Materials Letters 209 (2017) 175–177

Contents lists available at ScienceDirect

Materials Letters

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

Elasticity response of electrospun bioresorbable small-diameter vascular grafts: Towards a biomimetic mechanical response

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ARTICLE INFO

Article history:
Received 10 May 2017
Received in revised form 15 June 2017
Accepted 25 July 2017
Available online 26 July 2017

Keywords:
Vascular Grafts
Electrospinning
Biomimetic
Dynamic compliance

ABSTRACT

The elasticity response of synthetic vascular grafts is very important for the grafts long term success. Natural arteries possess a characteristic response to internal pressure, known as J-curve. Mimicking this feature is believed to be the path to obtain a vascular graft that does not fail over time. In this work, two synthetic bioresorbable polymers were selected to design small-diameter vascular grafts (SDVGs) based on their biomimetic mechanical response. Poly(L-lactic acid) (PLLA) was chosen for its similar response to collagen and a segmented poly(ester urethane) (PHD) was used to introduce elastomeric properties through its elastin-like behavior. A bilayered electrospun conduit with two different PLLA/PHD blends was fabricated by mimicking the natural collagen-to-elastin ratio in the media and adventitia layers. The biomimetic mechanical response, compliance and elastic modulus were studied under pulsated pressure conditions. The grafts nanofibrous morphology as well as its layered structure resulted in properties promising for bypass applications.

1. Introduction

Still to these days there is a strong need for small-diameter vascular grafts (SDVGs) for long-period implantation [1]. Despite the great effort and research done to overcome this problem, commercial Dacron® or expanded poly(tetrafluoroethylene) (ePTFE) vascular grafts are the only synthetic materials approved by U.S. Food and Drug Administration as replacement when failure in small-diameter blood vessels occurs [2]. These grafts are stiff and lack a regeneration potential. Even more, they are associated with different levels of thrombogenicity, stenosis, infection, and fail mainly due to reocclusion, attributed to intimal hyperplasia at the distal anastomosis. Recent studies have reported a strong correlation between graft mechanical properties and intimal hyperplasia onset and severity. In this sense, dynamic mechanical compliance mismatch between native artery and the artificial graft has been identified as a key determinant of SDVGs success [3]. Compliance mismatch disrupts blood flow and results in zones of recirculation, flow separation, and low wall shear stress at the endothelium [4]. Low wall shear stress initiates the release of vasoactive substances, gene activation, protein expression, and cytoskeletal rearrangement that stimulate intimal hyperplasia [5]. Lower difference between the vessel and the SDVG compliance values is believed to reduce intimal hyperplasia, therefore prolonging the graft patency [5]. Despite several studies proving the importance of reducing the biomechanical mismatch for the grafts success, there has been little progress in the research and development of SDVGs with biomechanical properties matching the native ones [6,7].

Natural vessel extracellular matrix components (elastin and collagen) are responsible for its unique mechanical response. Natural arteries show high compliance at low pressure ranges, which diminishes as pressure is increased [8]. This behavior is attributed to collagen fibers recruitment and smooth muscle cells activation [9]. The structure of arteries and the relationship between arterial tissue components is becoming the main subject of graft development [10].

Electrospinning emerged as a versatile technique to produce SDVGs with extracellular matrix-like structure and tailored sizes. Novel emerging electrospinning techniques have proven to

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http://dx.doi.org/10.1016/j.matlet.2017.07.110

successfully scale up this processing method for mass production [11]. Different approaches were addressed, with natural and synthetic polymers, and their blends, with incorporation of bioactive molecules, in a single layer or multiple layer structures [12,13]. Arterial mechanical response has proven difficult to reproduce with a single component. Therefore, blended and multilayered SDVGs were developed.

In this work, two synthetic bioresorbable polymers were used to design SDVGs based on their biomimetic mechanical response. Poly(L-lactic acid) (PLLA) was chosen for its similar response to collagen [14], and a segmented poly(ester urethane) (PHD) was used to introduce a elastin-like behavior [15]. A bilayered electrospun conduit with two different PLLA/PHD blends was fabricated by mimicking the natural collagen-to-elastin ratio in the media and adventitia layers [16,17]. The biomimetic mechanical response, compliance and elastic modulus were studied under pulsated pressure conditions, following criteria stated in our framework of arterial mechanics [14,18].

2. Materials and methods

2.1. Electrospinning

Electrospun SDVGs were obtained according to previously reported conditions [19]. Sequential electrospinning was performed to produce a bilayered SDVG, where the inner layer was electrospun first followed by the deposition of the outer layer. Thus, outer layer was selected to mimic natural arteries adventitia layer, whereas inner layer intended to mimic the media layer.

Table 1
%C and $E_{P\varepsilon}$ of PLLA, PHD and bilayered SDVG, and ovine femoral arteries for the pressure ranges (PR) studied.

Sample	PR (mmHg)	%C (10^{-2} mmHg)	$E_{P\varepsilon}$ (MPa)
PLLA (Ref. [14]) mean ± SD	50–90	$1.38 \pm 0.21^{b,c}$	$1.06 \pm 0.09^{b,c}$
	80–120	$0.93 \pm 0.13^{a,c}$	$1.43 \pm 0.15^{a,c}$
	110–150	$0.76 \pm 0.15^{a,b}$	$1.76 \pm 0.26^{a,b}$
PHD mean ± SD	50–90	$3.81 \pm 0.62^{b,c}$	$0.41 \pm 0.05^{b,c}$
	80–120	$2.76 \pm 0.43^{a,c}$	$0.57 \pm 0.07^{a,c}$
	110–150	$1.90 \pm 0.36^{a,b}$	$0.73 \pm 0.09^{a,b}$
Bilayered mean ± SD	50–90	$2.19 \pm 0.69^{b,c}$	$0.86 \pm 0.31^{b,c}$
	80–120	$1.27 \pm 0.20^{a,c}$	$1.10 \pm 0.18^{a,c}$
	110–150	$0.79 \pm 0.21^{a,b}$	$1.71 \pm 0.38^{a,b}$
Ovine femoral (Ref. [14]) mean ± SD	60–90	8.52 ± 1.15	0.166 ± 0.030
	100–130	0.79 ± 0.20^{d}	1.576 ± 0.478^{d}

a,b,c Statistical difference ($p < 0.05$) compared with 50–90 mmHg, 80–120 mmHg and 110–150 mmHg, respectively.
d Statistical difference ($p < 0.05$) compared with 100–130 mmHg.

2.2. Dynamic pressure diameter tests

A hemodynamic work bench simulator (HWBS) designed to measure instantaneous pressure and diameter in blood vessels and scaffolds was employed following the same protocol as reported before [14].

Diameter–pressure analysis (D-P) was performed following the criteria stated at ISO7198 standard [20]. D-P loops were evaluated at 50–90, 80–120 and 110–150 mmHg range. Dynamic compliance was calculated as defined in Ref. [20] as follows:

$$\%C = \frac{\frac{R_S - R_D}{R_D}}{P_S - P_D} \cdot 10^4 \tag{1}$$

where P_S is the highest-pressure value (systolic, mmHg), P_D is the lowest-pressure value (diastolic, mmHg), and R_S and R_D are the corresponding internal radii (mm). An incremental elastic modulus $E_{p\varepsilon}$ was estimated at mean pressure, for each of the pressure ranges, according to Ref. [14]:

$$E_{P\varepsilon} = \left.\frac{dP}{d\varepsilon_{\theta,inc}}\right|_{mean\ pressure} \tag{2}$$

$$\varepsilon_{\theta,inc} = \frac{\Delta D}{D} = \frac{\Delta R}{R} \tag{3}$$

here P represents the transmural pressure and $\varepsilon_{\theta,inc}$ the corresponding incremental circumferential strain, obtained by referencing the dynamic changes in diameter to its reference value.

2.3. Statistical analysis

Statistical analysis was carried out using the unpaired Student's *t*-test. A value of $p < 0.05$ was considered statistically significant.

3. Results

Table 1 presents the %C and $E_{P\varepsilon}$ mean values calculated from the obtained signals of the grafts internal pressure and external diameter values. Compliance values diminished as the transmural pressure was increased. In the same way, the elastic modulus increased with pressure. This behavior was also evidenced on the pressure vs. diameter loops (Fig. 1).

4. Discussion

As previously reported, PLLA and PHD present mechanical properties in the order of collagen and elastin [15]. Therefore, producing a SDVG with proportions of both polymers in similar ratio as

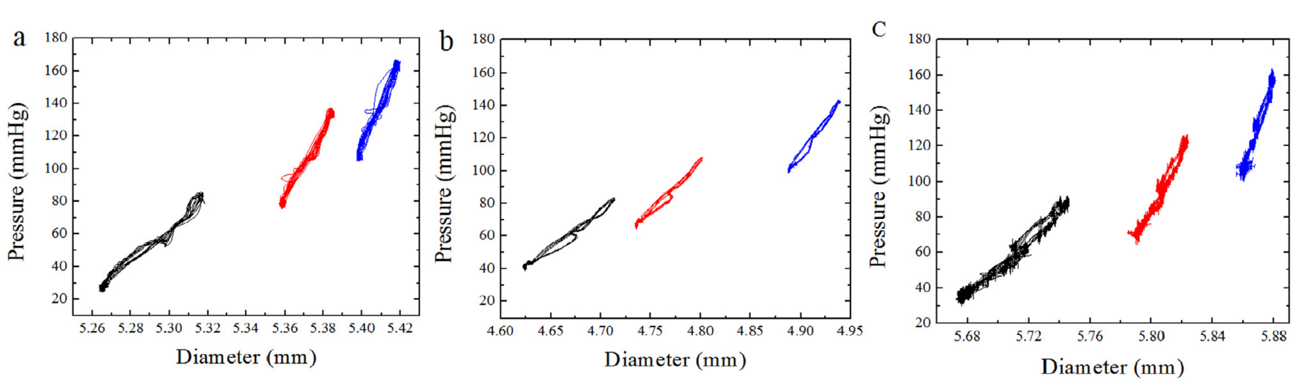

Fig. 1. Pressure vs. diameter loops for a) PLLA, b) PHD and c) bilayered SDVG for 50–90 mmHg (black), 80–120 mmHg (red) and 110–150 mmHg (blue). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

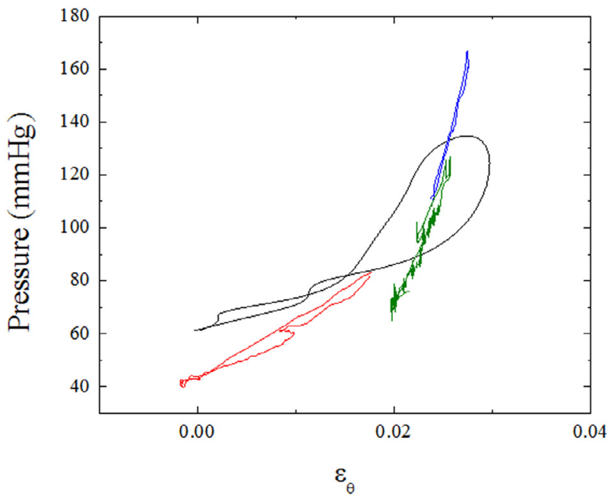

Fig. 2. Pressure-ε loops for electrospun PLLA graft (blue) at high pressure range, PHD graft (red) at low pressure range, bilayered graft (green) at physiological range and ovine femoral artery (black). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

natural arteries could result in a biomimetic compliant structure. Both PLLA and PHD grafts responses to internal pressure presented a biomimetic J-shape, where it could be noticed how both grafts stiffen with pressure with a more pronounced effect on PLLA. These SDVGs showed enough strength and stiffness to withstand elevated pressures. On the other hand, PHD grafts presented a more elastomeric behavior, with a more compliant nature.

Ovine femoral arteries elastic properties, characterized in previous work [14], were used to compare the mechanical biomimeticity of the SDVGs (Table 1). As reported before, when comparing the grafts response with ovine femoral arteries, PLLA SDVGs behavior could be associated to the collagen response in femoral arteries (100–130 mmHg) [14]. On the other hand, PHD grafts mechanical response and properties were similar to the ones corresponding to the pressure range of elastin (60–90 mmHg) (Fig. 2). In this way, the hypothesis that PLLA would behave mechanically like collagen and PHD to elastin was confirmed also in the pressure-diameter configuration.

Bilayered SDVGs also presented a J-shaped response (Fig. 1c). A good mechanical response, with biomimetic features was obtained due to the structure of the grafts, as well as the mechanical properties of the polymers used. Although with a less compliant nature than the ovine femoral artery, bilayered SDVG showed to be within the natural artery pressure-diameter loop in the physiological range (Fig. 2). The coupling between internal and external layers as well as the nanofibers progressive recruitment resulted in the stiffening observed. This characteristic was not seen in many synthetic grafts; in particular, the ones approved for bypass (ePTFE, Dacron®) have relatively constant compliance over a wide range of physiological or pathological mean blood pressures [5]. Even more, the electrospun bilayered SDVG showed a compliance value superior to the one presented for commercial ePTFE grafts (0.1%/100 mmHg) [21].

5. Conclusions

All SDVGs showed non-linear pressure-diameter response, with stiffness increasing with internal pressure. Bilayered SDVGs showed a PHD-like response for low pressure ranges and a PLLA-like response at high pressures, giving a J-shaped curve analogous to natural arteries. The measured elasticity properties agreed with this tendency, making them promising for vascular tissue engineering applications with long patency rates.

Acknowledgements

ANPCyT(PICT224), CONICET(PIP089), PEDECIBA-Física, and Proyecto Fondo Clemente Estable (ANII-1-2011-1-7172) grants are acknowledged.

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