The fiber orientation in the coronary arterial wall at physiological loading evaluated with a two-fiber constitutive model

Arjen van der Horst · Chantal N. van den Broek ·
Frans N. van de Vosse · Marcel C. M. Rutten

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Abstract A patient-specific mechanical description of the coronary arterial wall is indispensable for individualized diagnosis and treatment of coronary artery disease. A way to determine the artery's mechanical properties is to fit the parameters of a constitutive model to patient-specific experimental data. Clinical data, however, essentially lack information about the stress-free geometry of an artery, which is necessary for constitutive modeling. In previous research, it has been shown that a way to circumvent this problem is to impose extra modeling constraints on the parameter estimation procedure. In this study, we propose a new modeling constraint concerning the in-situ fiber orientation (β_{phys}). β_{phys} , which is a major contributor to the arterial stress–strain behavior, was determined for porcine and human coronary arteries using a mixed numerical–experimental method. The in-situ situation was mimicked using in-vitro experiments at a physiological axial pre-stretch, in which pressure–radius and pressure–axial force were measured. A single-layered, hyperelastic, thick-walled, two-fiber material model was accurately fitted to the experimental data, enabling the computation of stress, strain, and fiber orientation. β_{phys} was found to be almost equal for all vessels measured ($36.4 \pm 0.3^\circ$), which theoretically can be explained using netting analysis. In further research, this finding can be used as an extra modeling constraint in parameter estimation from clinical data.

Keywords Collagen fiber orientation · Parameter estimation · Coronary arteries · Netting analysis

1 Introduction

Insight into the mechanical properties of the coronary arterial wall can give valuable information concerning the genesis and progress of atherosclerosis, wall remodeling, and the prediction of the effects of medical intervention, e.g., balloon angioplasty (Holzapfel et al. 2000; Humphrey et al. 2009). A widely used approach to characterize the mechanical properties of arteries is based on a mixed experimental–numerical method, in which parameters of a constitutive model are fitted to experimental stress–strain data. In a previous study, it was shown that using a generic material parameter set, with average morphologic parameters, the mechanical behavior of different porcine coronary arteries could accurately be described (van den Broek et al. 2011). The only information needed then is a radius measurement at physiological loading and the corresponding pressure. This generic approach can be very useful, e.g., in the development of PTCA catheters, intended to be used in a patient population, from which the specific arterial properties are unknown a priori. However, for individualized diagnosis and treatment, this approach may not be applicable, since large variations in the material behavior are expected due to aging or disease. Other studies adopted a patient-specific modeling approach to assess the elastic modulus or distensibility from a clinically obtained pressure–radius relation (Hansen et al. 1995; Vavuranakis et al. 1999). More recently, constitutive models, which take the microstructure into account, were fitted to patient data (Masson et al. 2008; Stålhand 2009; Danpinid et al. 2010). This had the advantage that pathologies could be related to the parameters associated with different tissue components. An obvious challenge in the parameter estimation based on clinical data is the limited amount of information in the measured signals. For example, they do not provide any information regarding the axial strain, the radial deformations in the low

A. van der Horst (✉) · C. N. van den Broek · F. N. van de Vosse ·
M. C. M. Rutten
Department of Biomedical Engineering,
Eindhoven University of Technology, PO Box 513,
5600 MB, Eindhoven, The Netherlands
e-mail: A.v.d.Horst@tue.nl

pressure range, and the stress-free geometry. Including all these extra unknown parameters in the estimation procedure can easily result in over-parameterization. To overcome this problem, extra optimization constraints can be incorporated into the fitting protocol.

From in-vitro studies, it is well known that at physiological axial strain, the external axial force is independent of the internal pressure (van Loon 1977; Weizsäcker et al. 1983). Several studies used this pressure-invariant axial force constraint to fit models to clinical data. Stålhand and Klarbring (2005) incorporated it as a loose constraint into the estimation procedure in combination with a thick-walled, Fung type, material model and successfully validated it on data from a human aorta obtained in-vivo. Furthermore, making use of a methodology that was first proposed and successfully applied by Schulze-Bauer and Holzapfel (2003), Stålhand (2009) was even able to fit a more microstructurally based, thin-walled, two-fiber constitutive model (Holzapfel et al. 2000), to clinical data from human aortas. Besides the pressure-invariant axial force constraint, this methodology comprises a second constraint, which prescribes the ratio of axial to circumferential stress at a certain characteristic pressure. The combination of the two constraints avoided over-parameterization, thus rendering a unique set of parameters. A drawback of this approach is that the value of the stress-ratio constraint was adopted from in-vitro animal experiments (Fung et al. 1979), which may not directly apply to (pathological) human arteries. Since a thin-walled approach was used, residual stresses were not taken into account. Furthermore, in the studies mentioned, no validation with respect to the axial force and radius in the low pressure range was reported.

Stålhand et al. (2004) also used the two-fiber model but in combination with a thick-walled approach and without the extra constraints. The parameters of the model, including residual stresses, were successfully estimated from in-vivo human aortic data. However, to avoid over-parameterization, the parameter that accounts for the orientation of the collagen fibers in the stress-free configuration had to be prescribed. Since collagen is the main load-bearing structure in arteries at physiological load levels, it is evident that prescribing this parameter will highly influence the estimation results. There are several stress- or strain-based hypotheses that could explain the fiber organization in fibrous tissues (Baaijens et al. 2010). These hypotheses, however, do not provide a clear and unambiguous procedure how to tackle over-parameterization.

This study therefore aims to gain more insight into the fiber orientation at physiological loading conditions and to describe this with a relatively simple two-fiber constitutive model.

Hereto, in-vitro measurements were performed on porcine and human coronary arteries, at physiological axial pre-stretch. The inner radius and reduced axial force were

measured, while the artery was loaded with a dynamic pressure. Taking into account that the results should be applicable to clinical data, a constitutive model with a limited number of parameters is preferable. Therefore, a thick-walled, 1D, single-layered, fiber-reinforced model, of which the constitutive equations were developed by Holzapfel et al. (2000) and used for parameter estimation from clinical data (Stålhand et al. 2004; Stålhand 2009), was used in this study. Residual stresses were incorporated into the model by minimizing the circumferential stress gradients at physiological pressure by introducing a stress-free geometry with an opening angle (Chuong and Fung 1986; Takamizawa and Hayashi 1987). An estimation procedure was employed to fit the parameters of the model to the experimental data over the entire pressure range. The model was then used to compute the stress, strain, and global morphological parameters at physiological loading.

2 Material and methods

2.1 Experimental procedure

Since the experimental set-up has already been described in detail in van den Broek et al. (2011), only a short summary of the experimental procedure is presented here. Porcine hearts ($n = 7$) were obtained from a local slaughterhouse. Human coronary artery segments ($n = 2$) were obtained from explanted hearts from patients with heart failure receiving a donor heart at the Herz- und Diabeteszentrum Nordrhein-Westfalen (HDZ-NRW, Bad Oeynhausen, Germany). The study was approved by the local medical ethics committee. Patient details can be found in Table 1.

A proximal segment of the left anterior descending coronary artery (LAD) was excised from the heart, and cannulae were sutured to the proximal and distal ends of the segment. The length between the sutures was measured, representing the unstretched length (l_0). Side branches, about 5–6 per arterial segment, were closed using small stainless steel arterial clips (Ligaclip® Extra, Ethicon Endo-Surgery Inc., Cincinnati, OH). The vessel was placed in an organ bath (Fig. 1), containing a Krebs's solution, which was kept at a temperature of 37 and 38°C for the human and porcine arteries, respectively. The vessel was mounted to the set-up by

Table 1 Patient data, and the measured $\lambda_{z,phys}$. m, male; dTGA, dextro-Transposition of the great arteries; ITGA, levo-Transposition of the great arteries; Minor IT, Minor intimal thickening

	Sex	Age (years)	Heart disease	Status LAD	$\lambda_{z,phys}$
1	m	26	dTGA	Minor IT	1.3
2	m	41	ITGA	Minor IT	1.15

Fig. 1 Schematic representation of the experimental set-up. Adapted from van den Broek et al. (2011)

connecting the cannulae to silicone rubber tubes, making it part of a closed circuit. A pressure pump, which was driven by a pneumatic proportional valve (Festo, The Netherlands), was used to create a pulsatile pressure (P), which was measured with a pressure transducer (P10EZ, BD, USA). The length of the vessel could be controlled with a linear actuator and controller (235.5 DG and C843, Physik Instrumente, Germany), which was connected to the proximal cannula. The axial force (F_z) was measured with a force transducer (J&M Instruments, The Netherlands), which was connected to the distal cannula. An ultrasound scanner with a linear probe (8 MHz, Esaote Europe, The Netherlands), combined with an arterial analyzer (Art.Lab, Esaote Europe, The Netherlands), operated at 32 lines cm^{-1} in B-mode (30 frames s^{-1}), was used to measure the inner diameter ($D_i = 2r_i$, with r_i the inner radius), which was recorded simultaneously with the pressure. The linear actuator, the pressure–axial force acquisition, and the valve controlling the pressure were controlled using Labview software (National Instruments, USA).

2.1.1 Test protocol

The arterial segments were kept in the Kreb's solution for 30 min, after which papaverine (10^{-4} M) was added to induce vasorelaxation. After 15 min, the vessel was loaded with a cyclic pressure and stretched axially at a strain rate of 0.01 s^{-1} until the amplitude of the measured axial force signal was minimal. Several studies (van Loon 1977; Weizsäcker et al. 1983) have shown that this axial stretch (λ_z) is equal to the physiological axial pre-stretch ($\lambda_{z,\text{phys}}$) for the large elastic arteries. We assume a similar behavior for coronary arteries. At this $\lambda_{z,\text{phys}}$, the vessel was pressurized with a sinusoidal function with a mean and amplitude of 8 kPa. After reproducible signals were measured, the P – r_i and

P – F_z signals were recorded for one pressure cycle. The change in axial force during a pressure cycle (ΔF_z) was obtained by subtracting the axial force at $P = 0$. As some hysteresis was present, the P – r_i and P – ΔF_z relations at increasing pressure load were averaged with the corresponding relations at decreasing pressure load. The resulting P – r_i and P – ΔF_z relations were used in the estimation procedure described in Sect. 2.3. After the mechanical testing, a small ring was cut from the middle of the arterial segment and fixed in a 10% formalin solution in PBS. By measuring the inner and outer circumference of a stained ring section, the cross-sectional area of the unloaded segment (A_0) was determined. Previous research has shown that obtaining the unloaded inner and outer diameter from histology has a measuring inaccuracy of about 5–6% (Choy et al. 2005). While modeling the arteries, these possible inaccuracies were considered negligible.

2.2 Constitutive model

Considering the applicability to clinical data, a relatively simple constitutive model with a limited amount of parameters is used in this study. We therefore chose not to include smooth muscle activity (Zulliger et al. 2004b; Valentin et al. 2009; Kroon 2010), a layered structure (Wang et al. 2006), and more realistic fiber distributions (Gasser et al. 2006). Following Holzapfel et al. (2000), the artery is modeled as an incompressible, thick-walled, fiber-reinforced cylinder. The collagen fibers are modeled one-dimensionally, exerting only stress in the fiber direction ($\mathbf{e}_f^i$). The Cauchy stress $\boldsymbol{\sigma}$ is defined as:

$$\boldsymbol{\sigma} = -p\mathbf{I} + \hat{\boldsymbol{\tau}} + \sum_{i=1}^2 \tau_f^i \mathbf{e}_f^i \mathbf{e}_f^i, \quad (1)$$

with p the hydrostatic pressure, $\mathbf{I}$ the unity tensor, $\hat{\boldsymbol{\tau}}$ the isotropic matrix stress, and τ_f^i the fiber stress of fiber i . τ_f represents the contribution of all fibrous material and $\hat{\boldsymbol{\tau}}$ of all other (isotropic) tissue components. The isotropic matrix is described as a neo-Hookean material by

$$\hat{\boldsymbol{\tau}} = G(\mathbf{B} - \mathbf{I}), \quad (2)$$

with G the shear modulus and $\mathbf{B}$ the Finger tensor. $\mathbf{B}$ is defined as $\mathbf{B} = \mathbf{F} \cdot \mathbf{F}^T$, with $\mathbf{F}$ the deformation gradient tensor (see (9)). The fiber stress is defined as:

$$\tau_f = \begin{cases} k_1 \lambda_f^2 (\lambda_f^2 - 1) e^{k_2 (\lambda_f^2 - 1)^2} & \text{if } \lambda_f \geq 1 \\ 0 & \text{if } \lambda_f < 1. \end{cases} \quad (3)$$

Here, k_1 and k_2 are constants determining the stress–strain relation of the collagen fibers, and λ_f is the fiber stretch. The fibers can only exert force in tension. The fiber stretch can be calculated from the right Cauchy–Green tensor ($\mathbf{C} = \mathbf{F}^T \cdot \mathbf{F}$)

Fig. 2 The stress-free reference configuration Ω_0 , the unloaded configuration Ω_r and the loaded configuration Ω . Adapted from van Oijen (2003)

and the undeformed fiber direction ($\mathbf{e}_{f_0}$):

$$\lambda_f = \sqrt{\mathbf{e}_{f_0} \cdot \mathbf{C} \cdot \mathbf{e}_{f_0}}. \quad (4)$$

$\mathbf{e}_{f_0}$ of fiber i ($i = 1, 2$) can be described in matrix notation:

$$\mathbf{e}_{f_0}^i = [0 \quad \cos(\beta_0) \quad (-1)^i \sin(\beta_0)]^T, \quad (5)$$

with β_0 the angle of the fiber relative to the circumferential direction.

To take the residual stresses in the unloaded configuration (Ω_r) into account, we assume an open configuration (Ω_0) as the stress-free reference configuration (Fig. 2). In cylindrical coordinates (R, Θ, Z), the geometry of Ω_0 is then defined by

$$R_i \leq R \leq R_o, \quad 0 \leq \Theta \leq (2\pi - \alpha), \quad 0 \leq Z \leq l_0, \quad (6)$$

with R_i and R_o , the inner and outer radius, respectively, α the opening angle, and l_0 the length of the undeformed tube. The geometry of the deformed configuration (Ω) is defined in cylindrical coordinates (r, θ, z) by

$$r_i \leq r \leq r_o, \quad 0 \leq \theta \leq 2\pi, \quad 0 \leq z \leq l. \quad (7)$$

Here, r_i , r_o , and l represent the inner and outer radius and the length of the deformed tube, respectively.

When assuming isochoric deformation without torsion, the cylindrical coordinates (r, θ, z) can be written as:

$$r = \sqrt{\frac{R^2 - R_i^2}{k\lambda_z} + r_i^2}, \quad \theta = k\Theta, \quad z = \lambda_z Z, \quad (8)$$

with $k = 2\pi/(2\pi - \alpha)$. The deformation gradient $\mathbf{F}$ can be written as:

$$\mathbf{F} = \lambda_r \mathbf{e}_r \mathbf{e}_R + \lambda_\theta \mathbf{e}_\theta \mathbf{e}_\Theta + \lambda_z \mathbf{e}_z \mathbf{e}_Z, \quad (9)$$

with $\mathbf{e}_R$, $\mathbf{e}_\Theta$, $\mathbf{e}_Z$ the unit base vectors of (R, Θ, Z), and the following stretch ratios:

$$\lambda_r = \frac{\partial r}{\partial R} = \frac{R}{rk\lambda_z}, \quad \lambda_\theta = \frac{r}{R} \frac{\partial \theta}{\partial \Theta} = \frac{kr}{R}, \quad \lambda_z = \frac{l}{l_0}. \quad (10)$$

2.2.1 Balance equations

Neglecting body forces, inertia, and viscoelastic behavior, the conservation of momentum equation reads

$$\nabla \cdot \boldsymbol{\sigma} = \mathbf{0}. \quad (11)$$

Assuming axisymmetry and neglecting edge effects, only the radial component of (11) is relevant:

$$\frac{\partial \sigma_{rr}}{\partial r} + \frac{\sigma_{rr} - \sigma_{\theta\theta}}{r} = 0. \quad (12)$$

Using the boundary conditions, $\sigma_{rr}(r = r_o) = 0$ and $\sigma_{rr}(r = r_i) = -P$, together with $\boldsymbol{\tau} = \boldsymbol{\sigma} + p\mathbf{I}$, we obtain an expression for the internal pressure:

$$P = \int_{r_i}^{r_o} (\tau_{\theta\theta} - \tau_{rr}) \frac{dr}{r} = 0. \quad (13)$$

The deformation resulting from axial extension and an internal pressure is found by solving (13). Since, in general, (13) cannot be solved analytically, a numerical technique is used. We define the circumferential stretch at the inner surface as: $\lambda_{\theta_i} = \frac{kr_i}{R_i}$. For a given α and λ_z , the extra stress can be written as a function of λ_{θ_i} and r . Equation (13) can then be written as:

$$\int_{r_i}^{r_o} f(\lambda_{\theta_i}, r) \frac{dr}{r} - P = 0, \quad (14)$$

with $f(\lambda_{\theta_i}, r) = (\tau_{\theta\theta} - \tau_{rr})$.

A Newton iteration scheme was employed to linearize (14) with respect to λ_{θ_i} . The linearized equations were then solved by dividing the wall into 10 subdomains and performing piecewise quadratic Newton–Cotes integration. After solving (14), the reduced axial force could be computed using:

$$F_z = 2\pi \int_{r_i}^{r_o} \sigma_{zz} r dr - P\pi r_i^2. \quad (15)$$

2.3 Estimation procedure

The main idea of the estimation procedure is to minimize the difference between the experiments, consisting of the P - r_i and ΔF_z data, and the same signals computed with the model, by optimizing the model parameters. Keeping the clinical applicability in mind, we assumed here that ΔF_z is zero over the measured pressure range, since it is impossible to measure the axial force in-vivo.

First, to have an equal contribution over the pressure range, the data were re-sampled from time equidistant to pressure equidistant over the pressure range of 0–16 kPa with 25 samples. The difference between the experiment and

model was minimized by optimizing the four material parameters (G , k_1 , k_2 , β_0) and one geometrical parameter, for which the inner radius in the unloaded configuration ($r_{i\Omega_r}$) was chosen. To quantify the difference between experiment and model, the objective function ψ is defined as:

$$\psi(\Upsilon) = \frac{1}{N_s} \sum_{j=1}^{N_s} \left((r_{i,M}(j) - r_{i,E}(j))^2 + \varepsilon_F (\Delta F_{z,M}(j))^2 \right). \quad (16)$$

Here, Υ consists of the five parameters ($\Upsilon = \{G, k_1, k_2, \beta_0, r_{i\Omega_r}\}$), $N_s = 25$ is the number of samples, $\varepsilon_F = 0.01$ is a scaling parameter for ΔF_z , and subscript M and E represent the model and experiment, respectively. To introduce residual stresses in the unloaded configuration, we make use of the general idea that the arterial wall is able to remodel its microstructure toward a preferred biomechanical state. More specifically, the hypothesis that the circumferential stress gradient is minimal at physiological pressure ($P = 13.3$ kPa) and axial pre-stretch (Chuon and Fung 1986; Takamizawa and Hayashi 1987; Hayashi and Naiki 2009) is translated into a second objective function $\vartheta(\alpha)$:

$$\vartheta(\alpha) = \frac{1}{N_d} \sum_{m=1}^{N_d} (\Delta\sigma_{\theta\theta}(m))^2, \quad (17)$$

with $\Delta\sigma_{\theta\theta} = \sigma_{\theta\theta} - \sigma_{\theta\theta}(r_i)$, and $N_d = 10$ the number of sub-domains that make up the wall. It is assumed that the stretches going from the stress-free to the unloaded configuration are small, which means that the fiber contribution is very small. It can therefore be considered as a simple homogeneous bending problem, which means that the mid-wall circumferential stretch does not change between the stress-free and unloaded configuration. This, together with the incompressibility condition, means that the wall thickness does not change between the stress-free and the unloaded configuration (Taber and Eggers 1996). R_i and R_o can therefore be expressed in terms of $r_{i\Omega_r}$ and the measured unloaded cross-sectional area A_0 :

$$\begin{aligned} h_{\Omega_r} &= \sqrt{r_{i\Omega_r}^2 + \frac{A_0}{\pi}} - r_{i\Omega_r} = H, \\ R_i &= k \left(r_{i\Omega_r} + \frac{h_{\Omega_r}}{2} \right) - \frac{H}{2} = kr_{i\Omega_r} + \frac{h_{\Omega_r}}{2}(k-1), \\ R_o &= R_i + H = kr_{i\Omega_r} + \frac{h_{\Omega_r}}{2}(k+1). \end{aligned} \quad (18)$$

H and h_{Ω_r} are the wall thickness of the stress-free and unloaded configuration, respectively.

The estimation procedure (Fig. 3) started with the input for the model: the axial pre-stretch ($\lambda_{z,phys}$), the unloaded

Fig. 3 A schematic representation of the procedure to estimate $\Upsilon = \{G, k_1, k_2, \beta_0, r_{i\Omega_r}\}$ by minimizing the difference between the experiments (E) and model (M), while keeping the circumferential stress gradients minimal by optimizing α

cross-sectional area (A_0), and the pressure (P), obtained from the experiments, and an initial estimate of Υ ($\Upsilon^{(0)}$) and α ($\alpha^{(0)}$). Subsequently, ϑ was minimized (using Levenberg–Marquardt), leading to a new estimate of α . This continued until ϑ was minimized, resulting in an estimate of α for a certain Υ . This procedure of minimizing ϑ was repeated every time and one of the five parameters was changed, even while determining the Jacobian. The objective function ψ was minimized using the Levenberg–Marquardt algorithm, as implemented in the *lsqnonlin*-subroutine in Matlab (R2010a, The Mathworks, Natick (MA)). To prevent convergence issues in solving Eq. (14), the upper and lower bounds of Υ were $\{5 \text{ kPa}, 0.1 \text{ kPa}, 0.1, 10^\circ, 0.5 \text{ mm}\}$ and $\{500 \text{ kPa}, 50 \text{ kPa}, 100, 50^\circ, 2 \text{ mm}\}$, respectively. This resulted in an Υ and α , for which the model described the experimental data and which meets the uniform stress/strain hypothesis. To test whether a global minimum of ψ was found, the estimation procedure was repeated with three different initial parameter sets: $\Upsilon_1^{(0)} = \{30 \text{ kPa}, 3 \text{ kPa}, 3, 30^\circ, 1 \text{ mm}\}$, $\Upsilon_2^{(0)} = \{20 \text{ kPa}, 20 \text{ kPa}, 10, 20^\circ, 1.5 \text{ mm}\}$, $\Upsilon_3^{(0)} = \{200 \text{ kPa}, 1 \text{ kPa}, 15, 45^\circ, 1.7 \text{ mm}\}$. Furthermore, the eigenvalues of the Hessian at the converged solution were computed to assess whether any over-parameterization existed.

This estimation procedure was also repeated without the optimization of the opening angle ($\alpha = 0$), to gain insight into the effect of estimating the opening angle based on the uniform stress/strain hypothesis.

2.4 Data analysis

The variation of the parameters (R_i , α , G , k_1 , k_2 , β_0) between the different LADs was analyzed by determining the mean and standard deviation of each parameter.

For each LAD, the quality of the P - r_i relation obtained with the model was quantified by determining the mean relative difference between the model and the experiment:

$$\delta_r = \frac{1}{N_s} \sum_{j=1}^{N_s} \left| \frac{r_{i,M}(j) - r_{i,E}(j)}{r_{i,E}(j)} \right|. \quad (19)$$

The deviation of ΔF_z from zero was quantified according to:

$$\delta_F = \frac{1}{N_s} \sum_{j=1}^{N_s} |\Delta F_{z,M}(j)|. \quad (20)$$

The effect of including the opening angle in the optimization scheme on the estimated material parameters is quantified for each LAD according to:

$$\delta_\alpha = \frac{\Upsilon - \Upsilon_{\alpha=0}}{\Upsilon_{\alpha=0}}. \quad (21)$$

Since the anisotropic fiber part is very important in determining the stress-strain relations, especially in the high (physiological) pressure range, the mean fiber orientation, as well as the different stress components as a function of pressure, was determined for every artery.

3 Results

In Table 2, the geometric parameters obtained from the experiments ($\lambda_{z,\text{phys}}$ and A_0) and the optimization procedure (R_i , H and α) are shown for all 9 LADs. The two human LADs are represented by numbers 8 and 9. The unloaded arterial cross-sectional area A_0 , obtained from histology, was $(3.0 \pm 0.7) \text{ mm}^2$. The average physiological pre-stretch $\lambda_{z,\text{phys}}$ was 1.35 ± 0.09 . The other three geometrical parameters, R_i , H , and α , were derived using the fitting procedure described in Eqs. (16)–(18) and are also shown in Table 2. The minimization of the stress gradients at $P = 13.3 \text{ kPa}$, resulting in an estimate of α , was successful, as the circumferential stress gradient through the wall was close to zero at physiological pressure when residual strain was included (Fig. 4a). The resulting residual circumferential stretch in the unloaded configuration Ω_r was approximately $\pm 5\%$ (Fig. 4b). A typical result, in this case of one of the human arteries, of the P - r_i and P - ΔF_z relations from the experiment and the fitted model is shown in Fig. 5. For all measured porcine and human segments, the P - r_i and P - ΔF_z relations could be fitted accurately. The average relative deviation of P - r_i (δ_r) and

Table 2 Geometric parameter values of porcine LAD 1–7 and human LAD 8–9 and their means and standard deviations (SD); $\lambda_{z,\text{phys}}$, the physiological axial pre-stretch; A_0 the cross sectional area of the unloaded artery; R_i , H , and α , the final estimate of the stress-free inner radius, wall thickness, and opening angle from the estimation procedure

LAD	$\lambda_{z,\text{phys}}$	$A_0 \text{ (mm}^2\text{)}$	$R_i \text{ (mm)}$	$H \text{ (mm)}$	$\alpha \text{ (}^\circ\text{)}$
<i>Porcine</i>					
1	1.36	3.0	3.3	0.32	208
2	1.49	4.2	4.1	0.38	211
3	1.39	2.3	3.1	0.29	216
4	1.41	2.9	2.7	0.33	184
5	1.34	2.9	3.0	0.30	183
6	1.38	2.3	4.1	0.29	255
7	1.36	3.0	2.7	0.32	171
<i>Human</i>					
8	1.30	4.0	3.3	0.29	135
9	1.15	2.3	2.4	0.27	167
Mean	1.35	3.0	3.2	0.31	192
SD	0.09	0.7	0.6	0.03	35

Fig. 4 **a** Example of the circumferential Cauchy stress at mean physiological pressure ($P = 13.3 \text{ kPa}$) without ($\alpha = 0^\circ$) and with ($\alpha = 208^\circ$) opening angle, through the arterial wall thickness ($0 - 1 = r_i - r_o$); **b** The circumferential residual stretch in the unloaded configuration without ($\alpha = 0^\circ$) and with ($\alpha = 208^\circ$) opening angle through the arterial wall thickness ($0 - 1 = r_i - r_o$)

Fig. 5 Typical example of the model fit (solid line) of the experimental (circles) P - r_i **a** and P - ΔF_z **b** relations. The artery shown is LAD 9 (human) represented in Fig. 6 with $\diamond$

the average deviation of ΔF_z from zero (δ_F) were therefore also very small: 0.6% (or $10 \mu\text{m}$) and 0.4 mN, respectively (Table 3).

Table 3 Mean and standard deviation (SD) of the fitted material parameter values and the deviations in r_i and ΔF_z , of LAD 1–9

	G (kPa)	k_1 (kPa)	k_2 (–)	β_0 (°)	δ_r ($\times 10^{-3}$)	δ_F (mN)
Mean	21	2	8	36	6	0.4
SD	4	0.5	9	3	3	0.1

Fig. 6 The fitted material properties of all measured arteries. Each marker represents one LAD, human LADs 8 and 9 are represented by ∇ and $\diamond$. The errorbars represent the standard deviations of the parameters of all the LADs**Table 4** Mean and standard deviation (SD) of δ_α of LAD 1–9; the relative difference between the material parameters found with and without including the opening angle in the estimation scheme

	ΔG (%)	Δk_1 (%)	Δk_2 (%)	$\Delta \beta_0$ (%)	$\Delta \delta_r$ (%)	$\Delta \delta_F$ (%)
Mean	–4	–0.4	8	–1	8	–7
SD	1	1	1	0.3	6	5

The estimated material parameters are shown in Table 3 and Fig. 6. The maximal relative difference between parameters obtained with the three initial parameter sets ($\Upsilon_{1-3}^{(0)}$) was less than 0.3%. This indicates that a global minimum of the objective function (ψ) was found. Furthermore, the eigenvalues of the Hessian of the converged solutions were all greater than zero, indicating that the Hessian is convex near the solution and no over-parameterization existed. The parameters of the human arteries (represented with ∇ , $\diamond$) were not very different from the porcine arteries, apart from k_2 , which was much larger for LAD 8 (∇). While this might be an indication that the overall waviness of the collagen fibers of this vessel is less, we do not have an explanation for this feature.

The effect of including the opening angle on the parameters is shown in Table 4. The relative difference in the material parameters found was very small, indicating that the relative influence of the opening angle on the P - r_i and P - ΔF_z relations is small. Furthermore, the small relative difference in δ_r and δ_F shows that including the opening angle, via the homogeneous stress/strain hypothesis, does not have a negative impact on the quality of the fit.

Fig. 7 The average fiber (τ_f) and matrix ($\hat{\tau}$) contributions to the extra stress τ in the circumferential and axial direction as computed with the model **Fig. 8** The average fiber orientation β as a function of P at $\lambda_{z,\text{phys}}$, as computed with the model. Solid lines represent the porcine LADs, solid lines with ∇ , and $\diamond$ represent human LADs 8 and 9, respectively

Figure 7 clearly shows that the collagen fibers are the main load-bearing structure at physiological pressure. Compared to the matrix, the fiber contribution to the extra stress is approximately $5\times$ and $10\times$ higher in the axial and circumferential directions, respectively. Hence, when using a highly orthotropic model, the fiber orientation is very important in determining the stress–strain behavior. Figure 8 shows the fiber angle β for all vessels as a function of P . While the variation between the vessels is high at $P = 0$ ($\bar{\beta} = 48 \pm 4^\circ$), at physiological pressure, β is almost equal for all vessels; $(36.4 \pm 0.3)^\circ$ at $P = 13.3$ kPa.

4 Discussion

In this study, we used in-vitro inflation and extension experiments on porcine and human coronary arteries, to investigate the fiber orientation, as represented by a widely used two-fiber model (Holzapfel et al. 2000), at physiological loading conditions and was found to be very similar for all arteries measured. The experiments mimicked the in-vivo situation by stretching the arterial segments to $\lambda_{z,phys}$ but also enabled investigation of the mechanical behavior at the low pressure range. A microstructural-based constitutive model was successfully fitted to the experimental data, enabling the computation of the stresses and strains.

As already discussed in van den Broek et al. (2011), the main advantage of the adopted experimental approach is that the measurements are performed in a physiological environment. The structural integrity of the arterial segment is maintained, and damage is prevented since the maximum pressure does not exceed physiological values. The measurements were performed at an approximation of the physiological axial pre-stretch. Since measurements were performed on the epicardial coronary arteries, we assumed that the extravascular pressure, due to the cardiac contraction, was negligible. This also means that caution should be exercised when applying the current results to coronary arteries closer to the endocardium.

The main advantage of the single-layered model used is that there are a limited number of material parameters to be estimated, while the microstructure of the arterial wall is globally taken into account. It is well known that the arterial wall consists of three layers, with different constituents and related material parameters. Furthermore, it has been shown that a model with a fiber distribution is better able to capture observations from in-vitro studies (Gasser et al. 2006). Although adopting a model with a more realistic morphology, i.e., more layers, constituents, and fiber distributions, will yield a more accurate description of the mechanics of the arterial wall, including all these extra parameters in the estimation procedure will result in over-parameterization of the objective function, especially with the limited amount of information available in clinical data.

By adopting a thick-walled model, residual stresses could be taken into account. We chose a relatively easy way to implement the residual stresses, via the opening angle method as formulated by Taber and Eggers (1996). A approach based on an optimization law was chosen instead of experimentally determining the opening angles of the arteries. As already discussed in other papers (e.g., Rachev and Greenwald 2003), experimentally obtained open-sector geometries do not resemble a perfect circle with an uniform wall thickness. Considering that the method should be applicable clinically, we believe that the adopted approach is preferable. By introducing a second objective function (Eq. 17),

to minimize the circumferential stress gradient in the wall at physiological pressure and axial pre-stretch, a measure for the opening angle α was found. While other, more sophisticated, methods to incorporate residual stresses are available (VanDyke and Hoger 2002; Hoger 1997; Olsson et al. 2006), the current method proved to be relatively easy to implement and sufficient to minimize the stress gradients at physiological loading. A prerequisite for this method of inversely estimating α to work is that the $P-r_i$ and $P-\Delta F_z$ relations are relatively insensitive to small changes in α . This was confirmed by the small differences between the material parameters found with and without including the estimation scheme for α . Including the residual stress/stain, this way did also not negatively influence the quality of fit, as was shown by the small differences in δ_r and δ_F (Table 4). The average value of α was $(192 \pm 35)^\circ$, which corresponds to experimental values found by Guo and Kassab (2004) and Wang and Gleason (2010) for porcine coronary arteries and by Valenta et al. (1999) for human coronary arteries. Note that due to the minimization of the circumferential stress gradients, and therefore the strain gradients, the fibers throughout the wall thickness are all oriented in the same direction at $P = 13.3$ kPa.

A limitation of this study is that only circumferential residual strains are taken into account. Recent studies have clearly shown that (layer specific) axial residual strains exists and that they can have a significant effect on the stress distribution in the arterial wall (Holzapfel et al. 2007; Wang and Gleason 2010). Including these residual axial strains resulted in a decrease in circumferential stress gradients, while the axial stress gradients increased. In further research, it would be very interesting to include these residual axial strains into the optimization procedure. However, to be able do this for patient specific, intact arteries require an optimization rule that captures these effects.

The model was able to fit the measured $P-r_i$ and $P-\Delta F_z$ relations accurately, represented by an average deviation of only $10 \mu\text{m}$ ($\bar{\delta}_r = 0.006$) and 0.4 mN ($\bar{\delta}_F$) from the experimental data. Multiple initial parameter sets resulted in the same optimal parameter set Υ , indicating that a global minimum of the objective function (ψ) was found. An important parameter to fit both $P-r_i$ and $P-\Delta F_z$ relations accurately is the scaling parameter ε_F . ε_F was chosen in such a way that the contribution of the radius and axial force to the objective function (Eq. 16) was approximately equal. By altering ε_F either the radius or axial force data will therefore start to dominate the objective function, and a different global minimum will be found. If ε_F is chosen very high, which means a very strict axial force constraint, the solution space is likely to be restricted so much that it is unlikely that the constitutive equations are able to describe the found $P-r_i$ relations.

The relative variation in Υ between the different vessels is quite large, especially for the parameter k_2 . The relative

variation in the parameter representing the global fiber orientation β_0 is quite small, but, since the main load is taken by the fibers (Fig. 7), the P - r_i and P - ΔF_z relations are most sensitive to changes in β_0 . The value of β_0 corresponds to the average fiber angle of the adventitia of the human aorta as found by Holzapfel et al. (2002). Besides the value of k_2 of LAD 8 (∇), the material parameters of the human arteries were consistent with those of the tested porcine arteries. A clear limitation of this study is that we were able to only include two human specimens. Therefore, further research is needed to confidently translate the obtained results to human coronary arteries. The two human specimens, however, do contribute to the findings regarding the fiber orientation at physiological loading, while their axial pre-stretch was significantly lower.

With the experimental set-up, only the changes in axial force (ΔF_z) could be measured accurately, while other studies (Zulliger et al. 2004a; Rezakhaniha and Stergiopulos 2008) reported problems with fitting both P - r_i and P - F_z relations with similar fiber-reinforced models. Rezakhaniha and Stergiopulos (2008) proposed a model that included anisotropic elastin, which increased the axial stress, enabling fitting of both the radius and absolute axial force data. It would be interesting to use a model, which incorporates anisotropic elastin in future studies. Adding anisotropic elastin to the constitutive model used in this study will influence the material parameters found. More specifically, since the elastin fiber angle in the model of Rezakhaniha and Stergiopulos (2008) is more axially oriented, the fibers representing the collagen fibers will be oriented more circumferentially compared with the fiber angle found here. It should be noted, however, that increasing the number of material parameters is likely to result in over-parameterization. Furthermore, since clinically obtained data lack absolute force information, it is unlikely that this anisotropic elastin parameter can be fitted and should therefore be prescribed.

As mentioned before, in the physiological pressure range, the fibers bear almost all the load (Fig. 7). The fiber orientation (β) is therefore the main determinant of the stress-strain behavior at those pressures, especially in this two-fiber model. Note that β is determined by the axial and circumferential strains and the value of β in the stress-free configuration (β_0). For all vessels measured, the fiber orientation at physiological loading β_{phys} was almost equal being $(36.4 \pm 0.3)^\circ$, as indicated by a standard deviation of only 1%. An explanation for this particular fiber orientation can be found by applying netting analysis. In filament-wound composite theory (Gay et al. 2003), netting analysis is often used to describe the behavior of fiber-reinforced composite materials. The main assumption in netting analysis is that all loads are supported by the fibers only. Since we model the arterial wall as a filament-wound tube, netting analysis can be used to approximate the fiber orientation in the high pressure range.

As described in several papers (Spencer et al. 1974; Wild and Vickers 1997; Xia et al. 2001), an optimal fiber angle exists for which the fibers take all the load due to the internal pressure. This optimal winding angle is approximately 35° relative to the circumferential direction. This behavior is exactly what we see in our results, for high pressures β approaches 35° (Fig. 8). The derived angle aligns with the largest principal stress directions, which is in agreement with the theory proposed by Hariton et al. (2007), which hypothesized that the collagen remodeling is modulated by principal stresses.

It must be stressed that the fiber orientation found must not be viewed as the actual fiber morphology in the arterial wall but just as the net result of all fibrous material as described with the two-fiber model. The findings in this study are therefore mainly of interest as extra modeling constraints or for reducing the number of parameters, with similar, highly orthotropic, models.

In conclusion, porcine and human coronary arteries were subjected to inflation/extension experiments at physiological axial conditions and a pressure range of 0–16 kPa. The main finding was that the fiber orientation at physiological loading, as described with the two-fiber model (Holzapfel et al. 2000), is almost equal for all arteries measured, which could be physically interpreted using netting analysis and which may result from arterial remodeling as it is structurally based. In future studies, which use similar, highly orthotropic, models to estimate material parameters from clinical data, this may prove to be useful in reducing the number of parameters or as an extra modeling constraint.

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