Thesis title: Computational analysis of the mechanics of heart failure with preserved ejection fraction (HFpEF)

Student name: Jijo Derick Abraham

IIT D Entry number: 2020QIZ8588, UQ Student number: 46571179

Department: UQ-IIT D Research Academy, Department of Mechanical Engineering.

Abstract

Heart failure, defined as the heart's inability to pump an adequate amount of blood to meet the metabolic requirements of the body, is one of the leading causes of death worldwide. Heart failure with preserved ejection (HFpEF) is a rapidly increasing epidemic variant of heart failure in which the left ventricle (LV) of the patient exhibits a normal range (above 50%) of ejection fraction (EF). The current prevalence of HFpEF patients is more than 50 % among the heart failure patient population. Due to the lack of clarity about the pathophysiology of HFpEF, extremely limited treatment options are available for this heterogeneous disease. Hence, there is a pressing need to understand the underlying mechanism of this increasingly prevalent public health problem. Hence, there is a pressing need to understand the underlying mechanism of this increasingly prevalent public health problem.

The review of the literature shows that various pathological factors, including LV diastolic dysfunction and LV systolic dysfunction, right ventricle (RV) dysfunctions, pulmonary hypertension, left atrial dysfunctions, and chronotropic incompetence, have roles in HFpEF prognosis. However, the isolated influence of each abnormality on cardiac function in the context of HFpEF is unclear. Moreover, among the various symptoms of HFpEF, exercise intolerance is the most hazardous one, linked to a higher rate of hospitalisations and mortality. Understanding the underlying mechanics of exercise intolerance in HFpEF is crucial in controlling the mortality burden.

The current understanding of HFpEF is mainly established through clinical trials and experiments, which are often limited by various practical constraints. This dissertation employs a computational framework consisting of a finite element (FE) model of the heart ventricle coupled to a zero-dimensional model of the circulatory system to analyse the underlying mechanics of HFpEF, which is practically challenging via clinical studies. The FE model of the heart ventricle was solved using the open-source FE solver FEniCS. The framework utilises the active-stress formulation to couple the active and passive behaviours of the myocardial tissues.

Firstly, this work modified a previous single ventricle (i.e., LV) coupled computational framework by implementing the orthotropic Holzapfel-Ogden constitutive model in place of the transversely isotropic Guccione model. Further, the simulation parameters and LV dimensions are calibrated to establish a control case. With this validated approach, the study analysed the effect of different LV remodelling patterns, specifically concentric remodelling (CR), concentric hypertrophy (CH), and eccentric hypertrophy (EH), with and without LV wall thickening, on LV functional indices. Further, the geometries with a moderate level of remodelling from each pattern are subjected to fibre stiffening and contractile impairment to examine their effect in replicating the different features of HFpEF. The results show that the LV remodelling patterns play a crucial role in exhibiting characteristics of subtypes of HFpEF based on EF, which are reported in the recent clinical literature. With severe CR, LV could exhibit the characteristics of HFpEF with higher EF, as observed in the clinical studies. Controlled fibre stiffening can simultaneously increase the end-diastolic pressure and reduce the peak longitudinal strain without a significant reduction in EF, facilitating the moderate CR geometries to fit

into this phenotype. Similarly, fibre stiffening can assist the CH and 'EH with wall thickening' cases to replicate HFpEF with lower EF. These findings suggest that potential treatment for these two phenotypic groups should target the biological origins of their distinct ventricular remodelling patterns and the extent of myocardial stiffening.

Secondly, the input parameter to the computational framework used in the first part of the thesis is tailored to mimic various physiological changes happening during exercise. This approach was able to match the simulation output with the rest, and the three stages of exercise corresponding to the control case reported in the literature. With this simulation approach, the study analysed the isolated role of four abnormalities, namely, LV stiffening, high preload, chronotropic incompetence and LV remodelling on LV function during rest and 60% exercise conditions. Further, the combinations of these abnormalities were simulated to check their effectiveness in achieving the HFpEF thresholds. The results show that the simultaneous occurrence of LV stiffening and higher venous return is necessary to replicate the LV functions observed in the case of exercise intolerance in HFpEF. Although LV stiffening can worsen the LV function, which is favourable for inducing HFpEF, it cannot attain the thresholds of abnormal filling pressure during exercise without high venous return. The high venous return is the major driver for abnormal filling pressure during exercise observed in HFpEF. The remodelling majorly influences the range of EF in rest within the context of HFpEF. The reduction in heart rate is found to cause a decrease in cardiac output and an increase in filling pressure, despite a slight increase in stroke volume and strain. The study computationally predicts that the treatment for exercise intolerance in HFpEF should primarily target the reduction of venous return and LV stiffness, increasing the heart rate and reversing the LV remodelling.

Finally, the exercise simulation approach was extended to a coupled computational framework comprising a FE model of a biventricle, a lumped model having separate loops for the pulmonary and systemic circulatory networks. The validated approach was utilised to investigate the isolated role of RV abnormalities, namely RV stiffening, RV contractile dysfunction, and RV remodelling (i.e., RV CH, RV CR and RV EH) on biventricular performance in the context of HFpEF. Further, the study analysed the role of three forms of pulmonary hypertension (i.e., pulmonary arterial hypertension, pulmonary venous hypertension, and combined pre-capillary and post-capillary hypertension), as well as increased stressed blood volume at the systemic vein and pulmonary network. The results showed that pulmonary arterial hypertension can induce higher wall stress in the RV and reduce cardiac output. The adaptation in the form of RV CH can reverse the stress and compensate for cardiac output. The RV function worsens if the adaptation turns into RV CR and then RV EH. RV myocardial dysfunction in the form of stiffening is more favourable in inducing HFpEF than contractile impairment. Further, the study demonstrates that in comparison to pulmonary stressed blood volume, the systemic venous stressed blood volume has greater potential to raise the LV end-diastolic pressure, which can cause exertional dyspnoea.

Overall, the thesis provides important insights into the underlying mechanics of HFpEF, which could have significant clinical implications in advancing HFpEF diagnosis and treatment methods. The thesis also identifies new research avenues, such as model improvement by incorporating renal compartments, dynamic exercising loops and fluid-structure interaction modules for investigating left atrial dysfunctions and treatment testing.