Acta Biomaterialia 10 (2014) 1301–1313

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Passive biaxial mechanical properties and in vivo axial pre-stretch of the diseased human femoropopliteal and tibial arteries

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ARTICLE INFO

Article history:
Received 29 July 2013
Received in revised form 7 December 2013
Accepted 13 December 2013
Available online 24 December 2013

Keywords:
Femoropopliteal artery
Tibial artery
Biaxial mechanical properties
In vivo axial pre-stretch
Constitutive modeling

ABSTRACT

Surgical and interventional therapies for atherosclerotic lesions of the infrainguinal arteries are notorious for high rates of failure. Frequently, this leads to expensive reinterventions, return of disabling symptoms or limb loss. Interaction between the artery and repair material likely plays an important role in reconstruction failure, but data describing the mechanical properties and functional characteristics of human femoropopliteal and tibial arteries are currently not available. Diseased superficial femoral (SFA, $n = 10$), popliteal (PA, $n = 8$) and tibial arteries (TA, $n = 3$) from 10 patients with critical limb ischemia were tested to determine passive mechanical properties using planar biaxial extension. All specimens exhibited large nonlinear deformations and anisotropy. Under equibiaxial loading, all arteries were stiffer in the circumferential direction than in the longitudinal direction. Anisotropy and longitudinal compliance decreased distally, but circumferential compliance increased, possibly to maintain a homeostatic multiaxial stress state. Constitutive parameters for a four-fiber family invariant-based model were determined for all tissues to calculate in vivo axial pre-stretch that allows the artery to function in the most energy efficient manner while also preventing buckling during extremity flexion. Calculated axial pre-stretch was found to decrease with age, disease severity and more distal arterial location. Histological analysis of the femoropopliteal artery demonstrated a distinct sub-adventitial layer of longitudinal elastin fibers that appeared thicker in healthier arteries. The femoropopliteal artery characteristics and properties determined in this study may assist in devising better diagnostic and treatment modalities for patients with peripheral arterial disease.

1. Introduction

Peripheral artery disease (PAD) is primarily an atherothrombotic condition reducing blood flow to the lower limbs. It is a major contributor to the public health burden and is associated with high morbidity, mortality and impairment in quality of life [1]. The total annual costs in the US of hospitalizations for patients with PAD are in excess of $21 billion per year, and per-patient costs of PAD are higher than those for both coronary artery disease and cerebrovascular disease [2]. The high cost of PAD is partially attributed to the significant numbers of peripheral vascular operations and interventions that fail, resulting in poor clinical outcomes and a need for repetitive interventions [3–6]. Specifically, restenosis within 3 years after femoropopliteal bypass occurs in 27% of patients, while occlusion occurs in 19% [7]. The results for angioplasty and stenting in the lower extremity are even worse, with 50–85% of patients developing hemodynamically significant restenosis, and 16–65% developing occlusion within just 2 years after treatment [8], leading to reintervention in 37–54% of patients [6].

Although the underlying reasons for such alarmingly high rates of treatment failure are still not fully understood, the complex biomechanical forces that occur in the femoropopliteal artery during locomotion are thought to play a significant role [9–12]. These forces create repetitive trauma to both the artery and repair materials. Femoropopliteal artery stents appear to have the highest incidence of fracture [13] as limb-generated movements and forces are capable of crushing and tearing apart metallic stent devices over time. These same movements and forces are also likely culprits

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http://dx.doi.org/10.1016/j.actbio.2013.12.027

in the development of the primary arterial lesion, producing a chronic injury to the artery wall that leads to deleterious cellular and biochemical responses.

Data on the function of the femoropopliteal artery, its mechanical properties and the conditions of its surrounding local environment are essential for understanding artery-repair device interaction. Surprisingly, the mechanical properties of the infrainguinal arteries, such as the femoropopliteal and tibial arteries, have not been the subject of extensive study, perhaps due to difficulties associated with the supply of these tissues. Most existing human studies are limited to the proximal femoral portions of the artery [14] and utilize either duplex ultrasound for nondestructive in vivo testing, or uniaxial tensile testing for excised cadaveric arteries [15–19]. However, in vivo ultrasound and uniaxial tensile experiments are not sufficient to characterize the complex nonlinear anisotropic properties of arterial tissue [20,21]. Biaxial tensile testing is currently the most viable experimental method, although it also has limitations due to its 2-D nature [21–23].

The goal of the current work was to measure the passive biaxial mechanical properties of diseased human femoropopliteal and tibial arteries. Apart from measuring the mechanical response of the artery walls, we also calculated the constitutive model parameters and the in vivo axial pre-stretch that allows the artery to eliminate axial work and conserve energy during the pulse cycle [24]. Since in vivo axial pre-stretch cannot be measured directly in aged and diseased arteries as it is not equal to in situ retraction upon transection [25], we present the framework for calculating these values based on the measured arterial mechanical properties.

2. Materials and methods

2.1. Materials

With Institutional Review Board approval and after informed patient consent, 10 superficial femoral (SFA), 8 popliteal (PA), 3 tibial arteries (TA) and 4 SFA atherosclerotic plaques were harvested from 10 patients (63 ± 8.3 years old) after lower-extremity amputation for critical limb ischemia. Subject population data are presented in Table 1. All arteries were nonuniformly diseased and were classified into three stages of atherosclerotic severity based on visual inspection and manual palpation. Stage one (+) arteries demonstrated no obvious signs of atherosclerotic disease. Stage two (++) vessels demonstrated mild disease severity, consisting of palpable atheromas or thin-cap fibroatheromas that did not contain heavy calcification or result in complete occlusion. Stage two arteries typically contained lesions that would be considered suitable for conservative medical therapy and were not the main reason for amputation. Stage three (+++) arteries demonstrated severe atherosclerotic disease consisting of fissured, ulcerated, hemorrhagic, thrombotic, calcific or fibrotic lesions, often completely occluding the lumen of the vessel. These lesions frequently require angioplasty/stenting or bypass surgery. Severe disease in stage three arteries was the primary cause of amputation.

2.2. Mechanical testing

2.2.1. Specimen preparation

All tissues were transported to the testing facility in 0.9% NaCl physiological saline solution on ice and testing was done within 4 h of harvesting to preserve freshness. Prior to testing, an arterial ring of approximately 2 mm in length was cut from each specimen and photographed. The ring was then cut radially to release the residual stresses. Although some dispute exists in the literature as to whether one radial cut is sufficient to release all residual stresses in the tissue [21], this question merits a separate investigation and was beyond the scope of the current study. The opening angle α was measured between two lines drawn from the center of the sector to its outer tips (see Appendix) [26]. This definition of the opening angle follows Sommer and Holzapfel [29], and is different from the one in which α is calculated as the angle between two lines drawn from the midpoint of the arc of the inner vessel wall to the outer tips of the open sector [24]. This angle can easily be obtained from our measurements as $\frac{\alpha}{2}$.

After measuring the opening angle, the entire arterial segment was cut longitudinally and spread out into a flat sheet. Grossly disease-free square specimens 13 mm × 13 mm were then cut out of this sheet, preserving the in vivo longitudinal and circumferential orientations parallel with the specimen's square edges. Most specimens opened to initially slightly curved configurations that flattened out either under the specimen's own weight or after application of the 0.01 N tare pre-load (see Sec. 2.2.4 Test protocols below). Although such flattening may introduce residual stresses to the specimen, these stresses are small compared to those occurring in the sample during testing. Wall thickness was manually measured and averaged at six different locations using a Starrett 1010 Z caliper. Careful measurement technique ensured that the caliper lips touched the specimen, but did not compress it. Caliper-measured wall thickness values were corroborated with optical assessment using the photographs of the arterial rings during measurement of the opening angle. Dimensions of the specimen in the longitudinal and circumferential directions were measured with a Mitutoyo Electronic Digital Caliper.

Samples were attached to the biaxial testing device using stainless steel hooks and loops of thick nylon surgical suture [20,27,28]. Hooks were attached to the specimen as close to the edges as possible to minimize the influence of edge effects on strain measurements. Four graphite markers were attached to the arterial intima to track the deformations of the specimen (Fig. 1). During testing, specimens were completely immersed in 0.9% NaCl physiological

Table 1
Demographics of patients used for the study. CAD = coronary artery disease; DM = diabetes mellitus; HTN = hypertension; HLP = hyperlipidemia. Atherosclerotic disease severity ranges from nearly normal tissue (+) to severely diseased (+++) artery as determined by visual inspection and manual palpation.

#	Age	Risk Factors					Indication for amputation	Atherosclerosis Severity
		CAD	DM	HTN	HLP	Smoking		
1	55	+		+	+	+	failed bypass, infection	+++
2	76	+	+	+	+	+	N/A	++
3	66	+		+	+	+	N/A	++
4	55	+		+	+	+	thrombosis, gangrene	++
5	55	+		+	+	+	N/A	+
6	55	+		+	+	+	occlusion, gangrene	+++
7	63			+			popliteal aneurysm	+
8	66			+	+		ischemia/reperfusion injury	+
9	76	+	+	+	+	+	gangrene	++
10	60	+	+	+	+	+	N/A	+++