down and moving to the left which demonstrates lower volume and lower pressure with width is diminishing as the thickness of the heart increases. Since the LV contracts, it pumps the blood out of the heart and into the arteries. The thicker the walls of the LV, the more force is required to pump the blood out of the heart, so the stiffness of the wall increases. This causes a decrease in the pressure and volume within the LV.

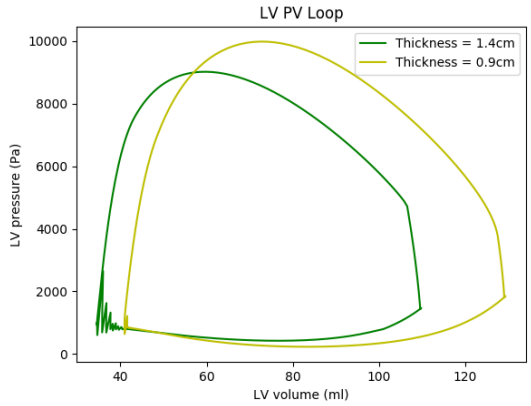
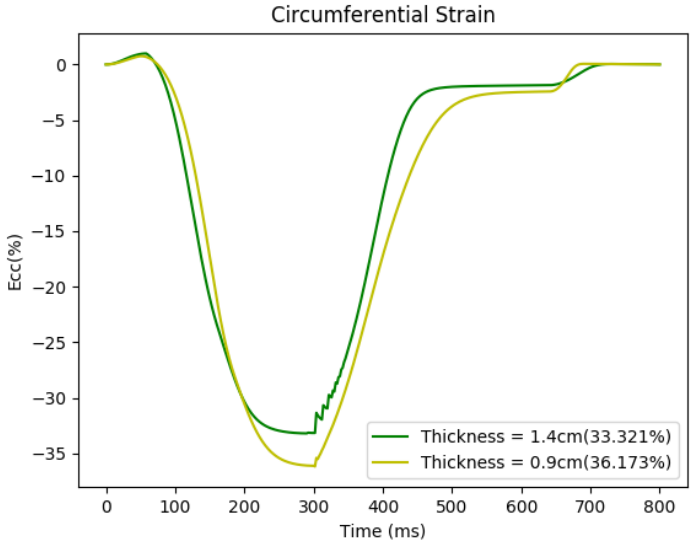
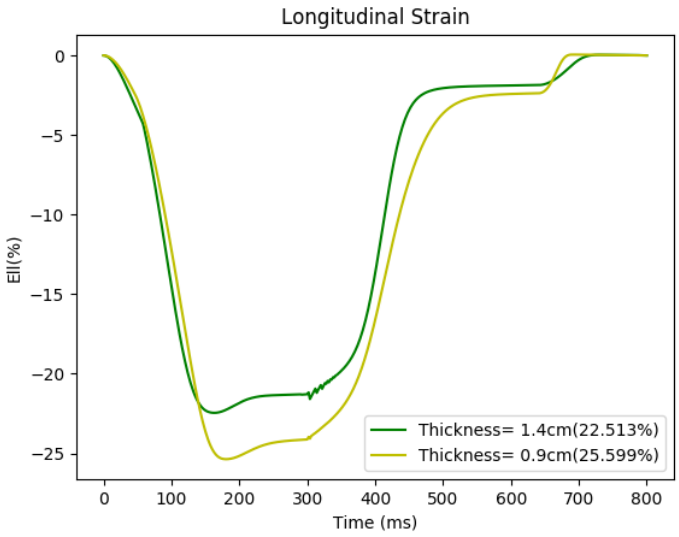


Figure 7. LV PV Loop with different thicknesses.

As seen in Figure 8, three strains- circumferential, radial and longitudinal – have been demonstrated for increasing wall thickness of a heart experiencing 70% regurgitation. The data includes that a left ventricle wall thickness of 0.9cm exhibited higher circumferential strain compared to 1.4cm wall thickness. As the wall thickness increases, the amount of stretching that the heart muscle undergoes during contraction decreases, leading to lower circumferential strain. Longitudinal and radial strain exhibit a similar trend, with strains decreasing as wall thickness increases. However, in all three cases, this decrease in strain is not significant enough to cause heart failure.



(a)



(b)

In addition to simulating severe mitral regurgitation (MR) cases, simulations were also performed by varying left ventricular (LV) preload and afterload to assess their effect on LV ejection fraction (EF). In severe MR cases with 70% backflow, simulations were performed by varying preload and afterload to understand the effect of LV loading conditions on EF. To study the effects of afterload, we increased the distal aortic resistance (Rad) in the simulations. Figure 9 shows the results of simulations with two different levels of afterload (Rad=80000 and Rad=250000). The figure shows that as afterload increases, the LV pressure-volume loop widens, indicating higher pressure and end-diastolic volume (EDV). A higher EDV indicated higher preload, and higher pressure indicates a higher EF. These results that changes in LV loading conditions can affect EF in patients with severe MR.

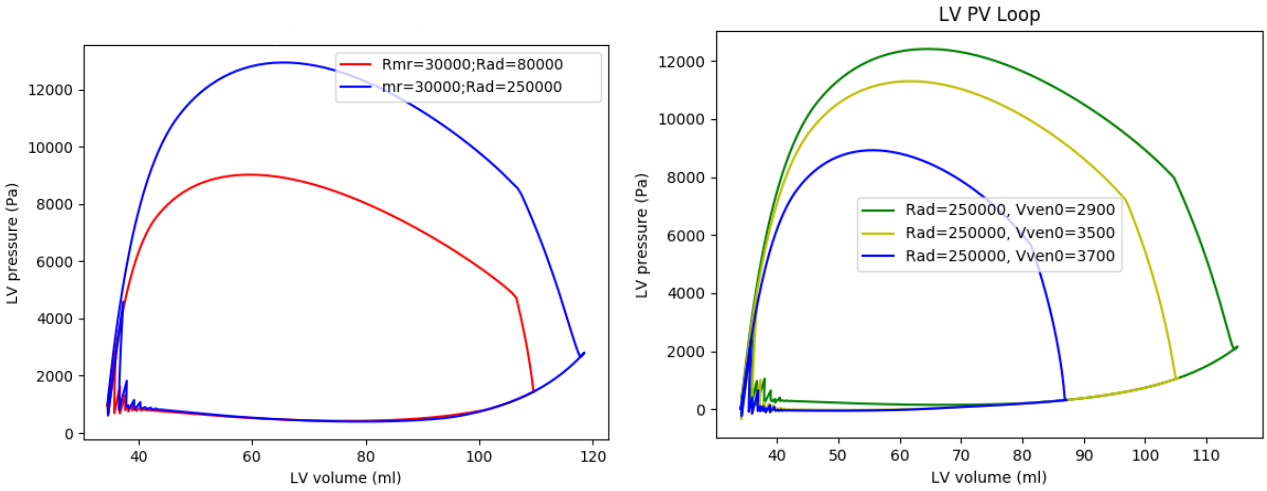


Figure 9. LV PV loop with different afterload

Now to understand the effect of afterload better simulations were run to keep the preload constant. Here, the parameter Vven0 is inversely related to EDV (preload). For different preload conditions, PV loops of the Left ventricle are shown in the Fig-10 where it is evident that with increasing preload, the PV loop is also expanding which indicates higher pressure and volume and ejection fraction. So, from the results it can be concluded that, increasing afterload is in fact results in increasing ejection fraction in severe MR cases. Afterload is the force that the left ventricle must work against to eject blood, and it is determined by the blood flow in the arterial system. An increase in the afterload can cause left ventricle to contract more forcefully, which can increase the ejection fraction. But normally, increased

afterload results in decreased ejection fraction. The relationship between afterload and ejection fraction is complex and can vary depending on the specific circumstances and parameters.

5. Conclusions and Future Work

In this study, we utilized a finite element model of the left ventricle and a closed loop lumped parameter circulatory model to investigate the impact of valve regurgitation on ventricular mechanics. We incorporated the backflow of blood due to mitral regurgitation by including a backflow resistance, Rmr, in the circuit. WE performed simulation of the normal and regurgitated hearts with increasing severity and evaluated various parameters such as pressure, volume and circumferential and longitudinal strain. Our results showed that pressure displayed and inverse relation with the severity of MR. The PV loop became more horizontal and the shape of the PV loop of a healthy heart distorted as the MR worsened. The inability of the ventricle to effectively generate pressure due to leakage of blood resulted in a decrease in ejection fraction. However, this was compensated for by a change in the ventricle's geometry, leading to an increase in ejection fraction with increasing severity of MR. The circumferential strain also showed a rising trend as the regurgitation intensified, while the longitudinal strain was unaffected by the severity of the MR.

To understand the effect of wall thickness on the ventricular mechanics, simulations were run for two different wall thickness for high severity MR case. For higher thickness the PV loop shrank down and moved left since thick wall indicates higher stiffness. Consequently, strains (circumferential, longitudinal and radial) showed decreasing trend for increased thickness. Simulations were also run on a particular severe MR case varying afterload and preload to understand its effects on ventricular mechanics. In both cases, increased loading (preload and afterload) indicates enhanced ejection fraction. Normally increased afterload results in decreased ejection fraction. Since ejection fraction and different loading condition of the left ventricle share a complex relation future works can be done to understand this phenomenon better.

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Biographies

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