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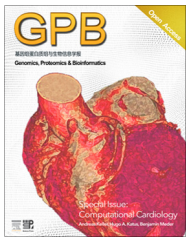

ORIGINAL RESEARCH

Personalized Computer Simulation of Diastolic Function in Heart Failure

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Abstract The search for a parameter representing left ventricular relaxation from non-invasive and invasive diagnostic tools has been extensive, since heart failure (HF) with preserved ejection fraction (HF-pEF) is a global health problem. We explore here the feasibility using patient-specific cardiac computer modeling to capture diastolic parameters in patients suffering from different degrees of systolic HF. Fifty eight patients with idiopathic **dilated cardiomyopathy** have undergone thorough clinical evaluation, including cardiac magnetic resonance imaging (MRI), heart catheterization, echocardiography, and cardiac biomarker assessment. A previously-introduced framework for

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creating multi-scale patient-specific cardiac models has been applied on all these patients. Novel parameters, such as global stiffness factor and maximum left ventricular active stress, representing cardiac active and passive tissue properties have been computed for all patients. Invasive pressure measurements from heart catheterization were then used to evaluate ventricular relaxation using the time constant of isovolumic relaxation **Tau** (τ). Parameters from heart catheterization and the multi-scale model have been evaluated and compared to patient clinical presentation. The model parameter global stiffness factor, representing diastolic passive tissue properties, is correlated significantly across the patient population with τ. This study shows that multi-modal cardiac models can successfully capture **diastolic (dys) function**, a prerequisite for future clinical trials on HF-pEF.

Introduction

The application of computational modeling to different organ systems has been gathering increasing interest from the research community. The possibility of performing *in silico* experiments on computer models that mimic patient's organs has revved up the momentum of the evolution of virtual patient-specific models. The surge of interest has been driven by the prospect of being able to control all the variables to open up new possibilities toward better health care in a risk-free and ethically acceptable setting for the patient. The exponential growth of computational imaging capacities has also broadened the possibilities toward such models. From simplistic models based on geometric shapes as early as the 1960s to multi-scale multi-physics models, the transformation in this field has been tremendous [1–6].

Heart failure (HF) remains the leading cause of death in developed countries [7–9]. The increasingly high incidence rates, hospitalization, and health expenditures compel a constant call for new strategies and progress in this field [10]. HF is a syndrome with diverse etiologies, characterized by the decline of cardiac systolic or diastolic function, resulting in insufficient blood supply to organs, organ dysfunction, and finally, failure [11–13].

A chronological retrospective analysis of HF therapy in patients with dilated cardiomyopathy (DCM) in the last century sheds light on difficulties in treating this disease. Expert guidelines currently outline HF therapy based on patients' clinical presentation, cardiac systolic function, and specific biomarkers, but oversee, to some extent, the pathophysiology and etiology that lead to reduced cardiac function [13]. These rigid therapy regimes focus on relieving cardiac symptoms and tackle less the individual progression and the cause leading to this disease. Over the past three decades, drug therapy has undergone rapid progression in lowering the mortality and morbidity rates in HF patients [14]. The mortality rates of patients that present with progressed HF symptoms and receive optimal medical therapy remain high [14,15]. Even the latest drug advancements present only a stepping stone toward the treatment of HF. The diversity of this disease, in its etiology and clinical presentation, suggests that the key to a better and cost-effective therapy is the individualized and personalized care. Personalized cardiac models have the potential in facilitating the achievement of this goal [16,17].

The role of left ventricular (LV) systolic dysfunction has attracted broad attention from both clinical and experimental researchers [18–23]. On the other hand, LV diastolic dysfunction has been relatively slow in gathering interest due to its complex role in the pathomechanism of HF [24,25]. General consensus defines LV diastolic dysfunction as irregular cardiac functional relaxation, distensibility, and LV filling, which causes higher end diastolic left ventricular pressures [26]. To completely understand the pathogenesis of diastolic dysfunction, a broad appreciation of cardiac physiology in the diastole and its diverse compensation mechanisms is needed. Dyspnea, as a symptom of HF, is often attributed to diastolic dysfunction after exclusion of other probable causes [27–30]. Its diagnosis remains a challenge in clinical settings because of the difficulties present in linearly quantifying the progression of this disease and assessing its significance to the patient [31]. The current non-invasive gold standard for the assessment of diastolic dysfunction remains the echocardiographic evaluation, especially Doppler measurements of transmitral flow and tissue Doppler imaging (TDI) [26].

The progress in the field of cardiac simulation has been on a rise in the last decade [32]. One of the first challenges in cardiac modeling is capturing the anatomical geometry of the heart. Simulating cardiac physical parameters relies heavily on ventricular geometry. Many of the early-proposed cardiac anatomical estimations were either based on geometrical models or post-mortem heart dissections. The first simplifications of the complex LV geometry have been based on spherical models [33]. Koushanpour and colleagues published one of the early simulations of LV dynamics based on spheroids in 1960s [34]. In this study, they compared the LV time course of tension using Laplace's surface tension law in cats and turtles. Their findings highlighted the importance of cardiac size and shape in determining LV function. A gradual shift toward anatomical models, based on *ex vivo* human and animal hearts, could be observed, capturing a more accurate representation of cardiac anatomy [35–37].

Progress in other fields of science, especially in physics and mathematics, and advancements in computer technology opened up new possibilities toward improving existing computer simulations. The application of the finite element method in diverse sectors of engineering represented one of the major turning points in cardiac computational modeling and simulation. The conception and refinement of this method enabled the analysis of complex structural and mathematical problems [38,39]. Janz et al. introduced one of the early cardiac mechanical models using the finite element method [40]. The cardiac model, in which the anatomical geometry is estimated from the hearts of Sprague–Dawley albino male rats, seemed to predict the gross free wall deformation with the assumption of an elastically linear and heterogeneous tissue [40]. Vinson et al. later described a human cardiac model using "36 brick type finite elements" representing the left ventricle [40]. As pointed out by the authors, one of the limiting factors at that time was