COMPUTATIONAL ANALYSIS OF ventricular mechanics in Hypertrophic Cardiomyopathy PATIENTS

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**Abstract:**

Hypertrophic cardiomyopathy (HCM) is a genetic heart disease that is associated with many pathological features, such as a reduction in global longitudinal strain (GLS), myofiber disarray and hypertrophy. The effects of these features on LV function are, however, not clear in two phenotypes of HCM, namely, obstructive and non-obstructive. To address this issue, we developed patient specific computational models of the left ventricle (LV) using clinical measurements of 2 female HCM patients and a control subject. Left ventricular mechanics was described using an active stress formulation and myofiber disarray was described using a structural tensor in the constitutive models. Unloaded LV configuration for each subject was first determined from their respective end-diastole LV geometries segmented from the cardiac magnetic resonance images, and an empirical single-beat estimation of the end-diastolic pressure volume relationship. The LV was then connected to a closed-loop circulatory model and calibrated using the clinically measured LV pressure and volume waveforms, peak GLS and blood pressure. Without consideration of myofiber disarray, peak myofiber tension was found to be lowest in the obstructive HCM subject (53kPa), followed by the non-obstructive subject (240kPa) and the control subject (334kPa). With increasing myofiber disarray, we found that peak tension has to increase in the HCM models to match the clinical measurements. In the obstructive HCM patient, however, peak tension is still depressed (cf. normal subject) at the largest degree of myofiber disarray found in the clinic. The computational modeling workflow proposed here can be used in future studies with more HCM patient data.

**Introduction:**

Hypertrophic cardiomyopathy (HCM) is a genetic heart disease that is associated with sudden cardiac death. This disease has a prevalence of 1 per 500 and a mortality rate that is 4-fold higher in young adults than the general US population [1]–[6]. There is no cure for HCM [7]; most treatments (e.g., septal myectomy and pharmacological treatments) are designed to alleviate symptoms and decrease the risk of sudden cardiac death [8]. This disease can be classified generally into two phenotypes based on whether the left ventricular (LV) outflow tract is obstructed (obstructive HCM) or not (non-obstructive HCM) [9], [10]. In both phenotypes, myocardial fiber disarray is a histopathological hallmark [11] that is either confined to some particular region in the LV or is distributed throughout the entire LV. Besides myofiber disarray, HCM is also associated with other key histopathological features such as asymmetrical septal hypertrophy in the LV, changes in the myocardial contractility, and cardiac fibrosis [12]–[20]. These features have been associated with changes in the LV function seen in HCM patients, such as a reduction in (global and segmental) longitudinal and circumferential strains [6], [21]–[23], active tension [24], an increase in relative ATP consumption during tension generation [25], and a reduction in myocardial work [26].

Given the multiple histopathological features present in HCM patients, how each of these features contributes to the changes in the LV function is not clear. Although clinical studies can help reveal abnormalities of myocardial structure (e.g., myofiber disarray) associated with HCM [27], the causal link of these features to LV function is difficult to ascertain in these studies . As such, the relative contribution of these remodeling features (i.e. asymmetrical hypertrophy, myofiber disarray) to the impairment of LV function in HCM patients still remains unclear. Mathematical modeling can help resolve this issue by quantifying the causal effects of the remodeling features to changes in the LV function in HCM patients. In relation to HCM, a few computational models have been developed to investigate the effects of remodeling features on LV function [28], [29]. Specifically, mathematical models based on an idealized ellipsoidal LV geometry has been developed to investigate how regional strain is affected by myofiber disarray [30] and sarcomeric mutation [28]. A study was also conducted on the effects of remodeling features associated with HCM by perturbing the heart geometry of a healthy volunteer [29]. These studies, however, do not consider the difference in LV mechanics between obstructive and non-obstructive HCM and patient-specific LV geometries that encapsulate the heterogeneous distribution of wall thickness associated with this disease. Other computational studies are focused only on obstructive HCM [32][33], but they did not consider the effects of myofiber disarray.

To address these limitations, we developed patient-specific finite element (FE) LV models based on clinical measurements from patients with 2 different types of HCM (obstructive and non-obstructive) and a control subject. These models were constructed based on patient-specific LV geometries that were segmented from cardiac magnetic resonance images of these subjects. The models were coupled to a closed loop circulatory model and calibrated using patient-specific clinical measurements of the LV volume waveform, blood pressures and peak global longitudinal strain (GLS). Contractile function of the cardiac muscle fibers in the 3 subjects were determined by the calibration. The calibrated models were then applied to investigate the effects of different degrees of myofiber disarray on LV function in both the obstructive and non-obstructive HCM subjects.

**Methods:**

***Clinical data:***

Clinical data of 2 female HCM patients (obstructive and non-obstructive) along with a control female subject were acquired from the University of California San Francisco Medical Center. Specifically, the data consists of cardiac magnetic resonance (MR) images, blood pressure measurements and peak global longitudinal strain (GLS) estimated from 3D echocardiographic images. Left ventricular (LV) cavity volume waveform of each subject was estimated by segmenting the endocardial wall from the MR images (**Fig. 1a**) over the cardiac cycle with MeVisLab (MeVis Medical Solutions AG). The clinical data are listed in **Table 1**. In addition to the patient-specific data, we also used published pressure waveforms from HCM patients and healthy human subjects to reconstruct the pressure-volume (PV) loop of each subject [34].

**Table 1:** Clinical measurements of each subject

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| --- | --- | --- | --- |
| **Parameters** | **Control** | **Obstructive** | **Non-obstructive** |
| Age (years) | 69 | 57 | 61 |
| Weight (kg) | 58.1 | 97 | 75 |
| Heart rate (bpm) | 60 | 51 | 66 |
| End diastolic volume (ml) | 63 | 114 | 82 |
| End systolic volume (ml) | 18 | 38 | 12 |
| Ejection fraction (%) | 70 | 66.8 | 85.3 |
| Global longitudinal strain (%) | -20 | -13 | -19 |
| Body surface area (m2) | 1.56 | 2.04 | 1.72 |
| Blood Pressure (mm Hg) | 126/65 | 151/80 | 133/66 |

***Reconstruction of LV FE model:***

Left ventricular endocardial and epicardial surfaces were segmented from the MR images associated with end-diastole (ED) (**Fig. 1b**). Patient-specific 3D LV geometries were then reconstructed from these surfaces and a finite element (FE) mesh was generated for each geometry. The meshes consist of approximately 13000 tetrahedral elements (**Fig. 1c**). Mean myofiber direction (**Fig. 1d**) was prescribed based on a linear transmural variation of the helix angle from +70° at the endocardium to −70° at the epicardium across the LV wall using a Laplace-Dirichlet rule-based algorithm [35].

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| **Figure 1:** Construction of the LV FE model. **a:** MR image segmentation; **b:** Segmented endocardium and epicardium of the LV; **c:** FE model overlaid on the MR image in a long axis view; **d:** Transmural variation of mean myofiber direction across the LV wall; **e:** Schematic representation of LV FE model coupled with a closed loop circulatory model. A sample representation is shown for non-obstructive HCM patient. |

***Computational framework:***

The computational framework consists of the LV FE model, left atrium (LA), the proximal (a,p) and distal (a,d) arterial and venous (ven) compartments that are connected in a closed-loop circulatory system (**Fig. 1e**)[36]–[38]. In the framework, the rate of change of volume in each compartment of the circulatory system is described by the difference between the inflow and outflow rates of the connecting vessels i.e.,

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| --- | --- |
| , | (1a) |
|  | (1b) |
|  | (1c) |
|  | (1d) |
|  | (1e) |

Flow rate associated with the compartments of the circulatory system depends on the prescribed compartment’s resistance (, ,, ,) and the pressure difference across the compartment (i.e., pressure gradient). The flow rates are given as

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| --- | --- |
|  | (2a) |
| , | (2b) |
| , | (2c) |
| , | (2d) |
| , | (2e) |

where and are the resistance of aortic and mitral valve, respectively.

Contraction of the left atrium (LA) was described using a time varying elastance function [39]–[41]. Specifically, pressure in the atria was prescribed to be function of the volume by the following equations

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| --- | --- |
| , | (3a) |
| , | (3b) |
| , | (3c) |
|  | (3d) |

In Eq. (3a-d), is the end-systolic elastance of the atria, is the volume-intercept of the end-systolic pressure volume relationship (ESPVR), and both and are parameters of the end-diastolic pressure volume relationship (EDPVR) of the atria. In the elastance function given in Eq. (3d), and are the time taken to reach maximal chamber elastance and the relaxation time constant, respectively.

On the other hand, pressure in each (arterial and venous) compartment depends on its prescribed compliance and the difference between the instantaneous volume and its prescribed resting volume by

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|  | (4a) |
| , | (4b) |
| , | (4c) |
| , | (4d) |

where, are constants representing the resting volumes and are the total compliance of venous, proximal and distal arteries, respectively. Finally, pressure in the LV, , was calculated from the FE model as described in the next section with the instantaneous volume, , as the input. The ODEs in Eq. (1) were solved using an explicit time integration scheme.

***Finite element model formulation:***

Finite element formulation of the LV model has been described previously [36], [42]–[44]. Briefly, denoting *z* as the apex-to-base axis and *x*, *y* are axes orthogonal to *z*, the functional relationship between pressure and volume of the LV in Eq. (4d) was obtained based on the Lagrangian functional given by,

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| . | (5) |

In the above equation, is the displacement field, is a Lagrange multiplier to enforce incompressibility of the tissue (i.e., Jacobian of the deformation gradient tensor), is the Lagrange multiplier to constrain the LV cavity volume to a prescribed value [45]. Both and are Lagrange multipliers to constrain rigid body translation in *x*, *y* directions and is the Lagrange multiplier to constrain rigid body rotation [46]. The functional relationship between the cavity volumes of the LV to the displacement field is given by,

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|  | (6) |

where is the volume enclosed by the inner surface and the basal surface at , and is the outward unit normal vector.

The first variation of the Lagrangian functional in Eq. (5) leads to the following expression:

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| . | (7) |

In Eq. (7), is the first Piola Kirchhoff stress tensor, is the deformation gradient tensor,,, , ,are the variation of the displacement field, Lagrange multipliers for enforcing incompressibility and volume constraint, zero mean translation along *x* and *y* directions and zero mean rotation along *z* direction, respectively. The Euler-Lagrange problem then becomes finding that satisfies,

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| --- | --- |
|  | (8) |

and (for constraining the basal deformation to be in-plane)

***Incorporation of myofiber disarray:***

Myofiber disarray was incorporated through a structure tensor [47] describing a conical dispersion of myofibers about a mean myofiber direction The structure tensor is given by

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|  | (9) |

where is the identity tensor and is a parameter representing the fiber distribution in an integral sense that describes the degree of anisotropy and myofiber disarray. At the lower limit of the disarray parameter (, myofibers are perfectly aligned along thedirection (i.e., the structure tensor reduces to . At the upper limit of the disarray parameter, the structure tensor reduces to **,** representinga distribution of myofibers that produces an isotropic material response (i.e., a complete myofiber disarray).

***Constitutive relation:***

Mechanical behavior of the LV was described using an active stress formulation in which the first Piola Kirchhoff stress tensorwas decomposed additively into a passive component and an active component (i.e. . The passive stress tensor was defined based on the strain energy function of the Holzapfel-Ogden constitutive model [48]–[50] given as

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| --- | --- |
| where | (10a) |
|  | (10b) |

In Eq. (10b), is the right Cauchy-Green deformation tensor, **F** is deformation gradient, is the structure tensor, are invariantsand with *i* ∈ (*s, n*) is a unit vector in the myocardial fiber (*f* ), sheet (*s* ) and sheet normal (*n* ) directions. The effect of myofiber disarray is incorporated via the invariant. Material parameters of the passive constitutive model are denoted by.

Active stress was calculated based on a previously developed active contraction model [38], [51], [52]. Specifically, the second Piola Kirchhoff stress tensor, is given

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|  | (11a) |

where is the structure tensor, *Tmax* is a scaling parameter that characterizes the myofiber contractility anddenotes the peak intracellular calcium concentration. We note that when (perfect alignment of the myofiber), and the active stress is directed only in the mean myofiber direction The first Piola Kirchhoff active stress tensor is given asLength dependent calcium sensitivity and the variable *Ct* are given by

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|  | (11b) |
| . | (11c) |

In Eq. (11b), *B* is a constant, is the maximum peak intracellular calcium concentration and is the sarcomere length at which no active tension develops. In Eq. (11c), *, and* are the time taken to reach peak tension, the duration of relaxation and the relaxation time constant, respectively. The sarcomere length can be calculated from the myofiber stretch by

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|  | (11d) |
|  | (11e) |

where is the relaxed sarcomere length.

***Simulation cases and protocol:***

For each subject-specific LV FE model, the following simulations were performed sequentially.

1. *Estimating the unloaded geometry:* First, the unloaded LV configuration was estimated from the LV geometry reconstructed from the MR images at ED using a backward displacement method [53]. To do so, passive material parameters in the Holzapfel-Ogden model were calibrated manually so that the EDPVR of the LV FE model matches that derived from the single-beat estimation by Klotz et al.[54], [55], which is also applied for HCM subjects.
2. *Simulation of a beating heart without myofiber disarray ( = 0):* Following the estimation of unloaded geometry,the unloaded LV FE model was coupled to a closed-loop lumped parameter model of the circulatory system to predict cardiac hemodynamics and mechanics. Myofiber contractility parameter *Tmax* in the active contraction model, resistances and compliances in the circulatory model in each subject-specific model were calibrated without myofiber disarray (i.e., = 0) to match the corresponding measured LV pressure and volume waveforms, blood pressure and peak GLS.

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| Fractional Anisotropy & Kappa |
| **Figure 2:** Relationship between fractional anisotropy and myofiber disarray |

1. *Simulation of a beating heart with disarray ( > 0):* Thereafter, the relationship between myofiber disarray (i.e., in **Eq. 9**) and myofiber contractility *Tmax* was investigated in the 2 HCM patients. To do so, different values of was imposed globally into the HCM LV FE models based on fractional anisotropy (FA) measured in HCM patients in previous studies [56]–[58]. The relationship between FA and myofiber disarray is shown in **Fig 2**, and was established by assuming the structure tensor to be equivalent to the diffusion tensor measured in the diffusion-tensor MR images (DTMRI). Following the formulation described in Mukherjee et al [59], the eigenvalues () of the structure tensor were used to compute the FA based on the following relationship:

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|  | (12) |

Based on the reported FA, the range of myofiber disarray parameter considered here lies between 0.0 to 0.22. For each value of myofiber contractility *Tmax* in the active contraction model was adjusted to match the clinical data. We note that the venous resting volume was also adjusted in the obstructive HCM subject in order to keep the EDV at the same value as the measurement.

***Postprocessing of simulation:***

The following quantities were obtained for each simulation of the 3 subjects. Specifically, total normal stress of the myofibers was described by

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|  | (13) |

where is the second Piola-Kirchoff stress and ***H***is the structure tensor. respectively. Normal Green-Lagrange strain of the myofibers was determined by

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|  | (14a) |
|  | (14b) |

We note that in the limiting case  *=* 0 (perfect alignment of myofibers), and . These stress and strain quantities are used to compute the work density of the myofiber over a cardiac cycle by

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|  | (15) |

Global longitudinal strain was calculated from the right Cauchy-Green stretch tensor with end diastole as the reference configuration by [37]

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| --- | --- |
|  | (16) |

***Determination of difference between model prediction and measurements:***

Relative difference between the model predicted EDPVR and the one based on the empirical relationship by Klotz et al.[54], [55] is defined as

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|  | (17) |

where and are the pressure at the same volume and is the number of equally-distributed volume data points in the EDPVR for calculation of the difference. On the other hand, the relative difference between the model predicted and clinical measurements of pressure and volume waveforms over a cardiac cycleis defined as

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| . | (18) |

In Eq. (18), and are, respectively, clinical measurements and model predictions of LV pressure and volume at a particular time point in the cardiac cycle. Also, is the no of equally-distributed time steps over a cardiac cycle used to calculate the difference. Relative difference between clinical measurements and model prediction of peak GLS and blood pressure was also calculated for each subject.

**Results:**

***Clinical data***

End diastolic volume (EDV) was higher in both HCM subjects (Non-obstructive: ) compared to the control subject (). Ejection fraction was highest in the non-obstructive HCM subject and was comparable between obstructive HCM subject () and the control subject (). Absolute peak GLS was reduced substantially in the obstructive HCM subject (, but was comparable between the obstructive HCM subject (and the control subject ().

***LV geometry***

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| **Figure 3 a.** LV geometry of the 3 subjects. **b.** Regional distribution of wall thickness (in cm) based on AHA segmentation and **c.** Violin plot of the wall thickness |

Left ventricular geometries reconstructed from the MR images as well as the regional wall thickness based on AHA segmentation for each subject are shown in **Fig. 3**. Septum wall thickness of the obstructive HCM subject ( cm) was largest followed by that of the non-obstructive HCM subject ( cm) and the control subject ( cm). In each HCM subject, LV free wall thickness was smaller (cf. septum), but was larger when compared to the same region in the control subject (Obstructive HCM: cm; Non-Obstructive HCM: cm; Control: cm). The resultant global wall thickness was higher in the HCM subjects compared to the control (Obstructive HCM: cm; Non-Obstructive HCM: cm; Control: cm).

***LV mechanics without consideration of myofiber disarray:***

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| **Figure 4**: Calibration of model parameters for each subject without myofiber disarray. **a.** EDPVR **b.** Volume waveform **c.** Pressure waveform **d.** PV loop **e.** Peak GLS **f.** Difference between model prediction and measurements. |

The calibrated models’ prediction of the EDPVR relationship is consistent with that obtained from the single-beat estimation based on the Klotz relationship (**Fig. 4a**). The calibrated models’ predictions of LV volume waveform, blood pressure and peak GLS also agree with the corresponding patient-specific clinical measurements (**Fig 4b - e**). While LV pressure was not measured in these subjects, the pressure waveforms predicted by the model are also comparable with measurements from previous clinical studies of HCM patients. Differences between the measurements and the model predictions are within about 10%, with the highest difference occurring in the comparison between the EDPVR derived from the empirical Klotz relationship and the model (**Fig. 4f**).

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| **Figure 5a.** Isometric tension plot; regional distribution of **b.** peak total fiber stress (in kPa) and **c.** peak longitudinal strain (absolute value in %) for each subject |

Peak (isometric) myofiber tension derived from the calibrated active stress model parameters was found to be substantially smaller in the HCM subjects when compared to the control subject (**Fig. 5a**). The obstructive HCM subject has the smallest peak myofiber tension of 53kPa and the non-obstructive HCM subject has a peak myofiber tension of 240kPa, which were both lower compared to that of the control subject (334kPa). The time to peak tension was also higher in the HCM subjects than the control subject. Peak myofiber stress averaged over the entire LV was smallest in the obstructive HCM subject ( kPa) followed by non-obstructive HCM subject ( kPa) and the control subject ( kPa) (**Fig. 5b**). Peak myofiber stress was lower at the septum than the LVFW in both HCM subjects, with the lowest value found in the obstructive HCM subject. Peak GLS was lower in the entire LV of the obstructive HCM subject compared to the other 2 subjects (**Fig 5c**). Longitudinal strain was higher at the LVFW ( ) compared to the septum () in the obstructive HCM subject. In the other 2 subjects, however, the difference between longitudinal strain at the septum and LVFW was not prominent (Control: septum vs. LVFW; non-obstructive HCM: septum vs LVFW).

Total myofiber work density (indexed by the area of the stress-strain loop along material direction) was lowest in the obstructive HCM subject (47.2 mmHg), followed by the non-obstructive HCM subject (86.4 mmHg) and the control subject (88.0 mmHg) (**Fig 6**). In terms of its regional distribution, myofiber work density was higher at the LVFW (control: 114.9 mmHg; non-obstructive: 94.4 mmHg; obstructive: 56.5mmHg) compared to the septum (control: 66.2 mmHg; non-obstructive: 74.4 mmHg; obstructive: 41.0 mmHg) for all subjects.

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| **Figure 6:** Work densities in the HCM and control subjects without myofiber disarray. **a.** stress-strain loop along mean fiber direction, **b.** regional distribution of myofiber work density. |

***Effects of myofiber disarray on the LV mechanics of HCM subjects***

With an increase in myofiber disarray, it is necessary to increase the scaling parameter *Tmax* (associated with myofiber contractility) to match the clinical data of the HCM subjects (see **Appendix A**). The resultant peak myofiber tension was therefore increased as a result with increasing myofiber disarray (**Fig.7**). Specifically, peak myofiber tension associated with the largest degree of disarraywas and for the non-obstructive and obstructive HCM patients, respectively. Peak GLS did not change substantially (~3%) with increasing myofiber disarray in both HCM subjects. Regional distribution of peak longitudinal strain, peak stress of the myofibers also did not change with different degree of myofiber disarray. In the obstructive HCM subject, peak stress of the myofibers was decreased in both LVFW and septum with increasing myofiber disarray (**Fig.7d**). Conversely in the non-obstructive HCM subject, peak stress of the myofibers was slightly increased with increasing myofiber disarray (**Fig.7e**).

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| **Figure 7**: Effects of myofiber disarray. Isometric tension-time plot of **a.** non-obstructive and **b.** obstructive HCM subjects. **c.** Peak GLS for the 2 HCM subjects. Peak stress of the myofibers at the septum and LVFW for **d.** obstructive and **e.** non**-**obstructive HCM subjects. |

Myofiber work density was reduced with increasing myofiber disarray in both non-obstructive HCM subject and obstructive HCM subject (Fig. 8a, b). The reduction in myofiber work density was highest in the septum and lowest in the anterior wall in the non-obstructive HCM subject (Septum: -73% ; Anterior: -70% at cf. . On the other hand, in obstructive HCM subject, posterior and LVFW regions have the highest and lowest reduction in myofiber work density, respectively (Posterior: -87% ; Anterior: -82% at cf. .

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| **Figure 8**: Effects of myofiber disarray on myofiber work densities for **a.** the non-obstructive and **b.** the obstructive HCM subject. |

**Discussion:**

We have developed a patient-specific computational framework of LV mechanics to investigate the effects of myofiber disarray using clinical data of 2 HCM subjects with different phenotypes (obstructive vs non-obstructive) along with a control subject. The key finding of this study suggests that the contractile force generated by the cardiac muscle cell is reduced in the obstructive HCM subject compared to the control subject. In the non-obstructive HCM subject, the contractile force is reduced only if the degree of global myofiber disarray is less than 0.14. Specifically, the study found that the contractile force generated by the cell to reproduce the clinical measurements is increased with an increase in global myofiber disarray. An increase in myofiber disarray led to a reduction in myofiber work density in both HCM subjects.

***LV wall thickness***

The reconstructed LV geometries of the HCM subjects are consistent with those reported in previous clinical studies. Specifically, the maximum LV wall thickness in the obstructive and non-obstructive HCM subjects are 17.4mm and 12.3 mm at the mid posterior and basal anterior wall, respectively. These values are consistent with previous studies [60], [61]. The ratio of maximum septum wall thickness to minimum posterior wall thickness for the non-obstructive (1.9) and obstructive (1.54) HCM subjects are also within the threshold (≥ 1.3) used to define asymmetric septal hypertrophy in HCM patients [62].

***LV function***

Both HCM subjects have higher EDV than the control subject (**Fig 3**), with the highest value found in the obstructive HCM subject. Ejection fraction is normal (67%) and supra-normal (85%) for the obstructive and non-obstructive HCM subjects, respectively. The supra-normal EF in the non-obstructive HCM patient is a result of its small ESV. Peak GLS is slightly smaller in the non-obstructive HCM subject (19%) compared to the control subject (20%), but is substantially smaller in the obstructive HCM subject (13%). The smaller peak GLS in the obstructive HCM subject is within the range of -9.65% to -16% reported in previous studies [21], [63]. It has been suggested in some studies that peak GLS is a sensitive indicator of global LV function as well as a prognostic marker to predict mortality and cardiac events in HCM and heart failure with preserved ejection fraction (HFpEF) [64]–[67]. It is, however, not quite clear the mechanism by which GLS is associated to LV function and mortality.

The results suggest that the reduction in peak GLS is associated with a reduction in myofiber contractility that is indexed by the peak muscle fiber tension. Without considering myofiber disarray, the models predicted that the peak tension to reproduce the clinical measurements is, respectively, 7% (absolute) and 1% (absolute) smaller in the obstructive and non-obstructive HCM subject when compared to the control subject. By considering myofiber disarray based on the range found in DTMRI studies with having values between 0 to, we found that the peak muscle fiber tension has to increase to compensate for an increasing degree of myofiber disarray in order to reproduce the clinical measurements. Within this range of , peak GLS varies by only +/- 2% (absolute) in the obstructive HCM subject and is still depressed compared to the control subject (**Fig 7c**). At the highest degree of myofiber disarray in the obstructive HCM subject, however, the peak muscle fiber tension is still about 72.8 % (absolute) lower than that in the control subject. For the non-obstructive HCM subject, we found that the peak muscle fiber tension is equivalent to the control subject at a disarray = 0.14. At that value of , peak GLS is -18 % and lies within the ranges reported previously [68], [69]. These findings therefore suggest myocardial contractility is likely reduced in the HCM subjects, especially in the obstructive phenotype, which can explain the results of a previous MRI study on HCM patients showing that a reduction in FA is associated with a reduction in myocardial strain [57].

The finding that a reduced peak GLS is associated with a reduction in myocardial contractility even with a normal EF is consistent with a previous modeling study based an idealized LV geometry[36]. In that study, only a reduction in myocardial contractility can explain the simultaneous features (including a reduction in GLS) found in patients with HFpEF. Specific to HCM, a reduction in myocardial contractility has also been found in animal studies and is attributed to the mutation of sarcomeric protein [70] [71]. For example, a small molecule, MYK-461, is identified in a mouse model of HCM that reduces contractility by decreasing the adenosine triphosphatase activity of the cardiac myosin heavy chain [72]. The lower peak tension found here is also consistent with the reduced myofibril density found in vitro studies of myocytes obtained from myocardial biopsies of HCM patients [73].

***Myofiber stress:***

Peak stress of the myofibers is heterogeneously distributed in the LV (**Fig 5b**). Compared to the control subject, peak myofiber stress is smaller in the HCM subjects, and is smallest in the obstructive HCM subject. This result is largely due to the increase in wall thickness in the HCM subject, and is consistent with previous studies of HCM patients [32], [74] . Peak myofiber wall stress is also lower in the septum (thicker region) than LVFW (thinner region) in all subjects. Between non-obstructive and obstructive HCM subjects, peak stress of the myofibers behaves differently with increasing myofiber disarray (**Fig. 5d, e**). With an increase in myofiber disarray, peak stress of the myofibers increases in the non-obstructive HCM subject, but decreases in obstructive HCM subject. This result suggests that the effects of myofiber disarray on myofiber stress may be sensitive to geometry.

***Distribution of work:***

Global myocardial work density, indexed by the pressure volume area, is linearly correlated to the cardiac metabolism and total myocardial oxygen consumption[75]–[77]. Local myofiber work density is determined from the area in the average myofiber stress-strain loop (**Fig 6**). Without consideration of myofiber disarray, our analysis shows that the control subject has the highest mean (87.8 mmHg), followed by the non-obstructive HCM subject (86.4mmHg), and the obstructive HCM subject (47.2 mmHg). With disarray where cardiac muscles are oriented in other directions other than the mean myofiber direction, decreases with increasing degree of myofiber disarray in both HCM subjects (**Fig 8**). These results showing a lower in the obstructive HCM subject than the non-obstructive HCM subject (and the normal) is consistent with published results of myocardial work index (pressure-strain loop area) assessed noninvasively using echocardiography and blood pressure measurement in HCM patients [78], [79]. The findings that septal is lower than that in the LVFW is also consistent with these studies, especially when in HCM phenotypes with substantial septal hypertrophy. We note that is defined differently from the myocardial work index measured in the clinic as the latter relies on a global index of stress (i.e., pressure) rather than the local stress of the myofibers. Nevertheless, both of these indices are metric of the total work of the myofiber over a cardiac cycle. Our finding suggests that the development of myofiber disarray further worsens the already lower myofiber work in the HCM subjects, further suggesting that this feature is a contributor to the lower myocardial work index found clinically in HCM patients. The lower work arises because myofibers are disoriented and not contributing efficiently to the overall contraction of the heart (e.g., myofibers oriented in the radial directions are not performing work when the wall thickens during contraction). Therefore, myofiber disarray is one of the key contributor to the worsening of myocardial work in HCM patients (in addition to other features such as mechanical dyssynchrony).

**Limitation:**

There are some limitations associated with this study. ***First***, this is a pilot study using only 2 HCM subjects with 2 broadly different phenotypes (i.e., obstructive and non-obstructive HCM). As such, the results can only provide some indications on the mechanics as well as the relationship between myofiber disarray on myofiber contractility in HCM. Nevertheless, the study can be extended in future to consider the broad range of disease pattern and variation of morphological phenotypes (such as apical hypertrophy) found in HCM patients. ***Second,*** we assumed a conical dispersion of the myofiber along a mean direction, and did not consider diffused and regional myofiber disarray that may be present in HCM patients. Local DTMRI measurements of myofiber disarray in HCM patients can be incorporated into the model in future studies. ***Third,*** we did not consider the presence of local or diffuse fibrosis in HCM. Patient-specific cardiac magnetic resonance imaging with late gadolinium enhancement can be used to quantify local fibrosis, that in turn, can be applied into the model. ***Last,***we assumed that homogeneous contraction of the heart in this study, and did not consider the presence of mechanical dyssynchrony that can occur in HCM [80]. Mechanical dyssynchrony can be considered in future studies using an electromechanics model [42], [43].

**Conclusion:**

We have developed patient-specific computational models based on clinical data acquired in 2 HCM (obstructive and non-obstructive) and a control subject to investigate LV mechanics and the relationship between myofiber disarray and myofiber contractility in this disease. Using these models, we show that myofiber contractility must increase to compensate for an increase in myofiber disarray associated with HCM in order to maintain same LV function. For the range of myofiber disarray measured in HCM patients, however, we found that the myofiber contractility in the obstructive HCM subject is still reduced compared to the control subject at the highest degree of myofiber disarray. Myofiber contractility of the non-obstructive HCM subject is close to that of the control subject only when myofiber disarray is substantial with a fractional anisotropy of 0.75. An increase in myofiber disarray also led to a reduction in myofiber work in the HCM subjects. These findings suggest that myofiber contractility is reduced in HCM patients, and the reduction in myofiber work seen in HCM patients may be due in part to myofiber disarray.

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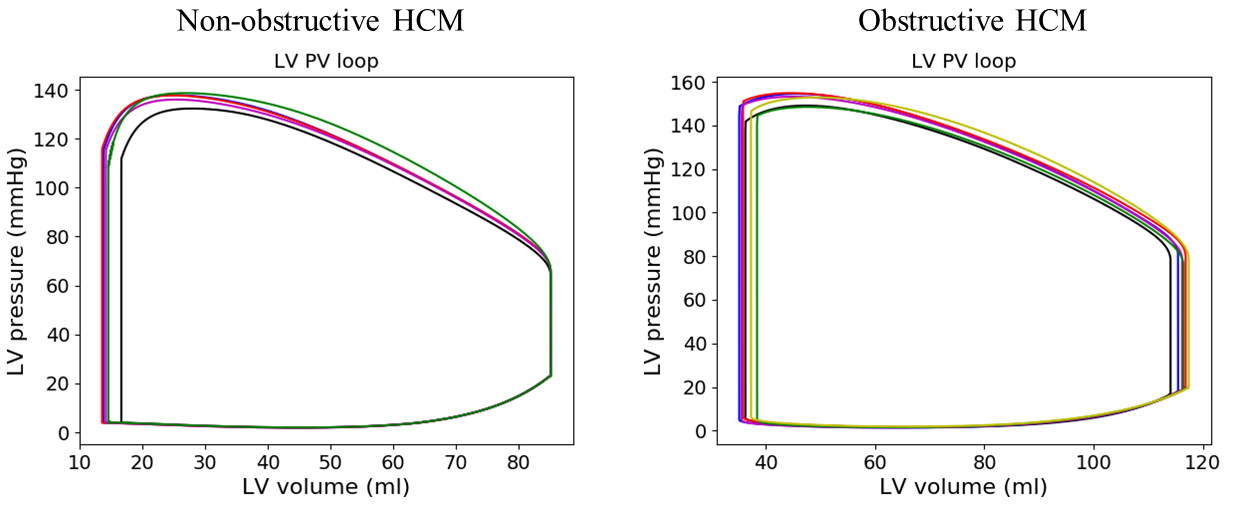
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**Appendix:**

**A: PV Loop for Obstructive & non-obstructive HCM cohorts**



**B. Model parameters without disarray**

The calibrated passive and active material described in Eq. 10 and Eq. 11, respectively, are enlisted in Table B.1.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **B.1: Material parameters** | | | | |
| Parameters | Unit | Control | Non-obstructive | Obstructive |
| **Holzapfel-Ogden model** | | | | |
| a |  | 46 | 400 | 200 |
| b |  | 12 | 5 | 4 |
|  |  | 7.51e03 | 37.5 | 15 |
|  |  | 5.893 | 1.47325 | 22.1 |
|  |  | 492 | 492 | 492 |
|  |  | 3.393 | 3.393 | 3.393 |
|  |  | 70 | 70 | 70 |
|  |  | 3.929 | 3.929 | 3.929 |
| **Guccione model** | | | | |
|  |  | 850000 | 800000 | 88350 |
|  |  | 25 | 40 | 35 |
|  |  | 360 | 400 | 420 |
| B |  | 4.75 | 4.75 | 4.75 |
|  |  | 600 | 800 | 450 |
|  |  | 1.55 | 1.55 | 1.55 |
|  |  | 4.35 | 4.35 | 4.35 |
|  |  | 4.35 | 4.35 | 4.35 |
|  |  | 1.85 | 1.85 | 1.85 |
| BCL |  | 1000 | 910 | 1180 |

The model parameters prescribed in circulatory model and time varying elastance model are enlisted in Table B.2.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **B.2: Circulatory and left atrium model parameters** | | | | |
| Parameter | Unit | Control | Non-obstructive | Obstructive |
| **Circulatory model** | | | | |
|  |  | 0.00208 | 0.00544 | 0.0048 |
|  |  | 0.2145 | 0.0561 | 0.0495 |
|  |  | 0.196 | 0.378 | 0.014 |
|  |  | 144 | 144 | 306 |
|  |  | 160 | 160 | 160 |
|  |  | 4500 | 3100 | 4500 |
|  |  | 3000 | 3000 | 4500 |
|  |  | 10 | 10 | 100 |
|  |  | 108000 | 90000 | 45000 |
|  |  | 127200 | 84800 | 159000 |
|  |  | 1000 | 1000 | 1000 |
| **Time varying elastance model** | | | | |
|  |  | 9 | 7 | 10 |
|  |  | 0.801 | 0.6675 | 4.005 |
|  |  | 0.0152 | 0.00475 | 0.019 |
|  |  | 10 | 10 | 10 |
|  |  | 120 | 120 | 150 |
|  |  | 25 | 25 | 25 |
|  |  | 140 | 140 | 140 |

**C. Model parameters with disarray**

The model parameters calibrated to match with clinical volume waveform and blood pressure with varying degree of disarray for 2 HCM subjects are listed below. Noted, the rest of the model parameters are same as described in Appendix B.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Parameter | Unit |  |  |  |  |  |
| **Obstructive HCM** | | | | | | |
|  |  | 90.25 | 95 | 104.5 | 114 | 152 |
|  |  | 4550 | 4640 | 4660 | 4660 | 4660 |
| **Non-obstructive HCM** | | | | | | |
|  |  | 1040 | 1080 | 1200 | 2800 |  |