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Constitutive modeling of human femoropopliteal artery biaxial stiffening due to aging and diabetes

Anastasia Desyatova, Jason MacTaggart, Alexey Kamenskiy *

Department of Surgery, University of Nebraska Medical Center, Omaha, NE, United States

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ABSTRACT

Atherosclerotic obstructive disease of the femoropopliteal artery (Peripheral Arterial Disease, PAD) is notorious for high treatment failure rates. Older age and diabetes mellitus (DM) are among the major risk factors for PAD, and both are associated with increased arterial stiffness. Our goal was to develop a constitutive model describing multiaxial arterial stiffening, and use it to portray aging of normal and diabetic human femoropopliteal arteries (FPA). Fresh human FPAs (n = 744) were obtained from 13–82-year-old donors. Arteries were tested using planar biaxial extension, and their behavior was modeled with a constitutive relation that included stiffening functions of age. FPA diameter, wall thickness, circumferential, and longitudinal opening angles increased with age, while longitudinal pre-stretch decreased. Diameter and circumferential opening angle did not change with age in subjects with DM. Younger FPAs were more compliant longitudinally but became more isotropic with age. Arteries with DM stiffened significantly faster in the circumferential direction than arteries without DM. Constitutive model accurately portrayed orthotropic stiffening with age of both normal and diabetic arteries. Constitutive description of FPA aging contributes to understanding of arterial pathophysiology and can help improve fidelity of computational models investigating device-artery interaction in PAD repair by providing more personalized arterial properties.

Statement of Significance

We have analyzed n = 744 human femoropopliteal artery (FPA) specimens using biaxial tensile testing to derive constitutive description of FPA aging in diabetic and non-diabetic subjects. The proposed model allows determination of FPA mechanical properties for subjects of any given age in the range of 13–82 years. These results contribute to understanding of FPA pathophysiology and can help improve fidelity of computational models investigating device-artery interaction in peripheral arterial disease repair by providing more personalized arterial properties. In addition, they can guide the development of new materials tunable to diabetic and non-diabetic arteries.

1. Introduction

Peripheral arterial disease (PAD) often manifests as occlusive atherosclerotic lesions in the femoropopliteal artery (FPA) obstructing blood flow to the lower limb. It is associated with high morbidity, mortality, and impairment in the quality of life. Older age and Diabetes Mellitus (DM) are among major risk factors for PAD [1], and patients with DM are 2-4-fold more likely to develop the disease [2], and are 15-fold more likely to have an amputation compared to non-diabetic PAD patients [3–5].

Significant evidence suggests that arterial stiffness is a key component in aging and in the pathogenesis of DM [6–8]. Aging is characterized by altered turnover and crosslinking of collagen, degradation of elastin, its replacement by collagen and proteoglycans, and increased production of advanced glycation end-products (AGEs) and cross-links resulting in overall stiffening of the artery [8]. Glycation and AGEs formation in the carbonyl-enriched environment of DM is believed to have profound effects on enhancing age-related arterial stiffening [8], but exact contribution of DM to arterial stiffness in human FPAs is poorly understood.

Arterial stiffness is a multi-directional measure because arterial properties are anisotropic. Human FPAs contain mainly circumferentially-oriented smooth muscle cells (SMCs) in the media, longitudinal elastic fibers in the external elastic lamina

* Corresponding author at: Department of Surgery, 987690 Nebraska Medical Center, Omaha, NE 68198-7690, United States.
E-mail address: Alexey.Kamenskiy@unmc.edu (A. Kamenskiy).

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(EEL) and adventitia, and helically-oriented collagen fibers in the adventitia [9–11]. Recent work [12] reported constitutive parameters for human FPAs in seven age groups, demonstrating that FPA undergoes multiaxial stiffening with faster changes occurring longitudinally due to degradation and fragmentation of elastin in the EEL [9,12]. This analysis was based on a large sample size (n = 579) that included a wide range of ages, but data were presented for seven discrete age groups with no means of interpolating arterial properties between the presented ages.

Current work further explores these data supplemented with an additional 165 human FPAs, and proposes a way of incorporating aging explicitly into the constitutive relation between Cauchy stresses and stretches to allow for continuous description of mechanical properties with respect to age. Using this approach, orthotropic FPA mechanical properties can be determined for subjects of any given age, not just the seven age groups described previously. In addition, the framework will be applied to describe age-related multi-axial stiffening of human FPAs in subjects with and without DM. In combination with morphometric data on arterial diameters, wall thickness, opening angles, and longitudinal pre-stretch in subjects with and without DM that will also be summarized here, these data will aid computational models by reducing the required number of inputs to simulate material response to just two parameters: patient's age and DM status. Furthermore, for cases when DM status is unknown, a set of constitutive parameters describing aging of FPAs irrespective of DM status will also be provided.

2. Methods

2.1. Arterial specimens, mechanical testing, and data reduction

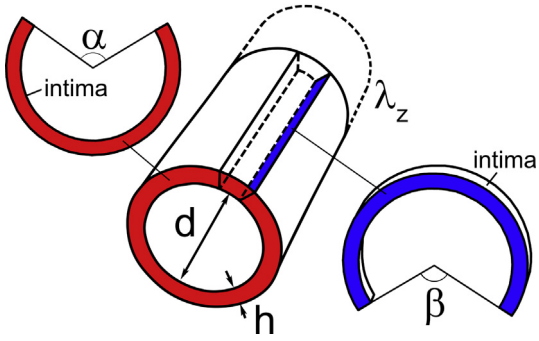
Fresh FPAs (n = 744) from organ and tissue donors (n = 466) were obtained from the Nebraska Organ Recovery System (NORS) within 24 h of subject's death after obtaining consent from the next of kin. Donors were predominantly Caucasian (94%) males (81%) and on average 55 ± 15 years old (range 13–82 years old). Self-reported DM was present in 26% of subjects, 47% had hypertension, 10% Coronary Artery Disease, 25% dyslipidemia, 54% were either past or current tobacco users, 21% abused alcohol, and 50% had Body Mass Index of ≥30. Longitudinal pre-stretch λ_z was measured prior to excision of the artery from the body using an umbilical tape [11]. Arterial rings and longitudinal sections were used to determine FPA diameter (d), wall thickness (h), and circumferential (α) and longitudinal (β) opening angles using photographs and image analysis [12]. Circumferential and longitudinal opening angles were measured according to schematic presented in Table 1.

Planar biaxial tests were performed on 13 × 13 mm (when permitted by diameter) arterial samples, and data were collected after the arteries were preconditioned for 10–20 equibiaxial cycles to achieve a repeatable response. The first 30% of samples were tested in load-controlled mode with 7 different force-ratios (1:1, 1:2, 1:4, and 1:10 on each axis) using a custom-build device [13]. Specimens were attached using stainless-steel hooks and loops of surgical suture which allowed the samples to shear freely. Since no sizable shear was observed [9], the other 70% of arteries were tested using the rake attachment system of CellScale. These samples were tested in stretch-controlled mode at 0.01 s^{-1} strain rate [12] using CellScale Biotester equipped with "250 g" (max load 2.5 N) Honeywell Sensotec load cells and 19 different stretch-ratios ranging from 1:1 to 1:0.1 on each axis. Equibiaxial stability checks were performed before and after the testing sequence to ensure that the specimens had not accumulated damage as they went through the battery of tests.

Experimental data obtained from both devices were then used to determine unique sets of constitutive parameters for the 4-fiber FPA constitutive model [11] using nonparametric bootstrapping. Bootstrapping allowed to assess parameter uniqueness irrespective of the type of test performed, i.e. load- or stretch-controlled. Specimens that produced a good fit ($R^2_{\theta,z} > 0.9$) were used to generate 19 stress-controlled loading protocols for each sample, which were then used to determine constitutive

Table 1
Morphometric parameters and residual stretches for all subjects considered together, and divided into non-DM and DM groups. Note that the total number of subjects in each group not necessarily equals to the sum of DM and non-DM subjects because DM status for several subjects was unknown. Here n is the number of specimens in the age group, d is the inner diameter, h is wall thickness (both in the load-free configuration), α is circumferential opening angle, β is longitudinal opening angle, λ_z is *in situ* longitudinal pre-stretch. Note that longitudinal strip curves intima outward, likely due to presence of pre-stretched longitudinally-oriented elastic fibers in the EEL [9]. Measurements of the opening angles are presented schematically in the right panel.

Age group, years	n	Mean age, years	d, mm	h, mm	α, °	β, °	λ_z
All subjects together							
11–20	34	16.5	2.81 ± 0.60	1.37 ± 0.32	125 ± 47	90 ± 86	1.55 ± 0.13
21–30	31	24.8	3.28 ± 0.76	1.42 ± 0.36	149 ± 69	107 ± 67	1.41 ± 0.13
31–40	56	35.7	3.64 ± 0.86	1.45 ± 0.39	151 ± 55	151 ± 60	1.38 ± 0.08
41–50	73	46.8	3.76 ± 1.22	1.58 ± 0.50	165 ± 63	183 ± 63	1.26 ± 0.08
51–60	174	56.1	3.74 ± 1.33	1.65 ± 0.57	165 ± 65	242 ± 45	1.19 ± 0.11
61–70	162	65.0	4.15 ± 1.28	1.91 ± 0.51	193 ± 78	268 ± 46	1.16 ± 0.07
71–80	43	75.7	4.65 ± 1.28	1.88 ± 0.47	155 ± 64	304 ± 30	1.12 ± 0.06
Subjects with DM							
11–20	1						
21–30	0						
31–40	3	40.0	4.14 ± 0.38	1.49 ± 0.14	181 ± 24	195 ± 74	1.30 ± 0.08
41–50	13	46.1	4.03 ± 1.01	1.66 ± 0.70	124 ± 61	171 ± 86	1.26 ± 0.10
51–60	51	56.7	3.96 ± 1.32	1.66 ± 0.56	156 ± 68	246 ± 50	1.15 ± 0.12
61–70	53	64.7	3.96 ± 1.35	1.96 ± 0.58	167 ± 84	270 ± 60	1.15 ± 0.07
71–80	18	76.7	4.81 ± 1.30	1.84 ± 0.42	148 ± 74	305 ± 30	1.08 ± 0.03
Subjects without DM							
11–20	32	16.4	2.80 ± 0.61	1.39 ± 0.32	125 ± 45	90 ± 88	1.55 ± 0.14
21–30	30	24.7	3.30 ± 0.75	1.40 ± 0.34	145 ± 65	108 ± 68	1.41 ± 0.13
31–40	52	35.3	3.57 ± 0.84	1.45 ± 0.40	149 ± 56	147 ± 59	1.38 ± 0.08
41–50	58	46.9	3.67 ± 1.28	1.55 ± 0.45	173 ± 57	184 ± 57	1.26 ± 0.08
51–60	117	55.7	3.62 ± 1.35	1.62 ± 0.58	167 ± 60	239 ± 42	1.21 ± 0.10
61–70	90	65.1	4.16 ± 1.14	1.88 ± 0.50	200 ± 71	262 ± 36	1.18 ± 0.07
71–80	21	75.3	4.43 ± 1.15	1.84 ± 0.51	152 ± 47	301 ± 32	1.12 ± 0.06



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