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Visco-elasto-plastic modeling of small intestinal submucosa (SIS) for application as a vascular graft

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ABSTRACT

In developing new tissue engineered for vascular grafts, the mechanical properties of the material and its evolution once implanted are of utmost importance because they determine the regeneration of the vessel and the blood flow through the conduit. In fact, compliance mismatch is considered the main determinant of graft failure. In this research, we analyze the dynamic properties of the small intestinal submucosa (SIS), and propose and validate a constitutive model to fit the material's behavior. A uniaxial creep and recovery test was performed on SIS tubes to find the constitutive parameters. The model was composed by an elastic element in series with two Kelvin-Voigt solid elements and a plastic slider. The first elastic component was defined using Mooney-Rivlin strain energy function, while the plastic component was defined using a third-degree polynomial function of the plastic stress. The viscoelastic behavior was defined using the creep compliance formulation for the Kelvin-Voigt model. The parameters for the plastic and non-linear elastic elements followed a normal distribution, while the spring and dashpot constants of the visco-elastic element had a linear dependence on the load applied. The constitutive model was then used to simulate the SIS under the geometrical and pressure conditions found in native vessels for 1000 cycles at a frequency of 60 cycles per minute. From the cases simulated, performance curve charts were obtained in terms of the compliance of the material. These curve charts can be used as a predictive tool of the graft's behavior based on its geometry.

1. Introduction

Cardiovascular diseases are the main cause of death and disability in the USA (CDC, 2010; Hoenig et al., 2006). Although different risk factors such as obesity, smoking and physical inactivity are involved in the progression of the cardiovascular disease, one of the most critical factor is the biomechanical behavior of the blood vessel wall (Taylor and Humphrey, 2009). For patients in need of vessel bypass procedures, autologous vessels are the prevailing choice. Even though these grafts show higher patency than other choices, their mechanical performance can be limited, and in the mid or long term, they can lead to aneurysms or atherosclerosis (Seifu et al., 2013; Hoenig et al., 2006). To address this issue, different alternatives have been developed. One of the most successful ones is the use of synthetic materials, such as polyethylene terephthalate (PET, Dacron) or expanded polytetrafluoroethylene (ePTFE, Gore-tex). These materials are commonly used for large arterial prostheses because they show satisfactory long-term results. However, when they are used as small vascular grafts (<6 mm diameter), these materials have inferior performance and lower patencies than autologous grafts (Pashneh-Tala et al., 2015; Seifu et al., 2013; Tara et al., 2014; Hoenig et al., 2006). The evidence suggests that synthetic materials are more likely to present intimal hyperplasia at the anastomosis or mid-graft thrombosis due to flow disturbances caused by a compliance mismatch at the anastomosis (Zilla et al., 2007; Tara et al., 2014; Salacinski et al., 2001). These findings show that the biomechanical environment not only has a critical role in the etiology of cardiovascular diseases, but also in the outcome of current therapeutic strategies.

To overcome the limitations of current synthetic materials, tissue engineered vascular grafts (TEVGs) have been actively studied. TEVGs can provide a favorable environment for the cells and are thus able to promote the formation of new tissue as well as arterial repair. However, current TEVGs are still far from ideal. In particular, there is a need to better understand the biomechanical properties of such materials and the requirements needed for the graft to fulfill its purpose (Pashneh-Tala et al., 2015).

The vascular wall is constantly changing in response to various chemical and mechanical stimuli, so it maintains homeostasis. Vascular

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cells regulate mass production and removal rate to control the geometry and biochemical behavior of the wall (Kim and Wagenseil, 2014). Once a graft is implanted, differences between the material and native vessel's mechanical properties cause a disruption of the hemodynamic forces along its length (Tresoldi et al., 2015), altering wall shear stress and wave pulse (Salacinski et al., 2001), and thus homeostasis. Additionally, these discrepancies can cause local turbulence and changes in the global vascular impedance (Amaya et al., 2015). All these events can induce gene expression of the luminal endothelial cells and activate blood cells, which might lead to thrombus formation, and in the long term, anastomotic intimal hyperplasia, among other complications (Salacinski et al., 2001). For that reason, the assessment of the mechanical properties of the material is a crucial aspect during the development of grafts for its success or possible failure once implanted (Pashneh-Tala et al., 2015). Among the different causes of graft failure, compliance mismatch is considered a main determinant (Seifu et al., 2013; Pashneh-Tala et al., 2015; Salacinski et al., 2001). As Miller et al. (2015) pointed out, there are multiple structural and material parameters which represent physical properties of the scaffold including elasticity, shear modulus, density, and compliance. Nevertheless, the material parameters commonly analyzed neither represent the dynamic behavior of the material nor its evolution due to tissue remodeling. Since the graft's working conditions are highly dynamic, scaffold design should consider possible changes in mechanical behavior in order to prevent the failure of the material or a pathological response.

In this study we present a methodology to study the dynamic properties of small intestinal submucosa (SIS) for its use as a vascular graft. SIS is an extracellular matrix (ECM) which has been extensively studied as a suitable vascular graft (Sandusky et al., 1995; Sánchez-Palencia et al., 2014; Pashneh-Tala et al., 2015). This ECM is mainly composed of different types of collagen, principally Type I and III, glycoaminoglycans, and different growth factors as the vascular endothelial growth factor (VEGF) (Badylak, 2014, 2008; Badylak et al., 1999, 1989). The combination of components of the SIS gives to this ECM a natural three-dimensional structure that enhances its biomechanical properties compared to the individual purified components (Badylak, 2008). Among its different properties, this material shows a non-linear stress-strain response that is similar to native vessels (Pashneh-Tala et al., 2015). To the extent of our knowledge, the time-dependent behavior of the material when used as graft has not been reported. Thus, we developed a constitutive model of the material's time dependent non-lineal elastic behavior, where the instantaneous, viscous and plastic responses of the material were included. The mechanical model was calibrated and validated using the results from creep and recovery tension tests. Compared to other studies in which the evolution of material stiffness was dependent on the material's degradation and remodeling (Miller et al., 2015), here the change of stiffness was induced by the loading conditions, so there were no variations in mass. The constitutive model formulation was used to simulate the behavior of the SIS over time as a vascular conduit. As such, the material was analyzed under different pressure ranges at different conduit radii and thickness.

2. Materials and experimental methods

2.1. Sample preparation

The porcine SIS that is used in this study, was prepared using the procedure presented in Sánchez-Palencia et al. (2014). All specimens were extracted from jejunum portions of small intestine harvested from the local abattoir. The tunica mucosa, muscularis externa, tunica serosa were removed by mechanical scraping. This procedure separates the submucosa from the rest of the layers of the small intestine while preserving the three-dimensional microstructure of the tissue (Luo et al., 2011). The intestine stratum compactum, that conforms a dense collagen luminal layer, was removed using a sodium hypochlorite and hydrogen peroxide solution, which also decellularizes and disinfects the tissue. Then the remaining tissue is rinsed with PBS (pH = 7.0) and type I water. Posteriorly, the acellular submucosa was rolled using a 5 mm mandrel until a 4 layer tube was formed, in such a way that the preferential longitudinal direction of the intestine was aligned with the circumferential direction of the tube. The conduit was dehydrated by air drying in a laminar flow hood. Once the tube was fully dry, the mandrel was demounted and the sample stored until use.

2.2. Creep test

SIS conduits were cut into 5 mm width cylinders. A micrometer was used to measure the thickness of the material. The samples were tested under uniaxial tension in a Bose Electroforce Planar Biaxial Test-bench (TA Instruments) using custom made clamps. Specimens were mounted on two 1.5 mm diameter rods so that a tensile force could be applied to the circumferential direction of the cylinder, thus the preferential orientation of the fibers, while the longitudinal strain was not restricted. One clamp was attached to a load cell with a 1 mN resolution and a 250 N capacity, and the other clamp was secured to the ElectroForce Linear motor. During the test, the specimens were completely submerged in a 37° water bath. Once the sample was mounted, the clamps were separated until a positive force <0.04 N was registered. At that position, the initial length was registered and the load reading adjusted considering the previously mention load offset.

Each specimen was then subjected to multiple load-creep-unload-recovery cycles. The loading and unloading phases were carried out at a strain rate of 0.02 N/s. The samples were subjected to loads of 0.041 N, 0.082 N, 0.103 N, 0.124 N, 0.145 N, 0.163 N, 0.330 N, 0.661 N, 1.323 N, 2.645 N, 5.29 N, 10.580 N and 21.160 N. The loads applied corresponded to the circumferential stresses assuming the sample as a thin wall cylinder under a range of internal pressure between 15 and 4000 mmHg. When the load was reached, it was maintained for 600 s. Then the load was released to the minimum force of 0.041 N and maintained for 600 s before applying the next step. The times for sustaining the load were chosen based on preliminary tests that showed the required time to reach a stable state. Furthermore, the order of magnitude of the times chosen agrees with previously reported creep tests on gastrointestinal tissues (Carniel et al., 2015). Because the experiment was a load-controlled test, when the load was released the specimen has to be subjected to the minimum load in order to avoid artifact errors in the data and damage to the machine. For each cycle, the load sensed and the displacement of the linear motor were measured. The load was used to calculate the engineering stress σ using the cross-sectional area. The total strain ϵ and stretch λ were calculated using the initial length of the sample. A total of 2048 points were recorded for each cycle.

3. Theory and calculations

The definition of the constitutive equation for the visco-elasto plastic response of the material is based on the procedure presented in Drescher et al. (2010). Due to the experimental test performed, some assumptions should be stated before the development of the formulation. First, assuming incompressibility of the material, and because the samples were tested under uniaxial tension, the stretch ratios in the principal directions are defined as:

$$\lambda = \lambda_1 = L_f/L_0; \tag{1}$$

$$\lambda_2 = \lambda_3 = 1/\sqrt{\lambda} \tag{2}$$

$$\epsilon = \lambda_1 - 1 = \Delta L/L_0 \tag{3}$$

where L_f is the length of the sample in the current configuration, L_0 is the initial length, and ϵ is the total time-dependent strain of the material for the load applied.

The constitutive equation for the material was defined based on a