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# Effect of Hypertrophy, Passive Stiffness and Contractility on Myocardial Strain in HFpEF: A Computational Approach

**Sazzad Hossain, Arafat Anzir and Sheikh Mohammad Shavik**
Department of Mechanical Engineering
Bangladesh University of Engineering and Technology (BUET)
Dhaka, Bangladesh
1610065@me.buet.ac.bd, 1610154@me.buet.ac.bd, shavik@me.buet.ac.bd

## Abstract

Over the years, the development of computational modeling of heart with a realistic representation of muscle characteristics and cardiac geometry has progressed remarkably. Clinical studies show that global longitudinal strain is reduced in heart failure with preserved ejection fraction (HFpEF), which indicates a decline in global left ventricular (LV) contractility. However, a preserved ejection fraction (EF) and changes in LV geometry, which can also impact global stresses, contradict this interpretation. In this study, we have used a validated computational framework to understand the effects of these contradicting factors on systolic functions and HFpEF features. The computational framework consists of a finite element LV model integrated with a closed loop lumped parameter circulatory model. To understand and quantify the effect of LV passive stiffness, contractility, and wall thickness on myocardial strain in HFpEF, a numerical investigation was conducted. Simulations were carried out under different conditions to understand their isolated and combined effects. Our study suggests that it is likely that hypertrophy with reduced LV contractility can reproduce the EF, global longitudinal strain, and global circumferential strain found in HFpEF patients, but the blood pressure falls out of range.

## Keywords
HFpEF, Myocardial contractility, Ejection fraction, Finite element modeling and Global longitudinal strain.

## 1. Introduction

Several probable causes of heart failure have been identified in the past, and it is becoming increasingly evident that heart failure is an epidemic. Conditions such as coronary artery disease, valvular heart disease, hypertension, cardiomyopathies, and the deleterious effects of drugs and toxins are included in this category. Heart failure with preserved ejection fraction (HFpEF) is a frequent clinical disease that is also a substantial cause of morbidity and death. This condition affects about 50% of people with heart failure (Bhatia et al. 2006; Owan et al. 2006). Patients with HFpEF are often older and have a higher frequency of hypertension than patients with heart failure with reduced ejection fraction (HFrEF) (Owan et al. 2006). Despite the fact that there are novel medications available (Asif et al. 2000; Liu et al. 2003; Solomon et al. 2012; van Tassell et al. 2014; Yamagami et al. 2015), there is presently no therapeutic option that has been shown to be effective for persons with HFpEF (Ponikowski et al. 2016; Roh et al. 2017). Previously, it was believed that diastolic dysfunction was the only mechanism creating HFpEF, which was originally known as diastolic HF (Borlaug and Paulus 2011; Zile et al. 2001) due to the occurrence of many clinical characteristics that inhibited LV filling (Sengupta and Marwick 2018). The characteristics are sluggish LV relaxation, cardiomyocyte stiffness (Zile et al. 2009), and concentric hypertrophy (Velagaleti et al. 2014). However, mounting evidence indicates that those with HFpEF may also have poor myocardial contractility. The fact that this evidence has been shown to influence systolic function calls into question the long-held view that it does not (Kraigher-Krainer et al. 2014; Morris et al. 2017; Shah et al. 2015; Zou et al. 2018). Due to seemingly contradictory evidence, it has been difficult to reach a consensus and find a solution to the problem of myocardial contractility in HFpEF. End-systolic elastance (*Ees*) and left ventricular ejection fraction (EF), as revealed by research, are either normal or elevated in people with HFpEF. This suggests that the overall ventricular contractility is either being preserved or increasing (Borlaug et al. 2009; Kawaguchi et al. 2003). On the other hand, these hearts exhibit a reduced global longitudinal strain, which indicates reduced myocardial contractility (Kraigher-Krainer et al. 2014). This was found by measuring the strain over the whole length of the heart. It is difficult to interpret these facts, which appear to contradict one another when relying exclusively on fundamental or clinical experimental

studies (normal or increased chamber contractility, but reduced myocardial motion). Increased vascular resistance (afterload), modified LV geometry, and increased LV mass—all of which are present in people with HFpEF—have a variety of effects on the longitudinal strain. These factors may make it more challenging to determine the relationship between longitudinal strain and myocardial contractility. The capacity to separate the variables that affect left ventricular function and motion in HFpEF patients to understand each one's unique role(s) and contribution(s) is one of the inherent advantages that computational modeling offers (Adeniran et al. 2015; Dabiri et al. 2018; Genet et al. 2016; MacIver and Townsend 2007). Since HFpEF has stiffer muscles, a thicker wall, and a decreased myocardial contractility, this work focuses on understanding the effect of these parameters by replicating HFpEF.

### 1.1 Objectives

This study attempts to associate passive stiffness with EF and overall longitudinal strain because it has been shown that the heart stiffens during HFpEF. We made an effort to determine if this parameter is entirely accountable for HFpEF. In many HFpEF patients, the ventricular wall thickens as the LV cavity shrinks. Because of this, we also looked for any connections between the geometry and HFpEF. Finally, we made an effort to comprehend how myocardial contractility affected global longitudinal and circumferential stresses as well as LV EF.

## 2. Literature Review

Paulus et al. (2007)showed that HFpEF is diagnosed when the LV ejection fraction is greater than 50% and heart failure symptoms are present (shortness of breath, fatigue, swollen ankles, and legs). Zile et al. (2004)identified HFpEF to be a form of diastolic heart failure (a stiff left ventricle with reduced compliance and dysfunctional relaxation, resulting in an elevation in end-diastolic pressure). Heinzel et al. (2015)observed that LV hypertrophy (an increase in ventricular myocardial mass) is the most prevalent geometrical abnormality of the heart linked with HFpEF. Kraigher-Krainer et al. (2014), Morris et al. (2012), and Su et al. (2014) observed myocardial hypertrophy in HFpEF using echocardiography and magnetic resonance imaging (MRI), but the myocardial strain in the LV wall was decreased during the systolic stage. Kawaguchi et al. (2003) demonstrated that individuals with HFpEF exhibit systolic-ventricular and arterial stiffening that exceeds that caused by age and/or hypertension. Dabiri et al. (2018) investigated the contribution of changed LV systolic mechanics as a mechanism of HFpEF by using a realistic FE model of the human LV. Genet et al. (2016) predicted chronic changes in ventricular geometry, chamber size, and wall thickness using computer models. These predictions are in good agreement with the clinical observations made in patients with diastolic and systolic heart failure. Adeniran et al. (2015)showed that HFpEF reduces systolic calcium levels at a cellular level, which results in a lowered systolic contractile force, but raises diastolic calcium levels, which results in an aberrant residual diastolic force. DH MacIver (2015)studied the mathematical relationship between LV ejection fraction and global myocardial strain using a computer simulation technique. Shavik et al. (2017)investigated the effects of preload and afterload on myocardial strains and found that the strains are sensitive to changes in loading conditions when LV contractility is held constant.Morishita et al. (2021) showed that both radial and circumferential strains decreased with increasing wall thickness (cardiac hypertrophy). Shavik et al. (2021)suggested that myocardial contractility is decreased in HFpEF patients.

## 3. Methods

In regard to HFpEF, the computational analysis of the ventricular mechanics and hemodynamics was carried by a computational framework which was already validated. This particular framework comprises a three-dimensional LV modeled by the finite element method which was coupled with a closed-loop-circulatory model. The framework is shown in Figure 1(a). An active stress formulation was adopted for the depiction of the mechanical behavior of the LV. A modified time-varying elastance model that takes into account the muscle fiber's length dependency was used to calculate the active force developed along the local myofiber direction (Guccione et al. 1993), while a transversely isotropic hyper-elastic constitutive model of the Fung type was adopted to describe the passive mechanical behavior (Guccione et al. 1991). The LV FE model was integrated with a closed-loop lumped parameter circulatory model demonstrating the systemic circulation. The circuit included mitral and aortic valves (with resistances Rao and Rmv), left atrium (LA), proximal and distal arterial and venous compliances (Ca,p, Ca,d, and Cven), and resistances. The LA contraction was described using a time-varying elastance function. The numerical investigation was carried out in open source PDE solver FEniCS(Logg et al. 2012).

### 3.1 Left Ventricular Geometry and Boundary Conditions

The LV characteristic of normal persons and HFpEF patients was modeled using an idealized prolate ellipsoid. Clinical studies have revealed that HFpEF patients' LVs had a greater wall thickness to cavity diameter (internal dimension) ratio and a longer apex-to-base length than healthy individuals(Maurer et al. 2005, 2007; Shah 2013). However, several investigations have discovered that the LV cavity diameter was either not considerably different or slightly decreased in HFpEF patients (although both with a thicker ventricular wall)(Prasad et al. 2010; Zile et al. 2015). We adopted two geometries in the modeling framework to replicate HFpEF, both with the decreased LV cavity but larger wall thickness, to cover the wide range of LV geometry reported in HFpEF patients. The two HFpEF geometries were both heavier than the typical case. The geometrical shape is visualized in Figure 1(b) and data is presented in Table 1. and the similar boundary conditions are applied to those two geometries as in earlier computational studies (Shavik et al. 2018, 2019, 2021) were applied to the LV model: (1) zero mean rotation of the overall geometry; (2) no translation of the overall geometry; and (3) fixed base surface of the LV, i.e., no translation along the z-axis. The relaxation time constantτ, chosen within the typical range, was chosen at 25 ms, (Zile et al. 2004).

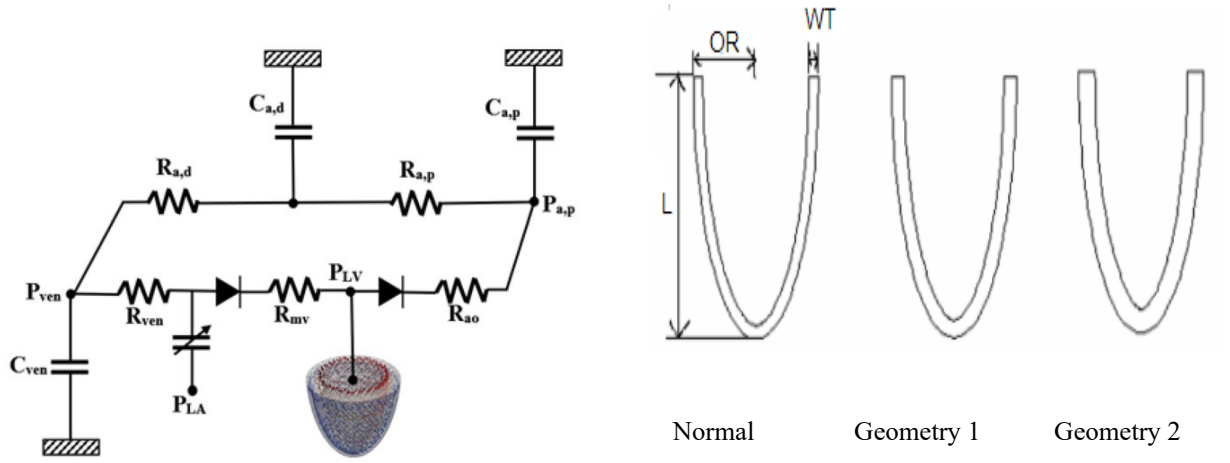


Figure 1. a) Schematic of the Computational Framework b) LV Geometry of Normal, Geometry 1 and Geometry 2

Table 1. Geometric Dimension and Mass of different LV geometry

| | Normal | Geometry 1 | Geometry 2 |
|---|---|---|---|
| WT (cm) | 1.13 | 1.25 | 1.48 |
| OR (cm) | 3.13 | 3.13 | 3.13 |
| L(cm) | 8.3 | 8.3 | 8.3 |
| Mass(g) | 108.9 | 113.1 | 126.5 |

### 3.3 Analysis of Strains

The global longitudinal strain ($E_{ll}$) and circumferential strain ($E_{cc}$) were calculated using a method provided by Shavik et al. (2017), where end-diastole served as the reference configuration. Using the following equation, the longitudinal and circumferential myofiber stretches, designated $e_l$ and $e_c$, were calculated:

$$\lambda = \sqrt{e_i}.\boldsymbol{C}.e_i$$

Here, $\boldsymbol{C}$= $\boldsymbol{F}^T\boldsymbol{F}$; right Cauchy-Green deformation tensor, F= deformation gradient tensor and $e_i$ where i ∈ (l,c) are unit vectors in the longitudinal and circumferential directions respectively.

The circumferential direction $e_c$ was perpendicular to the radial direction and the direction from apex to base. The longitudinal direction $e_l$ is perpendicular to both radial direction and $e_c$. The strain was calculated using the following equation: (Shavik et al. 2017)

$$\varepsilon_{ii} = \frac{1}{2}\left(1 - \frac{1}{\lambda_i^2}\right) \times 100\%$$

### 3.4 Simulation Cases

The value of parameters of various simulation cases that were run throughout the study are tabulated in Table 2 and Table 3. Table 2 shows us the change of passive stiffness for our study. Table 3 shows us the different geometry, stiffness and myocardial contractility values that were used.

Table 2. Simulation Cases to Observe the Effect of Passive Stiffness

| Geometry | Change in Passive Stiffness | Passive Stiffness, C (Pa) | Case |
|---|---|---|---|
| Normal | NC | 125 | Normal |
| | 80% ↑ | 225 | Stif-1 |
| | 400% ↑ | 625 | Stif-2 |
| | 560% ↑ | 825 | Stif-3 |
| | 800% ↑ | 1125 | Stif-4 |

Table 3. Simulation Cases to Observe the Effect of Wall Thickness, Passive Stiffness, Contractility

| Case | Wall Thickness (cm) | Passive Stiffness (Pa) | Contractility (kPa) | Case | Wall Thickness (cm) | Passive Stiffness (Pa) | Contractility (kPa) |
|---|---|---|---|---|---|---|---|
| G1 | 1.25 | 125 | 120 | G4 | 1.48 | 125 | 120 |
| G1S1 | 1.25 | 250 | 120 | G4S1 | 1.48 | 250 | 120 |
| G1S1C1 | 1.25 | 250 | 108 | G4S1C1 | 1.48 | 250 | 108 |
| G1S1C2 | 1.25 | 250 | 96 | G4S1C2 | 1.48 | 250 | 96 |
| G1S2 | 1.25 | 400 | 120 | G4S2 | 1.48 | 400 | 120 |
| G1S2C1 | 1.25 | 400 | 108 | G4S2C1 | 1.48 | 400 | 108 |
| G1S2C2 | 1.25 | 400 | 96 | G4S2C2 | 1.48 | 400 | 96 |

## 4. Results and Discussion

### 4.1 Validation of Normal Case

The normal case predictions made by this model agrees with the clinical measurements as validated by Shavik et al. (2021).

### 4.2. Graphical Results

#### 4.2.1. Effect of Changes in LV Passive Stiffness

In our analysis, stiffness was increased for a fixed geometry and contractility. Increasing the passive stiffness makes the heart stiffer and it makes the end-diastolic-pressure-volume-relationship (EDPVR) steeper which can be seen in Figure 2. Thus, the preload is reduced. Increased LV stiffness decrease the LV EF decreases, systolic blood pressure (SBP) and diastolic blood pressure (DBP) (Figure 3). Peak longitudinal strain and circumferential strain also decreases with the increased stiffness. From Figure 3, it can be observed that only Stif-1 and Stif-2 case had EF, $E_{cc}$, $E_{ll}$ within clinical range while Stif-2 was close to the clinical range. Other cases were out of the clinically measured range. However, none of the cases had blood pressure within the clinical range.

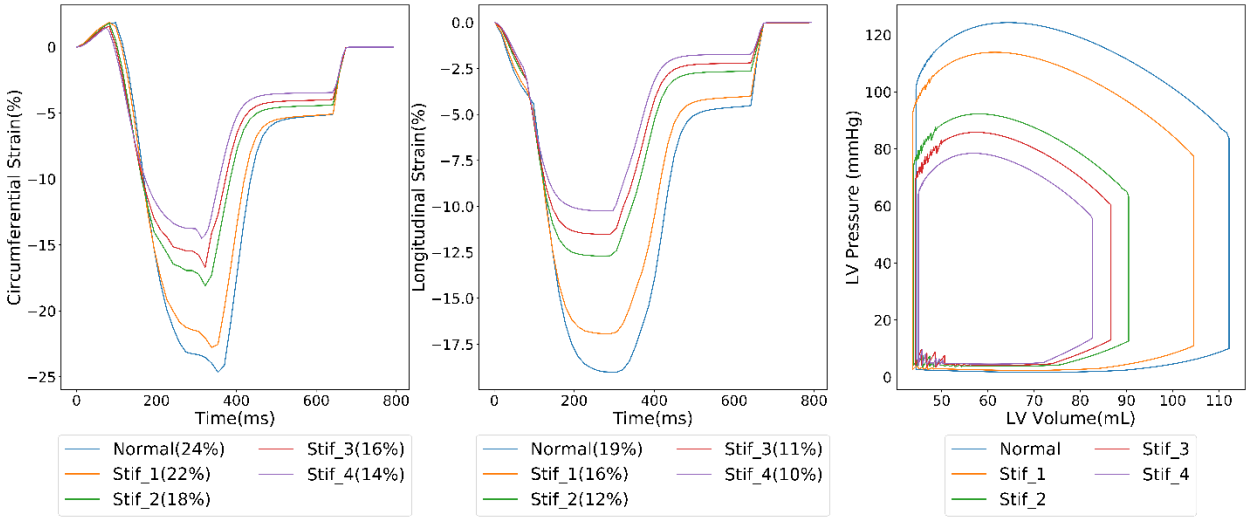


Figure 2. Effect of Stiffness on a) $E_{cc}$ strain-time profile b) $E_{ll}$ strain-time profile c) Pressure-Volume loop (the values in the legends indicate peak strain)

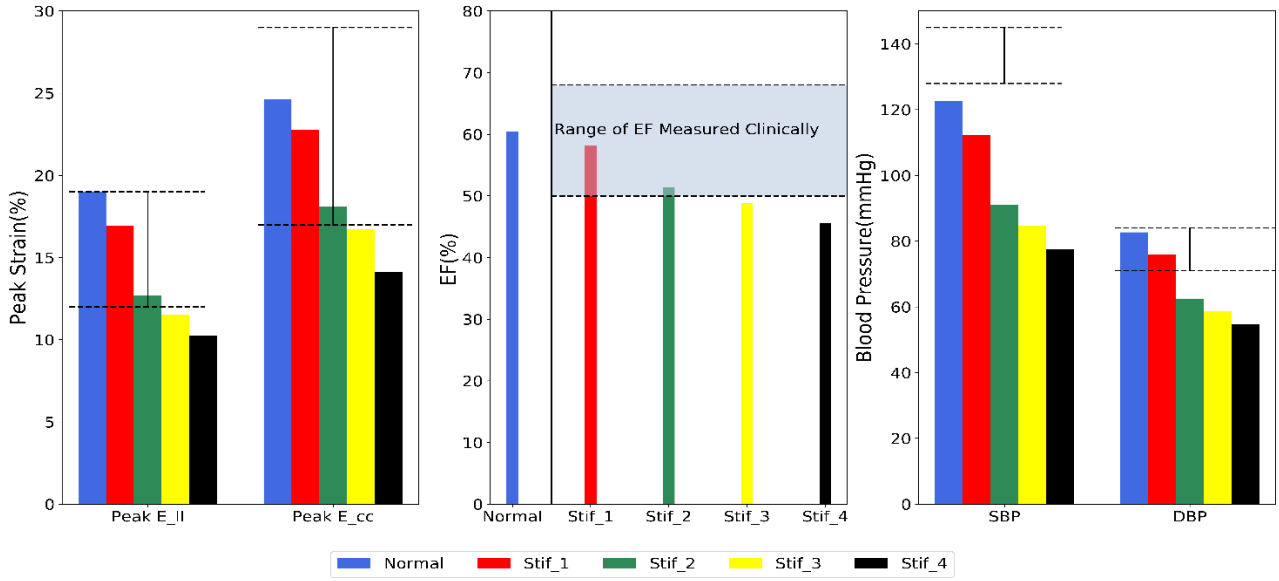


Figure 3. Effect of Stiffness on peak$E_{cc}$, $E_{ll}$, EF, SBP, DBP compared to clinical values observed in patients

**4.2.2 Effect of contractility**

Contractility is reduced for a specific wall thickness and stiffness. In this case, it was done for the wall thickness of 1.25 cm and for passive stiffness parameter, $C = 250$ Pa. Figure 4 shows that decreasing contractility reduced the LV EF and the peak longitudinal and circumferential strain. But, observing from Figure 5, if contractility is reduced too much, the SBP and DBP falls significantly below the clinical range. Figure 5 shows us that when contractility was decreased by 10%(G1S1C1) and 20%, peak $E_{ll}$ only decreased by 0.01% and 0.04% respectively. But peak $E_{cc}$ decreased by 1.1% and 2.4%. So, peak $E_{ll}$ is less sensitive than peak $E_{cc}$ to the reduction in myocardial contractility. SBP and DBP both decreases with decreasing contractility and none of the cases fall in clinical measurement range, as observed in Figure 5.

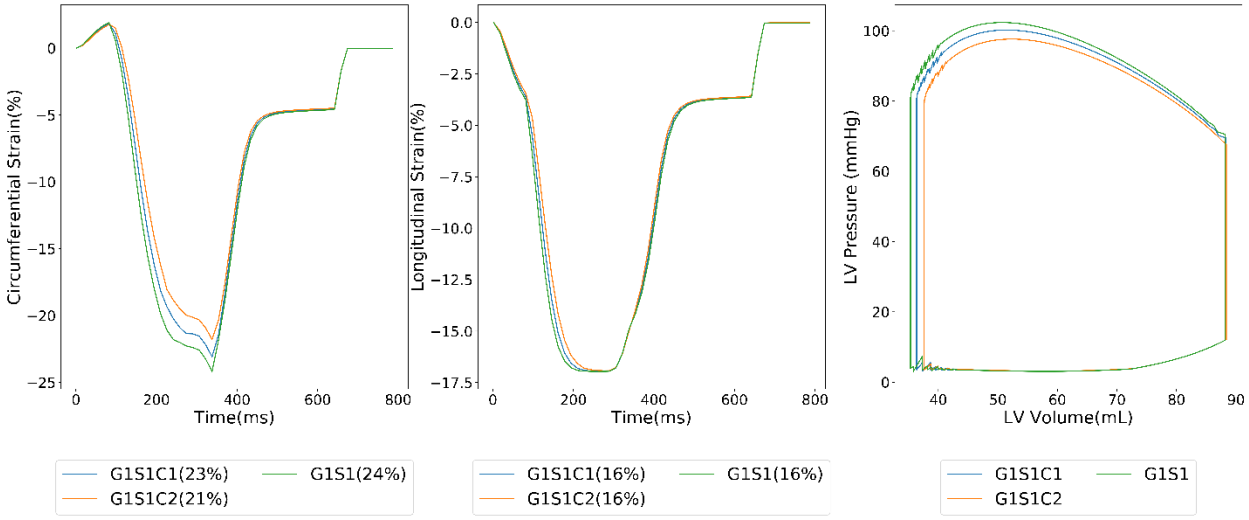


Figure 4. Effect of contractility on a) $E_{cc}$ strain-time profile b) $E_{ll}$ strain-time profile c) Pressure-Volume loop (the values in the legends indicate peak strain)

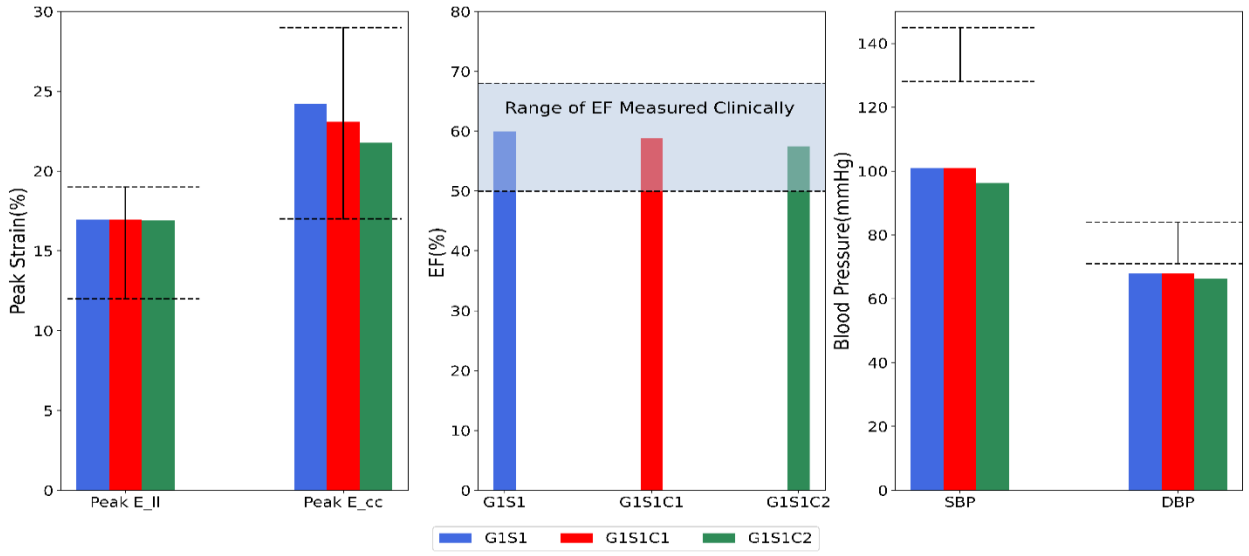


Figure 5. Effect of contractility on peak$E_{cc}$, $E_{ll}$, EF, SBP, DBP compared to clinical values observed in patients

### 4.2.3 Effect of Simultaneous Changes in Contractility and Passive Stiffness

In Figure6 and Figure 7, four particular cases have been shown for geometry 1. It is evident already that both decreasing contractility and increasing stiffness decreases EF. In both cases, reducing contractility too much or making the heart a lot stiffer will cause the EF to be out of clinical measurement range of HFpEF patients. For a change of passive stiffness from 250 Pa to 400 Pa, (Case $G1S1$ to Case $G1S2$) EF decreases by 3.1%. For Stiffness of 250 Pa, a decrease of contractility by 20%, (Case G1S1 to Case G1S1C2) Ef decreases by 2.5%. Combining these two, from Case $G1S1$ to Case $G1S2C2$, EF decreases by 5.4%. We've already seen that peak $E_{ll}$ is less sensitive to the reduction in contractility than peak $E_{cc}$.

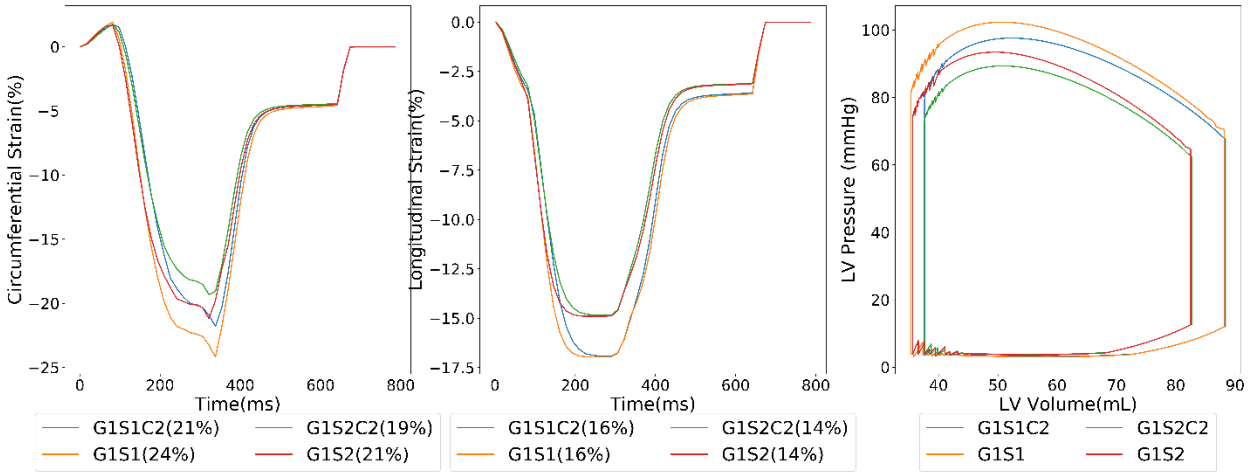


Figure 6. Effect of passive stiffness, contractility on a) $E_{cc}$ strain-time profile b) $E_{ll}$ strain-time profile c) Pressure-Volume loop (the values in the legends indicate peak strain)

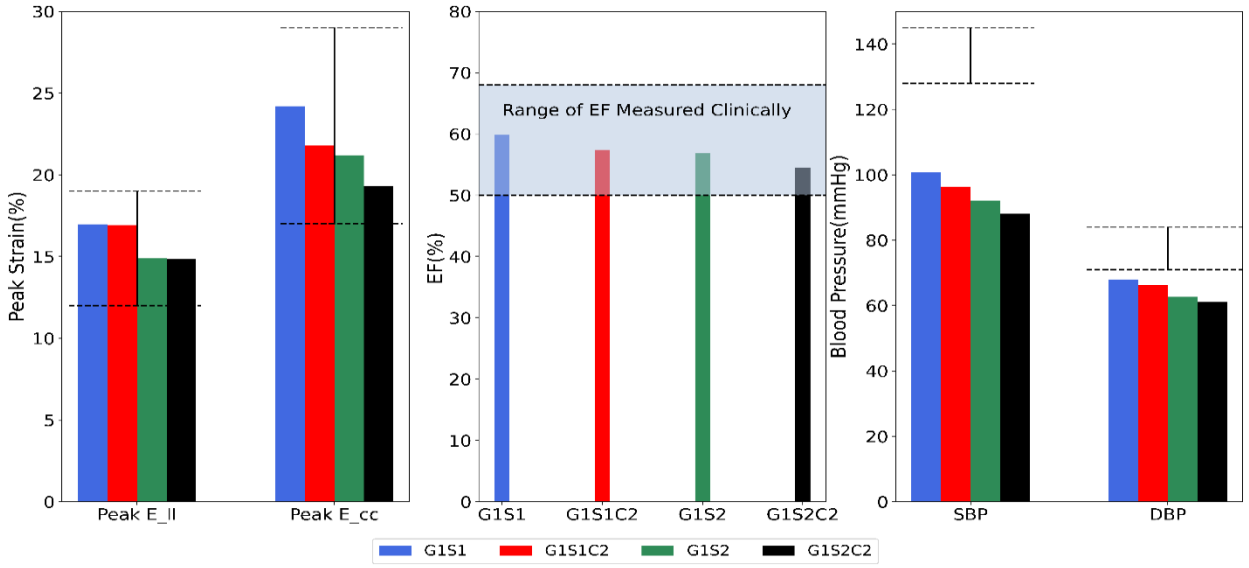


Figure 7.Effect of passive stiffness, contractility on peak$E_{cc}$, $E_{ll}$, EF, SBP, DBP compared to clinical values observed in patients

But both peak $E_{ll}$and peak $E_{cc}$is sensitive to change in stiffness. For a change of passive stiffness from 250 Pa to 400 Pa, (Case $G1S1$ to Case $G1S2$) peak $E_{ll}$decreases by 2.06% and peak $E_{cc}$decreased by 3%. For Stiffness of 250 Pa, a decrease of contractility by 20%, (Case $G1S1$ to Case $G1S1C2$) peak $E_{ll}$decreases by 0.01% and peak $E_{cc}$decreased by 2.4%. Combining these two, from Case $G1S1$ to Case $G1S2C2$, peak $E_{ll}$decreases by 2.11% and peak $E_{cc}$decreased by 4.864%. In all cases, the peak $E_{ll}$was in range of clinical range observed in patients.

### 4.2.4 Effect of Simultaneous Changes in Contractility and Wall Thickness

To understand the effect geometry had alongside contractility, a second geometry with lesser cavity and increased wall thickness and mass was considered (G4). For the increased wall thickness of 1.48 cm from 1.25 cm with smaller LV cavity has EF increased and peak $E_{ll}$ and $E_{cc}$ largely reduced. Figure 8 shows that because of smaller LV cavity both LV volume and LV pressure is reduced. The peak $E_{ll}$ and $E_{cc}$ decreased by 3% and 4% while EF increased by 6% (Figure 9).

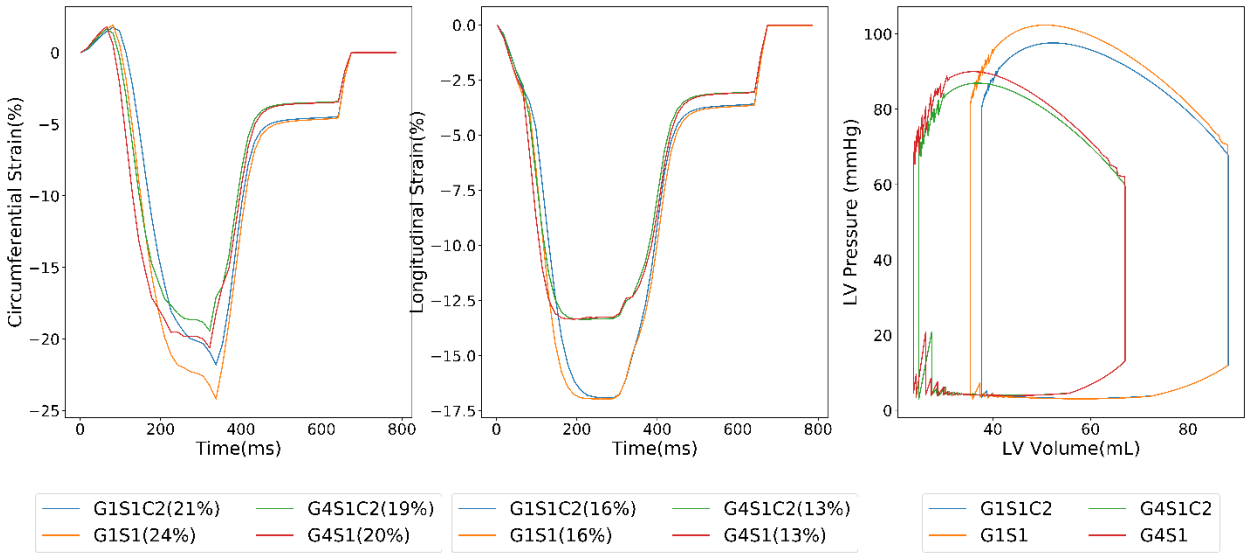


Figure 8. Effect of wall thickness, contractility on a) $E_{cc}$ strain-time profile b) $E_{ll}$ strain-time profile c) Pressure-Volume loop (the values in the legends indicate peak strain)

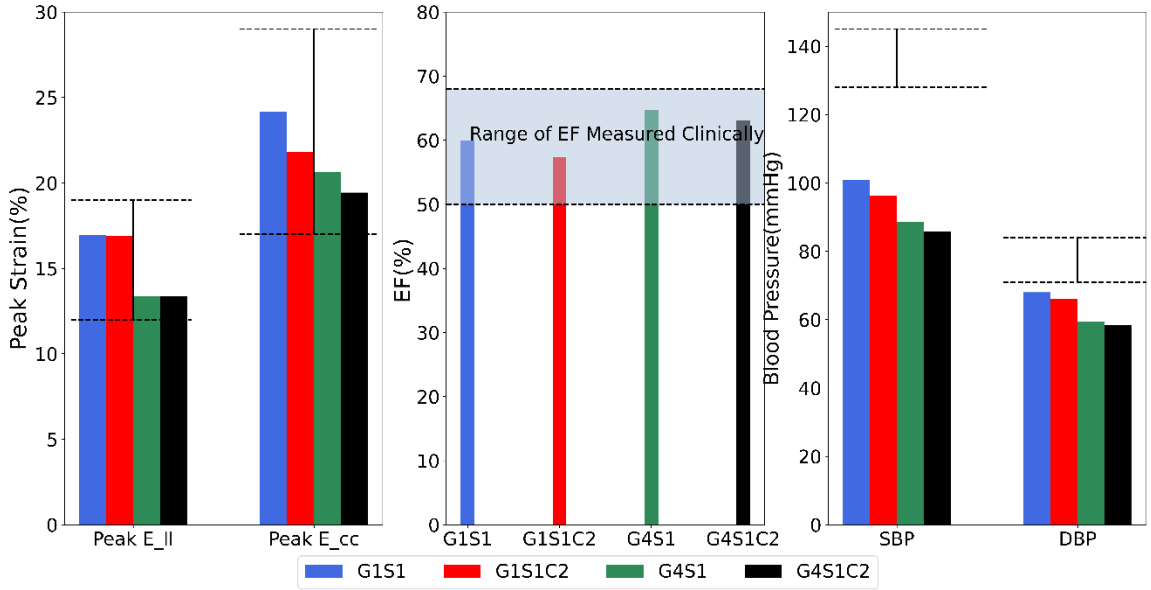


Figure 9. Effect of wall thickness, contractility on peak$E_{cc}$, $E_{ll}$, EF, SBP, DBP compared to clinical values observed in patients

### 4.3 Discussion

For HFpEF patients, the global longitudinal strain and circumferential strain decreases while the ejection fraction is preserved like normal heart. There a sonis, heart can't relax properly, i.e., they renot properly filled with blood even though its pumping job is done properly. So, the reason behind this might be hypertrophy, cardio myocytestiffening etc. Thus, we tried to understand how different parameters can impact blood pressure, longitudinal strain etc. In our study, we tried to understand the individual and simultaneous effect of passive stiffness, wall thickness and myocardial contractility. The model was already validated by Shavik et al. (2021). So, using a validated model for the normal case, we tried to analyze effects of different parameters regarding HFpEF. We tested our hypothesis that passive stiffness might be the reason which prevents heart from relaxing properly and cause impaired LV filling. Thus, we varied stiffness for few cases. We observed that with increasing stiffness, all of EF, peak $E_{cc}$ and $E_{ll}$ decreased. Needless to say, it is completely understandable that with heart getting stiffer, it will have problem relaxing and also pumping blood properly. Thus, the overall LV function worsens. Based on this, we conclude that HFpEF features cannot be explained or modeled by solely changing the passive stiffness, but it certainly affects the LV strains. Next, we have simulated the effect of hypertrophy, in this case, concentric remodeling on the LV strain reduction and preserved EF. To test our hypothesis, we conducted computational analysis for two different geometries with larger wall thickness keeping outer radius same. We observed that with increased wall thickness, the LV EF gradually increased with a reduction in LV longitudinal and circumferential strain. These findings are in agreement with the findings of Morishita et al. (2021)and DH MacIver (2015). Therefore, increased wall thickness alone can't model all the feature of HFpEF but it is one of the causes behind reduced LV peaks trains. Morishita et al. (2021)also suggested that hypertrophy and fiber stiffening are mechanical factors that differentially affect the strains which is also aligned with our findings. Previous studies suggest that LV peak longitudinal and circumferential strains were lower than that of the normal heart (Kraigher-Krainer et al. 2014; Morris et al. 2012). Lastly, we investigated the isolated effect of reduced contractility. Contractility is reduced for a specific LV wall thickness and stiffness. Decreasing contractility understandably reduced the LV EF but, the model showed that in order to match the reduction of peak longitudinal and circumferential strains found in clinical studies, the reduced contractility cannot preserve the LV EF rather the EF falls below the normal range. Thus, we can conclude that reduction in peak longitudinal and circumferential strain for HFpEF cannot be matched by isolated reduction of myocardial contractility.

### 4.4 Model Limitations

While interpreting the findings, we need to consider the potential limitations of our model. First, for simplicity, the LV geometry was assumed as an idealized truncated ellipsoid and because of this, it did not account for asymmetrical geometry, patient- specific variability, or potential interaction with right ventricular. So, there is scope of further studies by considering patient-specific geometries and hemodynamics. Second, regional or transmural myocardial contractility changes are not considered in this study. To understand the effects of transmural myocardial contractility variation in HFpEF requires further research. Thirdly, as clinical measurement was performed under resting conditions, ventricular properties only under resting conditions were considered. Fourth, the possible presence of left atrial (LA) dysfunction effects were not considered. Finally, the data collected from clinical studies contributing in developing the model characteristics do not distinguish between the time period over which HFpEF was developed.

## 5. Conclusion

In our study, a previously developed and validated FE model(Shavik et al. 2021)is used to study the isolated effects of LV geometry, passive stiffness and myocardial contractility on EF and circumferential and longitudinal strains. The simulation cases were compared with the clinical data found in HFpEF patients to replicate the HFpEF features. The increase in passive stiffness, reduction in myocardial contractility and increased wall thickness all can reduce the peak longitudinal and circumferential strain. But isolated change in passive stiffness, contractility or wall thickness cannot reproduce all the clinical features of HFpEF. Isolated change of these three parameters can produce the reduced peak strains observed in HFpEF patients but in all scenarios the systolic and diastolic blood pressure falls below the clinical ranges. Ouranalysisprovideda significant understandingofthemechanismbywhichLV longitudinal and circumferential strains are affected by isolated change in LV passive stiffness, contractility and wall thickness.

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## Biographies

**Sazzad Hossain** has completed his undergraduate degree in Mechanical Engineering in 2022 from Bangladesh University of Engineering and Technology (BUET). His research interests include computational mechanics, scientific machine learning etc.

**Arafat Anzir**has completed his undergraduate degree in Mechanical Engineering in 2022 from Bangladesh University of Engineering and Technology (BUET). His research interests include computational biomechanics, automobiles, renewable energy, CAD.

**Dr. Sheikh Mohammad Shavik**is currently serving as an Assistant Professor of Department of Mechanical Engineering at Bangladesh University of Engineering and Technology. He earned his Ph.D. in Mechanical Engineering from Michigan State Universityand B. Sc. in Mechanical Engineering from Bangladesh University of Engineering and Technology (BUET). His research interests include computational biomechanics, cardiovascular mechanics, developing multi-scale and multi-organ finite element (FE) model of human heart etc.