Compressibility and Anisotropy of the Ventricular Myocardium: Experimental Analysis and Microstructural Modeling

While the anisotropic behavior of the complex composite myocardial tissue has been well characterized in recent years, the compressibility of the tissue has not been rigorously investigated to date. In the first part of this study, we present experimental evidence that passive-excised porcine myocardium exhibits volume change. Under tensile loading of a cylindrical specimen, a volume change of $4.1 \pm 1.95\%$ is observed at a peak stretch of 1.3. Confined compression experiments also demonstrate significant volume change in the tissue (loading applied up to a volumetric strain of 10%). In order to simulate the multiaxial passive behavior of the myocardium, a nonlinear volumetric hyperelastic component is combined with the well-established Holzapfel–Ogden anisotropic hyperelastic component for myocardium fibers. This framework is shown to describe the experimentally observed behavior of porcine and human tissues under shear and biaxial loading conditions. In the second part of the study, a representative volumetric element (RVE) of myocardium tissue is constructed to parse the contribution of the tissue vascular and cellular loading conditions in bone marrow [13] and cartilage [14]. However, to the best of our knowledge, such modeling approaches have yet to be applied to the myocardium. In Sec. 3, we develop a representative volumetric element (RVE) of the myocardial tissue to (i) parse the contribution of the solid and vascular tissue components to myocardium compressibility and (ii) investigate the influence of microscale fiber alignment and dispersion on tissue-scale mechanical behavior. [DOI: 10.1115/1.4039947]

1 Introduction

Development of accurate models for tissue reorganization and device implantation is of central importance in heart disease research and requires a fundamental understanding of the structure and mechanics of ventricular myocardium. LeGrice et al. [1] revealed the laminar structure of the myocardium and mapped the myofiber orientations throughout the ventricle wall, while nonlinear anisotropic tissue behavior has been identified under shear and biaxial loading conditions [2–4]. Such investigations provide valuable insight into the role of the noncontractile tissue components in cardiac function and motivated the development of a constitutive law for simulating the passive ventricular myocardium [5].

Incompressibility is commonly assumed in the computational modeling of some soft tissues (primarily due to the fluid content within cells and interstitial components), though recent investigations have challenged such assumptions [6,7]. The incompressible condition for myocardium is supported by a study from Vossoughi and Patel [8]. However, Ashikaga et al. [9] revealed that there are regional changes in the myocardial volume up to 10% during the cardiac cycle that cannot be fully accounted for by the movement of blood through the vasculature. Recent computational investigations have also highlighted the need for further evidence [10,11]. In Sec. 2 of this paper, the compressibility of myocardial tissue is quantified through a joint experimental-computational investigation, revealing changes in the volume of passive-excised porcine myocardium tissue under both tensile and confined compression loading conditions. An appropriate nonlinear hyperelastic model is identified to capture the observed compressible mechanical behavior of the myocardium. This compressible model is then combined with the well-established Holzapfel–Ogden model for the anisotropic contribution of myocardium fibers [5], providing a full volumetric–isochoric–anisotropic hyperelastic model for the passive behavior of the myocardium.

While an accurate continuum description of the myocardium is extremely useful in tissue- and organ-level simulations, the tissue microstructure must be considered in order to better understand the factors that contribute to observed tissue anisotropy and compressibility. Microstructural models have previously been developed to examine the structure and the function of biological tissues. The work of Ahmadzadeh et al. [12] investigated the volume reduction observed in tendons under tensile loading. Other studies have developed micromechanical models to understand cellular loading conditions in bone marrow [13] and cartilage [14]. However, to the best of our knowledge, such modeling approaches have yet to be applied to the myocardium. In Sec. 3, we develop a representative volumetric element (RVE) of the myocardial tissue to (i) parse the contribution of the solid and vascular tissue components to myocardium compressibility and (ii) investigate the influence of microscale fiber alignment and dispersion on tissue-level mechanical behavior.

2 Compressibility and Continuum Modeling of Myocardium

In this section, we examine the myocardium at the macroscale. Previous histological studies have shown that the myocardium has a laminar architecture [1] composed primarily of cardiomyocytes that bind end to end forming myofibrillar structures. Parallel arrangements of myofibres are bound by endomysial collagen which, along with other collagenous components and elastin, form individual myolaminae (sheets). These sheets vary in orientation throughout the myocardium. This makes it possible to define a local right-hand orthogonal set of axes to define the myofiber ($f$) direction, the cross-fiber or sheet ($s$) direction, and the normal ($n$) direction to this plane. The anisotropic biaxial and isochoric shear behavior of the myocardial tissue has been carefully characterized.
in previous experimental studies [3,4]. Here, we investigate the passive compressibility of the tissue. We then show that a compressible anisotropic framework accurately describes experimental data for porcine and human tissues.

2.1 Experimental Methods. Tissue preparation: Tissue specimens are excised from porcine hearts, sourced from a certified abattoir (Brady’s, Athenry, Ireland). The organs are stored at −80 °C until required, and thawed in phosphate buffer solution at room temperature, in accordance with previous protocols [6]. The atria are removed and a transmural base-apex cut is taken between the posterior and the anterior papillary muscles from the lateral left ventricular wall (Fig. 1(a)) following the protocol of Dokos et al. [3]. Evans Blue dye is used to highlight the individual sheets, and 3 mm sections are cut along the sheet axis. These are then cut on the face normal to the fiber-sheet plane with a circular punch (radius 3 mm). The sample diameter and height are measured with an electronic Vernier caliper. As the myocardium exhibits local variations in the f and s directions, the aforementioned test specimen dimensions are chosen to be sufficiently small so as to avoid intraspecimen variations in fiber orientation [4]. A total of 13 samples are excised and tested.

Mechanical testing: The samples are rigidly bonded to lower and upper platens using a thin layer of cyanoacrylate adhesive (Loctite, Dusseldorf, Germany) as shown in Fig. 1(b). The platens are attached to a uniaxial mechanical testing machine (Zwick Z2.5, Ulm, Germany). The lower platen is fixed and the upper platen is displaced in the positive normal, n, direction so that the specimen is deformed at a nominal strain rate of $= 0.01 \text{s}^{-1}$ up to
a stretch of 1.3. Two video-extensometer cameras (1.31 MPx, 25 fps; uEye, IDS, Obersulm, Germany; videoTens software, Zwick, Ulm, Germany) are positioned so that sample deformation in two orthogonal planes is monitored. The recorded series of images from both orthogonal planes are used to reconstruct the three-dimensional (3D) deformation of the specimen. The image series from the orthogonal video-extensometer cameras are imported into and digitized in MATLAB (R2017b, The Mathworks, Natick, MA). The specimen is discretized into sections orthogonal to the n-axis, each of height \( h_i \). The total volume \( V \) of the specimen at a given time-point during the experiment is computed as

\[
V = \sum_{i=1}^{N} \left( \frac{a_i + a_{i+1}}{2} \right) \left( b_i + b_{i+1} \right)
\]

where the deformed section dimensions \( a_i \) and \( b_i \) at section \( i \) are determined from the digitized images of the specimen. Specimen volume is computed at 11 time-points (including the undeformed configuration) throughout the experiment for all 13 specimens.

To further investigate the volumetric deformation, confined compression testing is performed (Fig. 1(c)). Specimens are prepared as previously described for the tensile experiment. Samples are placed into a rigid die of the same radius. Die walls are coated with a thin film of lubricant (Unilever petroleum jelly, London, UK) to minimize friction during specimen compression. A loading indenter attached to a mechanical testing machine (Zwick 2225, Ulm, Germany) compresses the specimen at a nominal axial strain rate of 0.01 s\(^{-1}\). Due to the constraint on lateral deformation in the specimen, axial strain is equal to volumetric strain. The specimen is deformed to a volumetric strain of 0.1, and the nominal stress in the loading direction is plotted as a function of volumetric strain. A total of 13 specimens are tested.

2.2 Compressible Constitutive Law for the Myocardium

Following the approach of Holzapfel and Ogden [5], the mechanical behavior of the myocardium is divided into an anisotropic component (to describe the muscle and collagen fibers) and an isotropic component (to describe the cell nonmuscle components and elastin networks). The fibers are assumed not to contribute under shortening (compressive) loading conditions. When the specimen is stretched, as shown in Fig. 1(b), it results in a lateral shortening of the myofiber-sheet plane (on which the muscle and collagen fibers are oriented). It is, therefore, assumed that the material behavior is dominated by the isotropic component in the applied deformation.

All finite element simulations are performed using ABAQUS/Standard (v6.14, DS Simulia, RI). Constitutive equations are implemented via user-defined material subroutines (UMATs). The consistent tangent matrix is approximated numerically based on a forward difference perturbation of the deformation gradient matrix [15,16]. An inverse FE scheme [6] is implemented to identify a suitable constitutive model and to calibrate the associated material parameters (Fig. 1(d)) using the stretch/stress and volume change data from the tensile-stretching experiment (Fig. 1(b)). A reduced polynomial Yeoh isotropic hyperelastic model [17] is used to simulate the isotropic behavior of the myocardium, where the stress tensor \( \sigma_{iso} \) is given as

\[
\sigma_{iso} = \sum_{i=1}^{3} \mu_i (J - 1) \exp[ \psi_i (J - 1)] \left( \mathbf{B} - \frac{1}{3} J I_1 \mathbf{I} \right)
\]

Initial simulations confirm that the horizontally aligned muscle and collagen fibers shorten under the applied experimental loading conditions, as shown in Figs. 1(b) and 1(c). Therefore, anisotropic terms do not contribute to the material stress, and the experimental data can be used to calibrate the isotropic component of the tissue model.

2.3 Experimental Results and Simulations

The experimentally measured nominal stress–stretch relationship for the tensile stretching of porcine myocardium specimens is shown in Fig. 2(a). The observed relationship is nonlinear, exhibiting both concave and convex sections with an inflection point of about \( \dot{\lambda} \approx 1.15 \). The six-parameter Yeoh model provides a good fit to the experimental data \( R^2 = 0.995 \). Calibrated material properties are shown in Table 1 (porcine–isotropic). Specimen volume changes measured in the tensile-stretching experiments are shown in Fig. 2(b). Volume change increases with increasing applied stretch, reaching a value of 4.1 ± 1.95% at a stretch of 1.3. These data indicate that myocardial tissue shows compressibility. This could be the result of a volume increase in the porous extracellular matrix (ECM) and the vasculature. We do not expect any fluid to leave the system in such a tensile experiment when the volume is increasing. The Yeoh model also provides a reasonable fit to the volume change during the applied loading conditions \( R^2 = 0.951 \).

Experimental results for confined compression of the myocardium are shown in Fig. 2(c). The nominal stress–volumetric strain relationship is highly nonlinear. Initially, specimens exhibit little resistance to volume change, with a 5% volumetric strain occurring at a nominal stress of about 4 kPa. However, the resistance to volume change increases as the specimen is further compressed, with an applied nominal stress of 10% occurring at a nominal stress of about 49 kPa. Due to the confined nature of the experiment and the proximity of the indenter to the compression rigid wall, it is expected that the fluid loss in the system will not be significant. Using the Yeoh model (with parameters calibrated from the data in Fig. 2(a)), a good fit to the nominal...
stress–volumetric strain relationship during confined compression is obtained ($R^2 = 0.985$). In summary, the following key points should be noted: (i) the experimental data presented in Figs. 2(b) and 2(c) show that the myocardium undergoes significant volumetric strain under two distinctly different loading modes (positive volumetric strain during tensile stretching and negative volumetric strain during confined compression); (ii) a six-parameter-compressible Yeoh hyperelastic material law can describe the material behavior (including volume change) for both loading modes.

The compressible isotropic component of the myocardium constitutive law, Eq. (2), calibrated for porcine tissue in Fig. 2(a), is used in parallel with the anisotropic component of the model Eq. (3) to simulate the simple shear experiments of Dokos et al. [3]. The anisotropic parameters are calibrated to the experimental data using an inverse FE scheme whereby six modes of shear are simulated. While the material response to $ns$ and $n_s$ shear is described by the isotropic terms (with parameters previously calibrated to the volumetric experiments), the stress state associated with $s_n$, $s_f$, $f_n$, and $f_s$ shear modes is dominated by the anisotropic terms. As shown in Fig. 3(a), this framework provides an accurate description of experimental porcine myocardium data, with the associated anisotropic material parameters reported in Table 1 (porcine). A detailed description of the individual modes of shear is provided in Sec. 3 of this paper.

### 2.4 Modeling the Behavior of Human Tissue.

The mechanical behavior of human myocardial tissue under simple shear and biaxial loading was recently documented in a study by Sommer et al. [4]. The myocardium model presented in Sec. 2.2 is shown to describe the reported shear stress (Fig. 3(b)), with the parameter set (determined via inverse FE) provided in Table 1 (human). In a biaxial test, the relationship between the experimentally measured force and the material stress is complex, as has been highlighted recently by Nolan and McGarry [18]. Therefore, to simulate the reported biaxial data, an inverse finite element analysis scheme must be implemented whereby the experimental boundary conditions are applied. In the case of the experiments of Sommer et al. [4], 25×25×2.3 mm samples were excised, with the mean myofiber direction (MFD) and cross-fiber (sheet) direction (CFD) along the $x$- and $y$-axes, respectively. Five hooks were placed.

Table 1 Isotropic and anisotropic parameters for porcine and human myocardium

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<td>$\kappa_3$ (kPa)</td>
<td>$\alpha_f$ (kPa)</td>
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</tbody>
</table>

| Porcine | | |
|---------| | |
| 2.44 | 28.21 | 20.06 | 2.15 | 29.8 |
| -6.04 | 0.212 | 22.68 | 7.31 | 5.12 |
| 14.56 | 5.12 | 2.49×10^6 | 2.75 | 32.1 |
| 2.13 | 1.06 | 30.1 | 0.38 | 10.89 |
| 14.56 | 2.49×10^6 | 0.38 | 10.89 |

| Human | | |
|-------| | |
| 0.98 | 2.75 | 32.1 | 1.06 | 30.1 |
| -0.212 | 0.175 | 5.02 |
| 22.68 | 30.1 | 0.175 | 5.02 |
| 7.31 | 30.1 | 0.175 | 5.02 |
| 5.12 | 30.1 | 0.175 | 5.02 |
| 2.13 | 30.1 | 0.175 | 5.02 |
| 2.49×10^6 | 30.1 | 0.175 | 5.02 |

Fig. 2 (a) Experimental (mean ± standard error of the mean (sem)) and simulated nominal stress (kPa) during stretch of the myocardium specimens, (b) experimental (mean ± sem) and simulated volume change (%) during stretch, and (c) experimental (mean ± sem) and simulated nominal stress (kPa) during confined compression.
equidistant on each edge of the specimen. The material stretch was recorded by tracking markers located proximal to the sample center. These conditions are replicated in a 3D axisymmetric finite element model, with the hook tension described by nodal displacements. As per the experiment, the stretch is recorded at the marker positions, with the hook/nodal displacement adjusted accordingly to ensure an equibiaxial (1:1) 10% strain. The simulated strain nonuniformity in the tissue is shown in Fig. 3(c), and a reasonable description of the biaxial stress state is achieved (Fig. 3(d)).

While the aforementioned Holzapfel–Ogden model [5] assumes that the anisotropic behavior of the tissue is confined to tensile loading, the question of material anisotropy in compression is briefly discussed in the Appendix.

3 Microstructural Modeling

In this section, a multifaceted microstructural model of the myocardium is developed to replicate the complex experimental behavior shown in Figs. 2 and 3. In the experimental analyses of Sec. 2, it is assumed that the tissue is unperfused, and therefore, the empty vasculature may contribute to the recorded volumetric deformation. An RVE is generated as motivated by histological studies, and experimental confined compression is simulated to assess this contribution. Additionally, several modes of simple shear are applied to the RVE to investigate the mechanical significance of fiber stiffness and arrangement on a microscale.

Representative volumetric element development: An RVE of the myocardium is created, comprised of discrete regions to describe cardiomyocytes, the ECM, and the vasculature. Several histological and SEM images were analyzed to motivate a 2.7 × 10^6 μm³ RVE cuboidal structure [1,19–21], which is generated in ABAQUS 6.14 with the following geometry: the cardiomyocytes are assumed to account for approximately 60% of the tissue volume, with a typical width of 15 μm and a cuboidal shape. Circular capillaries occupy approximately 5% of the volume, with a mean diameter of 5 μm. The remainder of the RVE is accounted for by the ECM, which is largely composed of perimysial and endomysial collagen fibers (Fig. 4). In this analysis, the mechanical contribution of other cell phenotypes (such as cardiac fibroblasts) is not

![Representative volumetric element of the myocardium with discrete regions for the cardiomyocytes, the matrix surrounding the cells (ECM 1), and the matrix surrounding the myocardial sheets (ECM 2). Capillaries are included as empty vessels.](image-url)
considered. A thick band of ECM separates individual myocardial sheets, with a typical thickness of 10\textmu m.

3.1 Representative Volumetric Element Constituent Materials. In order to investigate the influence of microstructural morphology and composition on tissue-level mechanical behavior, we attempt to replicate the shear and confined compression data shown in Sec. 2 using a multicomponent RVE (Fig. 4). It should be noted that the continuum-level sheet-fiber constitutive law of Holzapfel and Ogden is not used at the microstructure level. Rather, the architecture and distribution of collagen fibers and cells are explicitly represented, and a single-fiber Holzapfel–Gasser–Ogden (HGO) formulation is used to represent the passive material behavior of each component.

Fiber anisotropic contribution: Collagen and muscle fibers are represented by a hyperelastic model, proposed by Holzapfel et al. [22], and recently modified for compressible materials by Nolan et al. [16]. The fiber stress is given by

$$\sigma_{j} = \begin{cases} \frac{2}{3} k_{1} (I_{uu} - 1) \exp \left[ k_{2} (I_{uu} - 1)^{2} \right], & I_{uu} > 1 \\ 0, & \text{otherwise} \end{cases}$$ (5)

where \(\sigma_{j}\) is the Cauchy stress of a single-fiber family, \(I_{uu}\) is the anisotropic invariant defined by \(I_{uu} = a_{0} \cdot (Ca_{0})\), and \(k_{1}\) and \(k_{2}\) are material constants. The fibers only contribute to the stress when in tension (i.e., \(I_{uu} > 1\)). The anisotropic stress tensor is given as

$$\sigma_{\text{aniso}} = \sum_{i=1}^{n} \sigma_{j} a_{i} \otimes a_{i}$$ (6)

where \(n\) is the number of fiber families, \(a_{0}\) is a unit vector indicating the myocardial sheet orientations, and \(a_{i}\) is the same vector in the deformed configuration given by \(a_{i} = F a_{0}\).

Fiber dispersion: In order to account for dispersion of collagen fibers about a mean direction in the ECM, we implement a model adapted from the angular integration framework [23], whereby the fiber directions are discretely modeled. This allows for an exclusion of the mechanical contribution of all fibers under compression. We consider that fibers can exist in a large number of directions. The distribution is normalized such that

$$\frac{1}{4\pi} \int_{\Omega} \rho_{i}(|a|) d\Omega = 1$$ (8)

where \(\Omega\) is a unit sphere. The fiber stress, i.e., Eq. (5), is computed in all \(m\) directions. The contribution of the dispersed fibers to the Cauchy stress tensor is then given as

$$\sigma_{\text{disp}} = \sum_{j=1}^{n} \rho_{i} \sigma_{j} a_{j} \otimes a_{j}$$ (9)

This discrete dispersion model is validated against the generalized structure tensor (GST) model [26]. In the GST model, fibers under compression are not necessarily excluded, as the tension condition is dependent only on the stretch in the mean fiber direction. Applied \(n\) shear of a unit cube is simulated for a single-fiber family in the \(s-n\) plane, with the mean fiber direction rotated \(60^\circ\) deg from the \(s\)-axis. In the GST model, the dispersion depends on parameter \(d\). Three cases of dispersion are compared (i.e., slight dispersion \((b = 10, d = 0.02)\), intermediate dispersion \((b = 1.5, d = 0.14)\), and near isotropic dispersion \((b = 0.1, d = 0.24)\)). In all cases, \(k_{1}/\mu = 5\) and \(k_{2} = 0.01\) (Fig. 5).

Material isotropy: In all regions of the RVE, we consider the presence of an underlying isotropic material described by a simple neo-Hookean hyperelastic model, with the Cauchy stress

$$\sigma_{\text{iso}} = \kappa (I - 1) + \mu \left( \frac{2F - F^{T}F}{3} \right)$$ (10)

The first term on the right-hand side represents the hydrostatic stress contribution due to volumetric deformation, and the second term represents the deviatoric stress contribution due to isochoric deformation, while \(\kappa\) and \(\mu\) are the bulk modulus and shear modulus, respectively.

Physiological motivation for fiber alignments: The cardiomyocytes are described by a single-fiber model in order to represent highly aligned myofibris Eq. (6) in a nearly incompressible isotropic cytoplasm Eq. (10). As the tissue is passive in the ex vivo experimental investigations considered in this study, active cellular contractility is not considered. Pope et al. [27] investigated the organization of collagen in the matrix surrounding the cardiomyocytes through extended volume confocal microscopy (EVM). Thick perimysial collagen fibers were observed to run parallel to the cells, and therefore, contribute to the high stresses reported for tissue stretch in the fiber direction. These fibers are represented by the single-fiber model described previously, i.e., Eq. (6). The orientation of the perimysial fibers that surround the myocardial sheets is more difficult to discern from EVM. We investigate here the arrangement of these fibers through a dispersion model, i.e., Eq. (9). The cardiomyocytes are bound together by endomy- lial collagen, and this is also described by fiber dispersion. The remaining constituents of the ECM are described by a compressible isotropic neo-Hookean model. Such a matrix (with embedded collagen fibers) has been shown to be compressible in several soft tissues [6,7,28], suggesting it is likely the source of nonvascular volume changes in the myocardium. The capillaries are modeled as empty inclusions. The relevant components of the Cauchy stress

\[\sigma_{\text{iso}} = \kappa (I - 1) + \mu \left( \frac{2F - F^{T}F}{3} \right)\]

\[\sigma_{\text{disp}} = \sum_{j=1}^{n} \rho_{i} \sigma_{j} a_{j} \otimes a_{j}\]

\[\frac{1}{4\pi} \int_{\Omega} \rho_{i}(|a|) d\Omega = 1\]

\[\sigma_{\text{disp}} = \sum_{j=1}^{n} \rho_{i} \sigma_{j} a_{j} \otimes a_{j}\]

\[\sigma_{\text{iso}} = \kappa (I - 1) + \mu \left( \frac{2F - F^{T}F}{3} \right)\]

\[\sigma_{\text{disp}} = \sum_{j=1}^{n} \rho_{i} \sigma_{j} a_{j} \otimes a_{j}\]
stress terms for each region are summarized in Table 2. As per Sec. 2, constitutive equations are implemented in the finite element software ABAQUS through UMATs.

Boundary conditions and simulations: Periodic boundary conditions (PBCs) are applied to the model to ensure that the deformation of opposing nodes remains continuous during the analysis, as per Dowling et al. [14] and Vaughan and McCarthy [29]. The PBCs consist of a series of equation constraints and can be expressed in terms of the nodal displacement. Detailed explanation on the implementation of PBCs can be found in Dowling et al. [14] and Vaughan and McCarthy [29]. The PBCs consist of a series of equation constraints and can be expressed in terms of the nodal displacement. Detailed explanation on the implementation of PBCs can be found in Dowling et al. [14] and Vaughan and McCarthy [29]. The PBCs consist of a series of equation constraints and can be expressed in terms of the nodal displacement. Detailed explanation on the implementation of PBCs can be found in Dowling et al. [14] and Vaughan and McCarthy [29]. The PBCs consist of a series of equation constraints and can be expressed in terms of the nodal displacement. Detailed explanation on the implementation of PBCs can be found in Dowling et al. [14] and Vaughan and McCarthy [29].

Under such loading conditions, all collagen and muscle fibers shorten, and therefore, do not contribute mechanically. Under such loading, the RVE stress state is governed by the isotropic elastic behavior of the cells and the ECM. As the cardiomyocytes are considered nearly incompressible, a high bulk modulus-to-shear modulus ratio was enforced in the cell regions of the RVE (Table 2). When the isotropic component of the ECM material is found to be slightly compressible (Table 2), a reasonable description of the experimental nominal stress–volumetric strain relationship is obtained (Fig. 7(a)). As shown in Fig. 6(a), the strain field throughout the RVE is nonuniform, with significant localized stress and strain concentrations in the material surrounding the capillaries. Figure 7(b) shows the simulated change in volume for each component of the RVE. At an applied confined compression strain of 0.05, the vascular volume decreases by 51.8%, the sheet (ECM2) by 6.2%, the matrix surrounding the cells (ECM1) by 6.0%, and the cardiomyocytes by 0.5%. In summary, the vasculature is predicted to contribute about 42% of the total volume change during confined compression to a strain of 0.05, with the remaining volume change occurring primarily in the collagen ECM.

We next apply six modes of shear deformation to the RVE to investigate the orientation and stiffness of collagen fibers in the

### Table 2 Cauchy stress terms and material parameters for RVE regions

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*The isotropic component of ECM1 and ECM2 is equivalent, simply denoted as ECM (iso). In the cases where fibers are aligned in a plane, they are rotated from the first direction stated.

Fig. 6 Maximum principal strain following loading of the RVE: (a) confined compression, cc; (b) shear in the ns plane; and (c) shear in the sn plane.

3.2 Representative Volumetric Element Results and Discussion. In confined compression simulation, all fibers shorten, and therefore, do not contribute mechanically. Under such loading, the RVE stress state is governed by the isotropic elastic behavior of the cells and the ECM. As the cardiomyocytes are considered nearly incompressible, a high bulk modulus-to-shear modulus ratio was enforced in the cell regions of the RVE (Table 2). When the isotropic component of the ECM material is found to be slightly compressible (Table 2), a reasonable description of the experimental nominal stress–volumetric strain relationship is obtained (Fig. 7(a)). As shown in Fig. 6(a), the strain field throughout the RVE is nonuniform, with significant localized stress and strain concentrations in the material surrounding the capillaries. Figure 7(b) shows the simulated change in volume for each component of the RVE. At an applied confined compression strain of 0.05, the vascular volume decreases by 51.8%, the sheet (ECM2) by 6.2%, the matrix surrounding the cells (ECM1) by 6.0%, and the cardiomyocytes by 0.5%. In summary, the vasculature is predicted to contribute about 42% of the total volume change during confined compression to a strain of 0.05, with the remaining volume change occurring primarily in the collagen ECM.

We next apply six modes of shear deformation to the RVE to investigate the orientation and stiffness of collagen fibers in the...
parametric study comprising 140 simulations (~$14 \times 10^9$ CPU core hours) was performed in order to uncover fiber orientations and stiffness in each region of the RVE so that a good description of the experimental results of Dokos et al. [3] is obtained. As shown in Fig. 8(a), the model parameters presented in Table 2 provide an accurate description of the multiaxial shear behavior of porcine myocardium, i.e., $f_s > f_n > s_f > s_n > n_f \approx n_s$. Analyses uncover the key constituents contributing to the stress under each loading condition. Non-linearity in the $n_s$ and $n_f$ shear stress is dependent on the dispersion of both the endomysial collagen surrounding the myocytes and the perimysial collagen surrounding the myolamiae (sheets). Correct trends are described only if the dispersion of perimysial fibers is included. The high stiffness response to $s_n$ and $s_f$ shear deformation is also primarily due to perimysial fibers, which have a dominant alignment in the sheet ($s$) direction. Myofibres in the cells and perimysial collagen fibers that run parallel to the cells provide a dominant contribution to the high stresses observed in $f_n$ and $f_s$ shear deformation. The difference in the $f_s$ and $f_n$ stress is caused by dispersion of the perimysial collagen fibers that surround the myolamiae.

A similar parameter study was performed for human myocardium data [4], again achieving an excellent representation of the stress response to the six modes of simple shear (Fig. 8(b)). Model parameters for human myocardium are presented in Table 2. There are some notable differences between the experimental observations for porcine and human tissue. The normal ($n$) and sheet ($s$) loading modes are observed to have a significantly stiffer response in the human tissue, while the fiber ($f$) loading modes are associated with a lower stress when compared to porcine data. These variances may be captured by alterations to the dispersion parameters and fiber stiffness, while dominant fiber orientations are similar to those determined for porcine tissue.

4 Conclusions

The compressibility of myocardial tissue is quantified through a joint experimental-computational investigation, where it is revealed that the passive tissue changes in volume under both tensile and confined compression loading conditions. We, therefore, suggest that the myocardium should be considered as a slightly compressible material, and we show that both the volumetric and isochoric contributions to the isotropic component of the myocardium are highly nonlinear. The compressible isotropic hyperelastic component can be combined with the anisotropic component of the constitutive law proposed by Holzapfel and Ogden [5] to provide a full description of the passive myocardium. The model describes the experimentally observed behavior of porcine [3] and human [4] myocardial tissues. Previous studies have demonstrated that there is no significant difference in the physiological mechanics of fresh and frozen/thawed arterial tissue [30,31]. However, such differences have not been specifically examined for myocardium, and this may be a potential limitation of the study. Future studies are recommended to determine that freezing of samples has a significant influence on the passive mechanical behavior of myocardial tissue. Investigation of the passive properties of freshly excised tissue would require inhibition of cross-bridge activity [3,4]. In addition to our compressible anisotropic hyperelastic framework, such studies may also consider porohyperelastic models [12,32] to investigate the volume change.

The change in vascular volume during the cardiac cycle has been well documented [33,34]. Yin et al. [20] monitored the blood

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**Fig. 7** (a) Experimental and simulated (from RVE) stress for confined compression; (b) volume decrease of each region following compression (i.e., the vasculature, cells, ECM1, and ECM2); and (c) proportion that the vascular and solid components account for the total volume change.

**Fig. 8** Simulated shear stress from RVE analyses of (a) porcine and (b) human tissue. Experimental data from (a) Dokos et al. [3] and (b) Sommer et al. [4] superimposed for reference.
volume of perfused myocardium under loading and found the vascular volume changed by up to 40% during stretching. It was, therefore, important that we attempted to parse the contribution of the solid tissue and vasculature to myocardial compressibility. An RVE of the myocardium was developed for this purpose. In the regional geometry assessed under confined compression, a reduction in vascular volume accounts for 42% of the volume change, while the solid tissue components accounting for the remainder. An important outcome of this modeling insight is that even if the blood dynamics were to be explicitly included in an analysis, the solid tissue should still be considered compressible. In our investigation, we assumed the vessels to be empty but if filled with blood it is expected that the solid tissue would contribute a larger portion of the volume change. Future studies may attempt to determine if the fluid is drained from the tissue during confined compression testing.

The RVE analyses also revealed the key constituents contributing to the stress under various modes of simple shear. The high stiffness reported for the $fs$ and $fn$ modes is due to stretching of the myofibers within the cells and the perimysial collagen that runs parallel to the cells. Dispersion of endomysial collagen and the perimysial fibers that surround the myolaminae dominate the RVE response to the $ns$ and $nf$ shear modes. The RVE developed in this study is based on published anatomical images [1,19–21] and provides new insights into the relationship between the cell/ECM microarchitecture and the tissue-level mechanical behavior. Variations in the myocardium microstructure, e.g., collagen orientation, stiffness, cell size, ECM volume, or capillary volume will have a significant influence on the mechanical behavior. In future work, the sensitivity of the RVE to constituent geometry (e.g., cell size, capillary density) should be investigated. Further developments of our RVE approach should incorporate the following: active dynamic contractility [35] and remodeling [36] of cardiomyocytes; mechanical contribution of cell nuclei [37]; fluid–structure interaction modeling of blood flow dynamics in capillaries. Such developments would provide a deeper insight into the effective time dependent tissue volume changes during a cardiac cycle.

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Appendix: Evidence of Weak Anisotropy in Compression

Anisotropy in the myocardium under tensile loading conditions has been well characterized experimentally, as presented in the shear and biaxial data of Fig. 3. This data can be accurately modeled through the constitutive framework proposed by Holzapfel and Ogden (2009). In this model, the anisotropic terms only contribute when the associated invariant is in tension (e.g., $I_4^f > 1$). This is controlled by a switching statement in the UMAT.

In the experiment described in Sec. 2, columnar samples of myocardium are stretched in the normal ($n$) direction. The deformation is recorded, and the volume change during the stretch is calculated. The midplane sample dimensions (see Fig. 9(a)) can

Fig. 9 (a) Cross section taken at midplane of simulated tensile experiment to measure ellipticity; (b) experimental and simulated ellipticity with porcine and human material parameters; (c) simulated nominal stress (kPa) versus volumetric strain for a simulated micromodel confined compression in $f$, $s$, and $n$ directions; and (d) simulated nominal stress (kPa) versus stretch for the micromodel under tensile loading.
be used to approximate the tissue anisotropy in compression by considering the ellipiticity (i.e., a/b). At a maximum stretch (Λ = 1.3), an ellipticly of 1.038 ± 0.0165 is calculated. This suggests that the myocardium exhibits weak anisotropy in compression, with the lowest contracture observed in the fiber direction.

The experiment is simulated using the properties outlined in Table 1. We exclude the aforementioned switch statement and allow the anisotropic terms to contribute in both tension and compression. Ellipticity values of 1.101 and 1.036 are observed for porcine and human parameters, respectively (Fig. 9(b)). In both cases, the material is observed to contract less in the fiber (f) direction than in the sheet (s) direction. To investigate the influence of the microstructure on tissue anisotropy in compression, confined compression in the f, s, and n directions is simulated with the model outlined in Sec. 3. Additionally, uniaxial tension is simulated in all three directions to highlight the anisotropy in tension.

Allowing for the mechanical contribution of fibers in compression (i.e., exclusion of switch statement) in the anisotropic modeling framework offers a possible means of describing the weak tissue anisotropy in compression, though the parameters calibrated for fibers in tension do not necessarily represent the compressive behavior (Fig. 9(b)). A computational study by Soares et al. [38] has recently demonstrated a weak mechanical contribution of a single discrete fiber subjected to compression. In this study, our RVE simulations suggest that tissue-level anisotropy will result, in part, from the microstructural arrangement of ECM and cells, even in the absence of a Fiber contribution under compression. The simulated microstructural anisotropic stress under confined compression is presented in Fig. 9(c), where clearly the tissue is slightly stiffer when compressed in the fiber (f) direction. Under tensile loading, the tissue anisotropy is significantly more pronounced due to the additional contribution of complex fiber distributions (Fig. 9(d)).

References


