STRUCTURALLY-DRIVEN CONSTITUTIVE MODELLING OF PASSIVE MYOCARDIUM IN HEART FAILURE

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SUMMARY

Most constitutive models of passive myocardium are formulated based on the functional form of non-linear stress-strain data. Although such constitutive models can reproduce the overall mechanical behaviour of myocardium, they generally do not reflect the microstructural and material changes that occur as myocardium progressively remodels during growth or disease. The present study proposes a novel structurally-motivated constitutive model of passive myocardium that directly links quantitative characteristics of myocardial collagen organisation to the mechanical function of the heart. As such, it provides insight into the biophysical relationship between structure and function of the myocardium.

Key words: *cardiac modelling, tissue mechanics, collagen morphology, heart failure*

1 INTRODUCTION

Heart failure (HF) is one of the most deadly and costly conditions in the developed world, despite the wide variety of research in medicine and improvements in clinical management. The pathological process of HF is associated with microstructural remodelling that leads to changes in ventricular geometry and impaired cardiac function. The role of myocardial microstructural remodelling in the mechanics of failing hearts remains poorly understood. Structurally-based constitutive modelling can aid in the understanding of the mechanisms of mechanical dysfunction during HF, and thus help to pave the way towards more effective treatments that target these underlying mechanisms of HF. In the present study, we propose a new structurally-motivated constitutive model of passive myocardium that biophysically links the observed changes in myocardial collagen organisation, acquired using confocal microscopy, to left ventricular (LV) mechanical function obtained from *ex vivo* chamber compliance measurements.

2 METHODOLOGY

2.1 Quantifying cardiac structural remodelling from imaging data

In vivo cardiac magnetic resonance imaging (MRI) and extended-volume confocal microscopy were used to quantify the remodelling of the LV geometry and myocardial microstructure, respectively, of 12-month-old spontaneously hypertensive rat (SHR) and an age-matched Wistar-Kyoto (WKY) rat as control. *In vivo* cardiac MRI images were processed using in-house software to construct three-dimensional (3D) LV geometry at all frames of the cardiac cycle. Surface points were generated from the 3D LV geometry at diastasis and used to customise a single-element, thick-walled, truncated axisymmetric prolate spheroidal model (Fig.1a).

Extended-volume confocal images, taken from the LV midwall, were acquired at a resolution of 1 µm per voxel edge, with a total imaging volume of 400 µm x 400 µm x 200 µm (Fig.1b). Given that the collagen network is the predominant structural component of the cardiac extracellular matrix, and the major stress-bearing component of the myocardium, a robust method to quantify collagen morphology from confocal images is important for understanding the role of collagen organisation in cardiac mechanical properties.
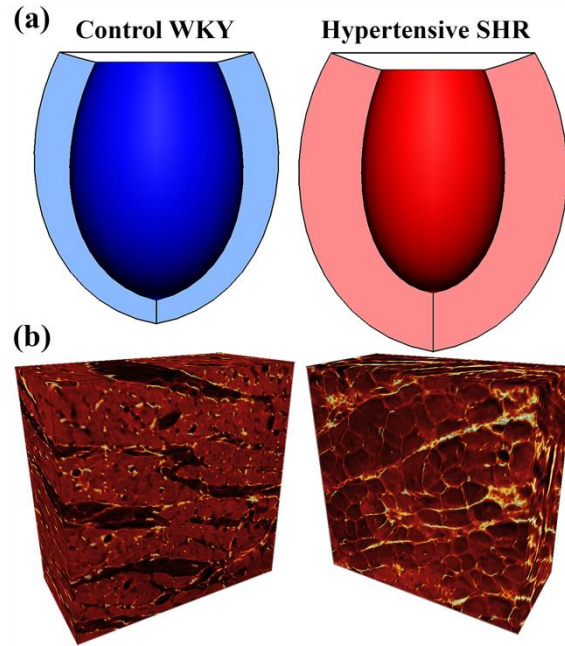

Figure 1: (a) 3D LV FE models constructed from subject-specific *in vivo* MRI data at diastasis. (b) Confocal image volumes: myocytes have variable intensity, while collagen appears bright.

The collagen network was segmented from the confocal images using a customised pipeline [1]. As collagen morphology is described at a local level, a number of regions-of-interest were extracted from the 3D segmented images for shape quantification. A representative collagen shape was then computed by averaging inertia matrices of segmented collagen structures (Fig.2a). As the eigenvalues $(\lambda_\alpha, \lambda_\beta, \lambda_\gamma)$ of the lumped inertia matrix indicate the collagen shape while the eigenvectors carry the orientations, two morphological parameters ($\mathbb{E} = \frac{\lambda_\beta}{\lambda_\alpha}$ and $\mathbb{A} = \frac{\lambda_\gamma}{\lambda_\alpha}$) based on the eigenvalues were used to quantify the morphological differences between healthy and diseased hearts. Eigenvalues denote the largest, middle, and smallest eigenvalues, respectively, and are constrained by the fact that $\lambda_\alpha \geq \lambda_\beta \geq \lambda_\gamma > 0$. Such morphological parameters allow the collagen network to be represented in a continuum sense (Fig.2b).

2.2 Quantifying cardiac functional remodelling

Ex vivo LV compliance measurements were used to characterise passive ventricular function by attaching the excised hearts to a Langendorff apparatus, and a saline-filled balloon catheter was inserted into the LV via the mitral valve. The balloon was inflated by plunging fluid to a maximum pressure of 30 mmHg, and then deflating. Pressure was measured using a differential pressure transducer connected to a side port in the balloon catheter. Compliance (the inverse of stiffness) was measured as the change in volume over the change in pressure. LV passive compliance, as a function of filling pressure, was then used to determine trends of LV chamber stiffness between healthy and diseased hearts independent of changes in LV size.
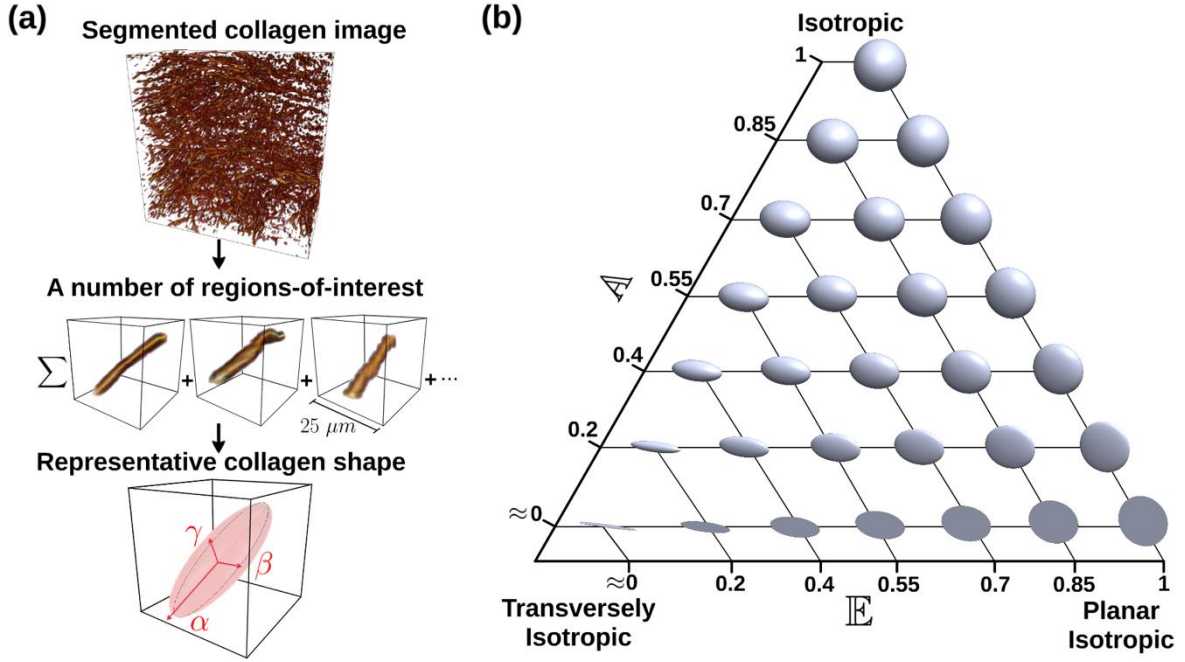
Figure 2: (a) A framework for quantification of collagen morphology in 3D. (b) Schematic visualisation of object shape variation based on structural parameters $\mathbb{E}$ and $\mathbb{A}$.

2.3 A structurally-driven model for passive myocardium

Bearing in mind the local organisation (α, β, γ) of the representative collagen structure (Fig.2), we represented myocardial tissue as an incompressible material with an exponential strain-energy function W with terms of Green-Lagrange strain tensors E_{ij} referred to the local collagen coordinate system.

$$W = \frac{a\,V_f}{b}[e^{b\,Q} - 1],$$
$$Q = E_{\alpha\alpha}^2 + \mathbb{E}\ E_{\beta\beta}^2 + \mathbb{A}\ E_{\gamma\gamma}^2 + 2\ [\mathbb{E}\ E_{\alpha\beta}^2 + \mathbb{A}\ E_{\alpha\gamma}^2 + \mathbb{E}\ \mathbb{A}\ E_{\beta\gamma}^2]$$

$$(1)$$

where $\mathbb{E}$, $\mathbb{A}$ and V_f (collagen volume fraction) are directly quantified from the confocal images and used to reproduce the anisotropic nature of the myocardium. The remaining two parameters, a (stiffness-like parameter) and b (dimensionless nonlinearity parameter), are determine the overall stiffness of the myocardium and the nonlinear nature of the passive mechanical response, respectively. This constitutive equation was then integrated into a finite element (FE) model of the LV (Fig.1a) using in-house FE analysis software. Myocyte orientations in both SHR and WKY rat FE models were set to vary from +60° at the endocardium to -70° at the epicardium, while the sheetlet orientation was fixed at +30° with respect to the short-axis plane in concordance with previous studies [2, 3]. Passive inflation of the LV was simulated by kinematically constraining the LV base and applying cavity pressures over the endocardial surfaces of the models. The pressure was applied homogeneously and increased in increments from 0 mmHg to 15 mmHg to span the range of physiological filling pressures. LV compliance was derived from the model-predicted pressure-volume curves to mimic the experimentally-derived compliance data. The material parameters (a, b) were identified using a nonlinear least-squares algorithm that minimised the differences between model-predicted and experimentally measured compliance data for both healthy and diseased hearts.

3 RESULTS AND CONCLUSIONS

To link the observed differences in cardiac microstructure and ventricular mechanical function, we built LV FE models (Fig. 1a) from *in vivo* cardiac MRI data. Microstructural data from the confocal images (Fig. 1b; Table. 1) were integrated into the LV mechanics models using Eq.1. A single pair of fitted constitutive parameters (a= 139.6 kPa, b= 49.6) were estimated to best fit the *ex vivo* LV

compliance data for both animals simultaneously (Fig. 3). This approach mechanistically linked the observed LV geometric and microstructural remodelling to explain the differences in passive LV mechanical function.
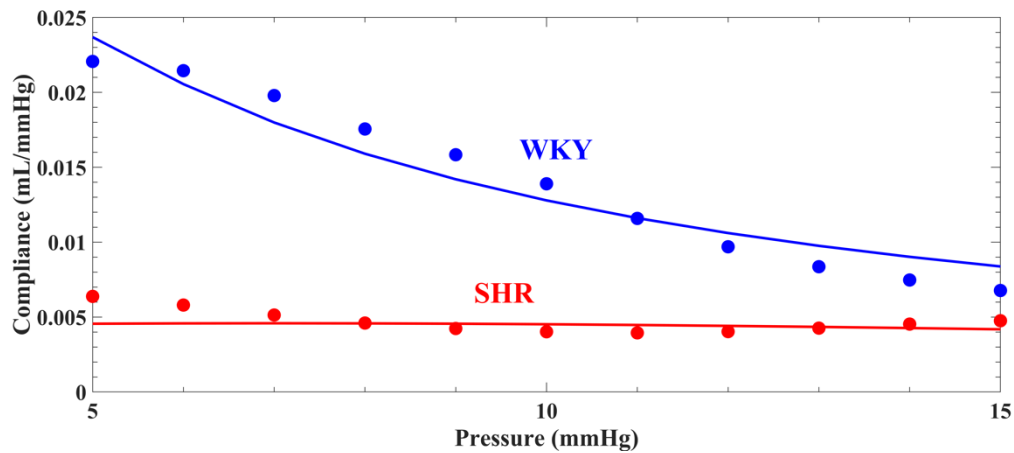

Figure 3. Model predictions of LV compliance (lines) versus experimental data (symbols) for 12-month-old diseased SHR (red) and age-match WKY rat heart (blue) as control. While subject specific geometric models (derived from *in vivo* MRI) and myocardial microstructural parameters (derived from confocal images) were used for each case, a single set of fitted material parameters (a= 139.6 kPa, b= 49.6) were used for both hearts.

Table 1: Microstructural parameters V_f, $\mathbb{E}$ and $\mathbb{A}$, quantified directly from myocardial confocal images (Fig.1a) for diseased SHR and WKY rat heart as control.

Animal	V_f	$\mathbb{E}$	$\mathbb{A}$
WKY	0.06	0.7	0.2
SHR	0.11	0.8	0.4

In this study, we have developed a new structurally-based constitutive model of passive myocardium to investigate the underlying biomechanical mechanisms of HF. Providing insight into the biophysical links between myocardial microstructure and ventricular function remodelling will advance our understanding HF pathophysiology and hence help to pave the way towards more effective treatments.

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