Published in final edited form as:

Acta Biomater. 2011 January ; 7(1): 287–294. doi:10.1016/j.actbio.2010.09.004.

Polymeric Endoaortic Paving (PEAP): Mechanical, Thermoforming, and Degradation Properties of Polycaprolactone/Polyurethane Blends for Cardiovascular Applications

John H. Ashton^a, James A. M. Mertz^b, John L. Harper^b, Marvin J. Slepian^c, Joseph L. Mills^d, Dominic V. McGrath^e, and Jonathan P. Vande Geest^{a,b,f,g}

^aBiomedical Engineering Graduate Interdisciplinary Program The University of Arizona 1657 E Helen Street PO Box 210240 Tucson, AZ 85721

^bDepartment of Aerospace and Mechanical Engineering The University of Arizona 1130 N Mountain Avenue PO Box 210119 Tucson, AZ 85721

^cSarver Heart Center The University of Arizona 1501 N Campbell Avenue PO Box 245046 Tucson, AZ 85724

^dDepartment of Surgery The University of Arizona 1501 N Campbell Avenue PO Box 245072 Tucson, AZ 85721

^eDepartment of Chemistry and Biochemistry The University of Arizona 1306 E University Blvd PO Box 210041 Tucson, AZ 85721

^fBIO5 Institute The University of Arizona 1657 E Helen Street PO Box 210240 Tucson, AZ 85721

^gDepartment of Biomedical Engineering The University of Arizona 1127 E James E Rogers Way PO Box 210020 Tucson, AZ 85721

Abstract

Polymeric endoaortic paving (PEAP) is a process by which a polymer is endovascularly delivered and thermoformed to coat or “pave” the lumen of the aorta. This method may offer an improvement to conventional endoaortic therapy in allowing conformal graft application with reduced risk of endoleak and customization to complex patient geometries. Polycaprolactone (PCL)/polyurethane (PU) blends of various blend ratios were assessed as a potential material for PEAP by characterizing their mechanical, thermoforming, and degradation properties. Biaxial tension testing revealed that the blends' stiffness is similar to that of aortic tissue, is higher for blends with more PCL content, and may be affected by thermoforming and degradation. Tubes of blends were able to maintain a higher diameter increase after thermoforming at higher PCL content and higher heating temperatures; 50/50 blend tubes heated to 55°C were able to maintain

© 2010 Acta Materialia Inc. Published by Elsevier Ltd. All rights reserved

Corresponding Author: Jonathan P. Vande Geest Phone: (520) 621-2514 Fax: (520) 621-8191 jpv1@email.arizona.edu Aerospace and Mechanical Engineering PO Box 210119 Tucson, AZ 85721.

Email Addresses of Authors Jonathan P. Vande Geest: jpv1@email.arizona.edu John H. Ashton: jhashton@email.arizona.edu James A. M. Mertz: mertz.james@gmail.com John L. Harper: johnny88@gmail.com Marvin J. Slepian: chairman.syns@gmail.com Joseph L. Mills: jmillsenator@gmail.com Dominic V. McGrath: mcgrath@u.arizona.edu

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

90% of the diameter increase applied. Delamination forces of the blends ranged from 41 to 235 N/m². In a *Pseudomonas* lipase solution, the 50/50 blend had a 94% lower degradation rate than pure PCL, and the 10/90 blend exhibited no degradation. These results indicate that PEAP, consisting of a PCL/PU blend, may be useful in developing the next generation of endoaortic therapy.

Keywords

Polymeric Paving; Aneurysm; Polycaprolactone; Polyurethane; Vascular grafts

1. INTRODUCTION

Polymeric Endoluminal Paving and Sealing is a method via which a polymer, either as a solid structural polymer, a gel, or a liquid, may be applied to the endoluminal surface of a tissue structure in the body and reconfigured to form an adherent endoluminal coating layer [1]. Solid paving has largely utilized biodegradable polymers as either tubes or sheets which are delivered locally and then thermoformed via catheter within an atherosclerotic artery to accommodate to the shape of the lumen [1–3]. This method allows the polymer to flow and adapt to the irregularities and interstices of the endoluminal surface, with the delivered paving layer serving as a wall support, physical barrier layer, and potential local intraluminal drug delivery vehicle. To date, solid paving has been utilized largely to deploy structural biodegradable polymers as advanced biodegradable arterial stent constructs in the coronary and peripheral arterial tree [4–6], the trachea [7], the esophagus [8], and the urethra [9]. Gel paving has also been fashioned to deploy biodegradable polymers as *in situ* photo-polymerized hydrogel barrier layers, including endovascular delivery to serve as anti-thrombotic barriers [10,11] and drug delivery means [12].

In the present study we explored the possibility of extending paving as a means of deploying elastomeric polymer blends for use in tissues that have significant elastomeric properties. Further we have examined the application of this method for use with predominantly non-degradable polymer constructs specifically for aortic aneurysm therapy, which we refer to as polymeric endoaortic paving (PEAP). Increasingly today, patients with abdominal aortic aneurysm (AAA) are treated via endovascular repair (EVAR) utilizing relatively rigid conventional stent-grafts. Among individuals currently considered for AAA treatment, about 32% are declined EVAR due to anatomic limitations (e.g. short proximal neck and tortuous, heavily calcified, or stenotic iliac arteries) [13]. Of those that receive EVAR, there is a 14% secondary intervention rate within 4 years [14], mostly due to device migration and persistent or *de novo* endoleak. Drug treatments that halt AAA growth are currently under investigation [15–18]. We believe that PEAP will allow the treatment of aneurysms with complex anatomy and reduce migration and endoleak by providing an implanted polymer graft which conforms to a patient-specific AAA shape, while also providing a drug delivery vehicle.

Polycaprolactone (PCL)/polyurethane (PU) blends have been investigated for various biomaterial applications due to their relative biocompatibility, compliance, shape memory ability, low cost, and ease of fabrication [19,20]. PCL is blood compatible and has been investigated in cardiovascular devices [3,19,21]. While pure PCL has a melting temperature around 60 °C, the phase transition temperature of PCL/PU blends decreases below this point as PU content increases [19]. As temperature approaches 37°C, this relationship may allow PCL/PU-based implants to be thermoformed *in vivo*. Additionally, since PCL degrades *in vivo* on the order of years [22,23], this may allow for long-term drug delivery to be incorporated into PEAP treatments [24].

We are interested in using Tecoflex® as the PU since it is also blood compatible [25,26] and is currently used in several cardiovascular devices [27,28]. PU is more compliant than PCL, and therefore inclusion of PU into the blend may provide better compliance matching to the mechanical environment of the implant. Since PU is biodegradable, it may reduce or eliminate biodegradation of the blend, allowing portions of the implant to remain long-term, while other portions (containing higher concentrations of PCL) could act as a drug delivery vehicle.

While there have been reports on the shape memory properties of PCL/PU blends [19] and degradation of PCL-PU copolymers [29,30] and PCL blends with other copolymers [31–33], there are currently no reported experimental studies, to the authors' knowledge, on the coupled thermoforming and degradation characteristics of PCL/PU blends. The present work also represents the first characterization of PCL blends with the commercially available PU Tecoflex®. The purpose of this work was to investigate the potential of using PCL/PU blends as paving materials for PEAP by characterizing their mechanical, thermoforming, and degradation properties.

2. MATERIALS AND METHODS

2.1 Stiffness of Aortic Tissue

To approximate the stiffness range that a PEAP material should have to match the mechanical environment of the aorta, stiffness values of abdominal aorta (AA) tissue and AAA tissue were estimated from a model previously derived from biaxial tension data of AA and AAA tissue [34]. The second Piola-Kirchoff stresses (S) in the circumferential (θ) and longitudinal (L) directions are a function of Green's strain (E):

$$S_{\theta\theta} = b_0 \left(b_1 E_{\theta\theta} e^{\frac{1}{2} b_1 E_{\theta\theta}^2} + b_3 E_{LL} e^{b_3 E_{\theta\theta} E_{LL}} \right) \quad (1)$$

$$S_{LL} = b_0 \left(b_2 E_{LL} e^{\frac{1}{2} b_2 E_{LL}^2} + b_3 E_{\theta\theta} e^{b_3 E_{\theta\theta} E_{LL}} \right) \quad (2)$$

where b_i are constants derived from data fitting, which are shown in Table 1. For equibiaxial strain ($E = E_{\theta\theta} = E_{LL}$), values of incremental modulus can be determined with the following derivatives:

$$\frac{dS_{\theta\theta}}{dE} = b_0 \left((b_1 + b_1^2 E^2) e^{\frac{1}{2} b_1 E^2} + (b_3 + 2b_3^2 E^2) e^{b_3 E^2} \right) \quad (3)$$

$$\frac{dS_{LL}}{dE} = b_0 \left((b_2 + b_2^2 E^2) e^{\frac{1}{2} b_2 E^2} + (b_3 + 2b_3^2 E^2) e^{b_3 E^2} \right) \quad (4)$$

Equations 1 and 2 were used to determine the strain value for each tissue at which the stress was equal to 0.64 MPa (choice of this is explained below). From this strain, values for tangential moduli were found for each tissue using Equations 3 and 4.

2.2 Polymer Blend Tube and Sheet Fabrication

PCL (MW 70,000, Fisher Scientific, NC9498824) and PU (Lubrizol, Tecoflex® SG-80A) were blended in various ratios (% wt PCL/PU: 10/90 to 50/50) by dissolving pellets of each in chloroform. Tubes and sheets of each blend were fabricated via solvent casting. PCL/PU blends containing more than 50% PCL were not used due to preliminary thermoforming tests which resulted in ripped specimens (thermoforming is described in section 2.5).

2.3 Anisotropic Stiffness of PCL/PU Blends

Planar biaxial tensile testing was used to mechanically characterize PCL/PU blends and determine if stiffness was affected by thermoforming and blend ratio. Square sheets, approximately 10×10×0.3 mm (50/50 having a thickness of 0.2mm, 10/90 was 0.4mm), were made from 50/50 and 10/90 blends (9 each). These were chosen as representative blend ratios near both ends of the spectrum of thermoformable specimens. Thermoformed square sheets of each blend were prepared as follows (9 each). Rectangular sheets were secured in a uniaxial tension device and submerged in a room temperature water bath. The temperature was then raised to 55 °C for 5 minutes, after which the samples were uniaxially strained 40%. The temperature was cooled to 37 °C and the 40% strain was held for 5 more minutes. Specimens were removed from the uniaxial tension grips and kept in 37 °C water for 5 additional minutes. Specimens approximately 10×10×0.3 mm were cut from these sheets.

Specimen dimensions were measured using calipers and biaxial tensile testing was performed using a custom-built biaxial tensile testing device, which has been previously described [35,36]. Briefly, the specimen was mounted using barbless hooks, four to a side, connected to carriages that allow for self-equilibrated loads on each line. The entire test was performed in a water bath at 37 °C. Equal tension was cyclically loaded in both directions for 10 cycles, increasing from 0 to 440 N/m over the series of cycles. The first 9 cycles were preconditioning and data from the 10th cycle was analyzed. Specimen deformation was determined by tracking 4 markers on the specimen (initially a ~3×3 mm square) using a CCD camera. For the thermoformed samples, the Y direction was the direction of strain during thermoforming.

Specimen stiffness was approximated as the tangential modulus from a plot of 2nd Piola-Kirchhoff stress versus Green's strain. This was calculated as the slope of a least-squares line fit through the 4 nearest data points to 0.64 MPa, which we estimate is the stress (S) on the PEAP material implanted in an aorta based on the law of Laplace for a cylinder 2 cm in diameter (D) and 0.25 mm thick (t) at 120 mmHg of pressure (P):

$$S = \frac{P \times D}{t \times 2} \quad (5)$$

Signed rank tests (Wilcoxon) were used to compare X vs. Y direction stiffness values to determine anisotropy of each group, and rank-sum tests (Mann-Whitney) were used to determine if thermoforming and blend ratio affect stiffness (X and Y directions of each group were compared to X and Y directions of other groups, respectively).

2.4 Thermoforming of Blends

Tests were performed to evaluate the thermoforming ability of PCL/PU blend tubes and to measure the relationship of temperature and PU/PCL ratio on the diameter increase a blend tube can maintain following the thermomechanical cycle. Tubes that underwent thermoforming were cylindrical with approximate initial dimensions of 12 mm length, 6 mm

diameter, and 0.25 mm wall thickness. Dimensions of each tube were measured using digital calipers.

Five heating temperatures were tested: 37, 40, 45, 50, and 55 °C. One tube of each blend ratio was tested at each temperature. To measure variance, 8 tubes each of the 50/50 and 10/90 blends were tested at 55 °C. The tube was set on a deflated balloon catheter (Cook Medical, G31192) and put in water bath at the heating temperature for 5 minutes. A syringe pump was then used to expand the balloon within the tube to 200 kPa. Unrestrained, the balloon diameter expands to 8.5mm at 200 kPa, and it appeared to expand this same amount when thermoforming all tubes. The expanded tube and balloon remained in the heated water bath for several seconds, after which they were transferred to a water bath at 37 °C for 5 minutes. The balloon was then deflated and removed while the tube was kept in the 37 °C bath for 5 more minutes to equilibrate. The thermoformed tube dimensions were then measured again.

2.5 Delamination of Blends

The PEAP graft may be delivered as modular components, and these components must seal together to avoid a Type III endoleak. Delamination tests were run to evaluate the extent that separate pieces of blends could be laminated, or fused, together and how blend ratio and temperature affected this bond. Preliminary tests indicated that delamination force was not dependent on the length of time or amount of pressure applied.

Rectangular sheets (~10×20×0.3 mm) of 50/50 and 10/90 blends were made. Two specimens of the same blend were overlapped in a 10×10 mm area. The overlapped section was placed between 2 glass squares (10×10 mm) and placed on a wooden support beam. A strap, with 1300 grams hanging in an attached container below for a 960 mmHg lamination pressure, was set on the top glass slide. The entire set-up was then submerged in a heated water bath (37 to 60 °C) for 1 minute, after which the applied load was removed from the samples. Figure 1 illustrates the above process.

Samples were delaminated using a uniaxial tension testing device (TestResources, 200R). The sample was secured vertically by inserting the non-overlapped ends into the grips, which were separated by 15mm. The grips were then moved apart (30mm/min), while load was measured, until the two specimens completely separated. Delamination force is reported as the maximum load measured.

2.6 Degradation of Blends

Biodegradation tests were performed to study the biostability of PCL/PU blends. There were 3 groups of specimens. Thermoformed tubes (group 1): tubes of 50/50 and 10/90 blends (8 per blend), were prepared and thermoformed via the above protocol. Regular squares (group 2): specimens of pure PCL (9), pure PU (8), 50/50 blend, and 10/90 blend (9 per blend) were prepared, approximately 10×10×0.3 mm (pure PCL and PU had thicknesses of 0.4mm). Thermoformed squares (group 3): square specimens of 50/50 and 10/90 blends (9 per blend) were prepared using the same methods reported in section 2.4.

The main mode of degradation for PCL is hydrolysis, which is affected by the size, hydrophilicity, and crystallinity of the polymer and the pH and temperature of the environment [37,38]. *Pseudomonas* lipase accelerates hydrolysis and has previously been used in biodegradation studies of PCL and PCL-blends [33,39,40] to reduce experimentation time, since PCL normally degrades over years. Our lipase solution was prepared by dissolving amino lipase from *Pseudomonas fluorescens* (Sigma-Aldrich, 534730) and sodium azide (Sigma-Aldrich, S8032) in phosphate buffered solution to final concentrations of 40 units/mL and 0.2 mg/mL, respectively. Each specimen was weighed, placed in a vial

with 5 mL of lipase solution, and set in an incubator at 37 °C. Every 3 days the specimens were removed, washed twice in water baths, dried by dabbing with paper towels, weighed, and returned to the vials which had been emptied and replenished with 5 mL of fresh lipase solution. After 15 days, all pure PCL specimens had fully degraded so biodegradation testing concluded. Calibers were used to measure dimensions of all biodegradation specimens before and after the 15 days in lipase solution. Signed rank tests (Wilcoxon) were used to statistically compare mass and dimensions of sample groups before and after 15 days in lipase solution. Biaxial tensile testing was then performed on the lipase-degraded samples using the methods described in section 2.4.

2.7 Atomic Force Microscopy (AFM) and Scanning Electron Microscopy (SEM) of Blends

AFM and SEM testing was performed on pure PCL, pure PU, and 40/60 blend as a preliminary assessment of the surface. Specimens for both techniques were rectangular sheets prepared using the above methods. For AFM, the samples were flattened by placing them between two glass slides and setting them in an oven at 65 °C for 30 minutes with a mass of about 250 grams placed on top. Samples were cooled to room temperature and were easily removed from the slides. A Dimension 3100 AFM (Veeco) was used to gather AFM images from 3 areas per sample. A NSC-15 (Mikromasch) cantilever was used in tapping mode obtain images at about 0.5 Hz (512 samples per image). Images were flattened with a 0–3 order polynomial. Average mean roughness of each image was calculated using AFM software (NanoScope III). For SEM, the samples were coated with platinum and imaged with secondary electrons in a Hitachi 3400N at 5kV.

2.8 PEAP in Porcine Aorta

As a preliminary test, PEAP was performed in a section of fresh porcine aorta maintained in a physiological phosphate buffered solution. Aorta retrieval was performed according to an approved IACUC protocol (08–083). One tube of PCL/PU 50/50 was thermoformed inside the aorta as follows. The PCL/PU tube was placed inside the aorta and set on a deflated balloon catheter (Cook Medical, G31192), which was a semi-compliant cylindrical balloon. The initial outer diameters of the tube and aorta were 12.4 and 15.3 mm, respectively, and the balloon was inflated to a nominal diameter of 13.3 mm by applying a 200 kPa pressure. The balloon, polymer aorta construct was then placed in water at 55 °C for 5 minutes. The balloon was inflated and the balloon/paving set-up was moved to 37 °C water for 5 minutes. The balloon was then deflated and removed and the tube in the aorta remained in the 37 °C water for 5 more minutes, after which the outer diameter of the aorta was measured.

3. RESULTS

3.1 Anisotropic Stiffness of Aortic Tissue

AA and AAA tissue had tangential moduli of 32 and 59 MPa, respectively (see Figure 2). In both sets, the tangential moduli in the circumferential and longitudinal directions differed by less than 0.1 MPa.

3.2 Anisotropic Stiffness of Blends

Tangential moduli of the blends that underwent biaxial testing are shown in Figure 3. Anisotropy was present in the 10/90 blend, where the Y direction was stiffer than the X direction. Thermoforming resulted in a stiffness decrease in the Y direction of the 10/90 blend. The 50/50 blends displayed a higher stiffness than corresponding 10/90 blends in three out of four comparisons (the fourth $p=0.0503$). The 50/50 blends had higher variance than the 10/90 blends. Stiffness of the blends and aortic tissue are compared in Figure 4.

Stiffness of the 10/90 blends were less than that of nonaneurysmal aorta, while that of the 50/50 blends approached the stiffness of aneurysmal tissue.

3.3 Thermoforming

The percent diameter increases that the tubes were able to maintain after thermoforming are shown in Figure 5. Diameter increase is greater at higher PCL content and higher heating temperatures. The 50/50 and 10/90 blend tubes heated to 55 °C had $39.0 \pm 0.9\%$ and $4.8 \pm 0.9\%$ (SE) outer diameter increases, respectively, which are 90% and 11% of their maximum potential increase based on full the balloon expansion to 8.5 mm at 200 kPa. A model was fit to the results to predict the percent diameter increase (OD) a tube would maintain in this test set-up based on percent weight of PCL (pwPCL) and heating temperature (HT):

$$OD = C_1 + C_2 e^{C_3 pwPCL C_4 HT} \quad (6)$$

where the C's are fit constants. Nonlinear regression performed in SigmaStat yielded fits of $C_1 = 2.58$, $C_2 = 1.72E-7$, $C_3 = 0.0485$, and $C_4 = 0.305$, with an R^2 of 0.95. Figure 6 is a graph of the model compared to the data.

3.4 Delamination

Results from the delamination test are shown in Figure 7. The delamination force of the 50/50 blend ranged from 41 to 235 N/m², while the 10/90 blend ranged from 49 to 110 N/m². Generally, the 50/50 blend displayed higher forces than the 10/90 blend, especially at higher lamination temperature.

3.5 Degradation

The average percent mass loss of each group over the course of degradation is shown in Figure 8. Of the square specimens, the PCL specimens completely degraded, the 50/50 regular squares had a mass loss of $6.1 \pm 1.9\%$ (St Error), and none of the other groups had significant mass loss ($p > 0.1$). Of the thermoformed tubes, the 50/50 tubes and 10/90 tubes had mass losses of 13.4 ± 0.8 and $3.8 \pm 0.2\%$, respectively.

All of the square samples had significant decrease in length (all had $P < 0.05$ except thermoformed 50/50 had $P = 0.055$). For the thermoformed samples, this is the direction of thermoforming. The 50/50 blends decreased an average of 2.6 and 2.3% for the regular and thermoformed specimens, while the 10/90 blends decreased 3.9 and 1.9%, respectively. Of the thermoformed tube samples, the diameter of the 50/50 blend decreased 1.8% while the 10/90 blend had no significant decrease ($p > 0.05$).

Tangential moduli of regular blends versus those that had been in lipase solution are shown in Figure 9. One of the lipase-degraded 50/50 specimens was discarded as a statistical outlier. Anisotropy was present in the lipase-degraded 50/50 blend and the combined thermoformed and lipase-degraded 10/90 blend. The combined thermoformed and lipase-degraded 50/50 blend was less stiff than the regular 50/50 blend in the X direction, while the combined thermoformed and lipase-degraded 10/90 blend was more stiff than the regular 10/90 blend in the X direction.

3.6 AFM and SEM

Representative AFM images are shown in Figure 10. Fibers were seen in the PCL images, but are not present in the PU images. Fibers appeared in one of the 40/60 blend images, but seem to be more spread out compared to the pure PCL. In the other 2 blend images, no

fibers appeared. Table 2 lists average roughness values analyzed by the AFM software (NanoScope® III). There were not enough samples taken for a statistical analysis, but results indicate that the PCL/PU 40/60 blend is the roughest, pure PU is the least rough, and pure PCL is somewhere in between.

The SEM images are shown in Figure 11. The surface of the 40/60 blend had craters while the PCL and PU alone did not. In the blend, the bottoms of the craters have visual features similar to the pure PCL, while the regions around the craters have features similar to the pure PU. This indicates possible phase separation of the two components at the surface.

3.7 PEAP in Porcine Aorta

Our preliminary test indicated that PEAP was able to successfully pave porcine aorta. The outer diameter of the aorta increased from an initial value of 15.3 mm to 16.2 mm after PEAP. Patency between the tube and aorta was achieved, as shown in Figure 12. The applied polymer appeared to be in intimate contact with the endoluminal surface over the entire vessel circumference. Further animal tests will be required to determine if the degree of contact is able to exclude the aneurismal sac.

4. DISCUSSION

In this study we demonstrated that PCL/PU blends may be deployed via the endoluminal paving method to form conformable, endoaortic layers. We were able to successfully employ PEAP on a section of porcine aorta. This initial result was performed on a cylinder, and in the future we expect to be able to apply PEAP to more complex geometries, such as tortuous sections and bifurcations.

Mechanical testing of the blends shows that stiffness is affected by blend ratio, and may be affected by thermoforming and lipase degradation. There was high variance of stiffness for the 50/50 specimens, the cause of which is unknown. Blend stiffness is similar to AA and AAA tissue stiffness. One limitation to this comparison is that AA and AAA stiffness were obtained by extrapolating the reported model beyond the data range from which it was derived. This was a result of the blends having a much smaller thickness than that used in the AA versus AAA report these equations were taken from. Our results suggest that adjusting blend ratio and amount of thermoforming may allow for future optimization of graft functional performance *in vivo*.

Thermoforming tests suggest that the shape of PCL/PU grafts may be modified *in vivo* at temperatures approaching body temperature. AAA dimensions vary widely from patient to patient. The purpose of this work was to investigate how blend ratio and heating temperature affect thermoformability. Even though the dimensions of the tubes we tested are smaller than what would be deployed in a patient, we believe that they can be scaled up correspondingly. We are currently developing a method to fabricate the initial PEAP implant into a patient-specific shape based on AAA geometry reconstruction from CT imaging, which would minimize the amount of thermoforming that the PEAP needs to undergo *in vivo*. Thermoforming would primarily occur in the proximal and distal regions to ensure the aneurysm sac is sealed off. Although the highest amount of thermoforming was achieved at 55 °C, our goal is to keep PEAP dimension changes under 10% which may allow us to thermoform around 45 or 50 °C.

Thermoforming *in vivo* introduces the potential of thermal damage to surrounding tissue and blood. This can be minimized by reducing the time and temperature of thermoforming as much as possible. We propose to achieve this through a photo-thermal technique in which a photosensitive dye is incorporated into the polymer and illuminated via a fiber-optic catheter

with a light wavelength that maximizes light absorbance by the dye and minimizes absorbance of vascular tissue. Such a system has been developed for paving PCL within the vasculature of animal models [5], and a similar approach is being developed to actuate shape-memory polymers in the treatment of cerebral aneurysms [41] and arterial stenosis [42]. Pos et al. showed that platelet adhesion to arterial tissue is actually decreased at temperatures around 75 °C compared to 37 °C. Ortega et al. modeled the temperature map and thermal damage to surrounding tissue and blood of a shape-memory polymer which is expanded within a cerebral aneurysm using photo-thermal actuation [43]. Although the surface of the polymer reached 77 °C, they suggested that no thermal damage of vascular tissue would occur and thermal damage of blood would be minimal if expansion time is less than 100 seconds at a laser power less than 1.7W. Buller et al. investigated the effects of thermal-perfusion balloon angioplasty in canine coronary arteries *in vivo* at temperatures up to 80 °C for up to 15 minutes with angiographic assessments after 24 hours and 4–6 weeks [44]. They reported that no coronary spasm, occlusive thrombus, or ischemic myocardial infarction occurred and concluded that the procedure could be safely applied in canine coronary arteries. Brassalet et al. showed that locally heating atherosclerotic arteries to 50 °C after stent angioplasty reduced in-stent restenosis and neointimal hyperplasia in a rabbit model [45]. These studies indicate that thermoforming PCL/PU blends *in vivo* as part of PEAP is reasonable for further development.

Ajili et al. showed shape change of PCL/PU blends by heating, applying a force, and cooling [19]. However, PCL/PU blends have shape-memory properties, so this thermoforming shape change is only an intermediate conformation; after heating the blend again under no load, the blend returned to its original shape. Preliminary tests in our laboratory were the same, where thermoformed tubes returned to their original diameter after heating them back to 55 °C. However, we hypothesize that this intermediate conformation, or thermoformed shape, can remain stable for the lifetime of the patient *in vivo* as long as it isn't heated again above the phase transition temperature. Evidence for this was provided; the 50/50 tubes were thermoformed, increasing the diameter 39%, and then kept in lipase solution at 37 °C for 15 days, where diameter decreased only 1.8%. We believe that this minimal decrease in diameter was due to some degradation of the PCL portion of the blend and may be eliminated by adding a thin coating of pure PU to the tube. Ongoing research within our laboratory is aimed at further testing this hypothesis.

Delamination tests indicate that PEAP implant design may be modular (i.e., be thermoformed together), facilitating the ability of using multiple instances of PEAP in complicated geometries. Degradation tests indicate that blending PU with PCL significantly reduces PCL's degradation and may allow long-term implantation. Liu et al. also performed degradation studies on PCL and blends of PCL and polylactide-based polymers (PCL/PLA) using *Pseudomonas* lipase [33,40]. For Liu et al., PCL degraded 78% after 72 hours, whereas ours degraded 48% after 3 days. This may be attributed to differences in the studies: 1. Liu et al. used 8 U/ml lipase, we used 40 U/ml; 2. Liu et al. had PCL specimens 0.2 mm thick, ours were 0.4 mm; 3. Liu et al. changed the lipase solution every 24 hours, we changed it every 3 days. Similar to our result that PCL/PU blends degrade slower than pure PCL, Liu et al. showed that PCL/PLA blends degraded slower than pure PCL. However, it should be noted that PLA is biodegradable, but its method of degradation is different than PCL. The PU from our study (Tecoflex®) is not biodegradable.

Additionally, Gan et al. studied PCL degradation in *Pseudomonas* lipase [39]. Their PCL specimens completely degraded after 96 hours, whereas ours took more than 12 days. This may be due to Gan et al. using thinner specimens (0.1–0.3 mm, ours were 0.4 mm) and a difference in activity of lipase solution (lipase concentration (U/ml) is not specified by Gan et al.).

Our results showed that the degradation of thermoformed tubes is different than that for thermoformed sheets. The tubes lost more mass over the course of the test, but had a lower dimension decrease in the thermoformed direction (diameter for tubes and length for sheets). This relationship is counter-intuitive and the cause of this discrepancy is currently unknown.

Lam et al. showed that PCL degradation accelerated with sodium hydroxide (NaOH) is different than degradation in PBS [32]. It took PCL specimens 6 weeks to degrade in NaOH, while the PCL specimens in PBS had about 12% mass loss after 45 months. PBS degradation was more bulk degradation driven, which takes place when a medium (water) is able to penetrate through the entire polymer and random hydrolytic chain scissions take place throughout the matrix in a uniform manner. NaOH-accelerated degradation was more surface degradation driven, which takes place when medium diffusion into the polymer is extremely slow compared to the chain scissions. In our study, the 50/50 specimens (both squares and tubes) were thinner ($\sim 1/2$ the thickness) than the 10/90 specimens (tubes: 0.13 vs. 0.21 mm, squares: 0.2 vs. 0.4 mm) and therefore had a larger surface area to volume ratio. If PCL degradation accelerated by *Pseudomonas* lipase is similarly surface degradation driven, the difference in degradation between 50/50 and 10/90 specimens may be reduced if the same thickness was used. While there are certainly differences between accelerated lipase degradation and true *in vivo* degradation, the results reported here are a first step towards understanding more general PEAP biodegradation.

5. CONCLUSIONS

Our results suggest that PEAP, consisting of a PCL/PU blend, may be useful in developing the next generation of endovascular therapy for AAA. Due to their mechanical, contact, and support characteristics, PCL/PU blends are an effective biomaterial family for endovascular deployment via the polymeric endoluminal paving method. In addition, we showed that their mechanical properties are adjustable, primarily through altering the blend ratio, which may allow for optimization both globally and in local specific areas of the AAA.

We are currently investigating if adding a thin coating of pure PU on the outside of the graft completely eliminates biodegradation without having a significant effect on thermoforming. In addition, our team is using finite element analysis to determine if PEAP can reduce pressure on the AAA sac, implementing PEAP in mock-aneurysm flow-loops, measuring the pull-out forces of PEAP in arteries, and further developing the fabrication PEAP in patient-specific AAA geometries [46]. We also plan to more thoroughly investigate the shape memory characteristics of our PCL/PU blends. Animal studies will be used for *in vivo* investigations of the effects thermoforming, biodegradation, and aneurysm wall pressure reduction for further PEAP development. Future animal studies will also allow us to investigate the impact of blood circulation and AAA on PCL/PU degradation.

Acknowledgments

We would like to thank Brooke Beam for AFM help, Daniel Warren for SEM help, Mark Borgstrum for statistics help, and Megan Alexander for help with the biaxial tests. Funding for this project was provided by the ARCS Foundation, the NIH Biomedical Engineering Cardiovascular Training Grant HL007955, and NSF Career Award 0644570 (JPVG).

REFERENCES

1. Slepian, MJ. Polymeric endoluminal paving and sealing: therapeutics at the crossroad of biomechanics and pharmacology. In: Topol, EJ., editor. Textbook of interventional cardiology. WB Saunders; Philadelphia: 1989. p. 647

2. Slepian MJ. Polymeric endoluminal paving. A family of evolving methods for extending endoluminal therapeutics beyond stenting. *Cardiol Clin* 1994;12:715. [PubMed: 7850840]
3. Slepian MJ, Schindler A. Polymeric endoluminal paving/sealing: a biodegradable alternative to intracoronary stenting. *Circulation* 1988;78:408.
4. Slepian, MJ. Stents: State-of-the-art. Scientific Information Services; Philadelphia: 1994. Polymeric endoluminal paving: Evolving therapeutic methods for extending the spectrum of local endovascular interventions.
5. Slepian, MJ. Polymeric endoluminal paving: A family of evolving methods for extending the spectrum of endovascular therapeutics. In: Sigwart, U., editor. *Endovascular Stenting*. Saunders; Philadelphia: 1996. p. 102
6. Slepian, MJ. Polymeric endoluminal paving for TIPS: A glimpse of the future. In: Conn, HO.; Palmaz, J.; Rosch, J.; Rossle, M., editors. *Transjugular Intrahepatic Portal-systemic Shunts: TIPS*. Igaku Shoin Medical Publishers; New York: 1996. p. 339
7. Slepian MJ, Habib MP, Dehdashti B, Massia SP. Polymeric endotracheal paving: A biodegradable alternative to stenting. *American Journal of Respiratory and Critical Care Medicine* 1994;149
8. Slepian MJ, Mokhashi MS, Dehdashti B, Sampliner RE. Polymeric endoesophageal paving: A biodegradable alternative to stenting. *Gastro Endos* 1998;47
9. Slepian, MJ. Polymeric endoluminal paving: Local endourologic polymer systems for support, barrier creation and site-specific drug delivery. In: Yachia, D., editor. *Stenting the Urological System*. ISIS Medical Media; Oxford, UK: 1998.
10. Hill-West JL, Chowdhury SM, Slepian MJ, Hubbell JA. Inhibition of thrombosis and intimal thickening by in situ photopolymerization of thin hydrogel barriers. *Proc Natl Acad Sci U S A* 1994;91:5967. [PubMed: 8016098]
11. Slepian MJ. Polymeric endoluminal gel paving: therapeutic hydrogel barriers and sustained drug delivery depots for local arterial wall biomanipulation. *Semin Interv Cardiol* 1996;1:103. [PubMed: 9552500]
12. Slepian MJ, Hubbell JA. Polymeric endoluminal gel paving: Hydrogel systems for local barrier creation and site-specific drug delivery. *Advanced Drug Delivery Reviews* 1997;24:11.
13. Cotroneo AR, Iezzi R, Giancristofaro D, Santoro M, Quinto F, Spigonardo F, Storto ML. Endovascular abdominal aortic aneurysm repair: how many patients are eligible for endovascular repair? *Radiol Med* 2006;111:597. [PubMed: 16779545]
14. Norwood MG, Lloyd GM, Bown MJ, Fishwick G, London NJ, Sayers RD. Endovascular abdominal aortic aneurysm repair. *Postgrad Med J* 2007;83:21. [PubMed: 17267674]
15. Baxter BT, Terrin MC, Dalman RL. Medical management of small abdominal aortic aneurysms. *Circulation* 2008;117:1883. [PubMed: 18391122]
16. Bartoli MA, Parodi FE, Chu J, Pagano MB, Mao D, Baxter BT, Buckley C, Ennis TL, Thompson RW. Localized administration of doxycycline suppresses aortic dilatation in an experimental mouse model of abdominal aortic aneurysm. *Ann Vasc Surg* 2006;20:228. [PubMed: 16572291]
17. Vammen S, Lindholt JS, Ostergaard L, Fasting H, Henneberg EW. Randomized double-blind controlled trial of roxithromycin for prevention of abdominal aortic aneurysm expansion. *Br J Surg* 2001;88:1066. [PubMed: 11488791]
18. Miyake T, Aoki M, Masaki H, Kawasaki T, Oishi M, Kataoka K, Ogihara T, Kaneda Y, Morishita R. Regression of abdominal aortic aneurysms by simultaneous inhibition of nuclear factor kappaB and ets in a rabbit model. *Circ Res* 2007;101:1175. [PubMed: 17885220]
19. Ajili SH, Ebrahimi NG, Soleimani M. Polyurethane/polycaprolactane blend with shape memory effect as a proposed material for cardiovascular implants. *Acta Biomater* 2009;5:1519. [PubMed: 19249261]
20. Kenawy ER, Abdel-Hay FI, El-Newehy MH, Wnek GE. Processing of polymer nanofibers through electrospinning as drug delivery systems. *Materials Chemistry and Physics* 2009;113:296.
21. Pektok E, Nottelet B, Tille JC, Gurny R, Kalangos A, Moeller M, Walpoth BH. Degradation and healing characteristics of small-diameter poly(epsilon-caprolactone) vascular grafts in the rat systemic arterial circulation. *Circulation* 2008;118:2563. [PubMed: 19029464]
22. Sun H, Mei L, Song C, Cui X, Wang P. The in vivo degradation, absorption and excretion of PCL-based implant. *Biomaterials* 2006;27:1735. [PubMed: 16198413]

23. Pitt CG, Chasalow FI, Hibionada YM, Klimas DM, Schindler A. Aliphatic Polyesters .1. The Degradation of Poly(Epsilon-Caprolactone) In vivo. *Journal of Applied Polymer Science* 1981;26:3779.
24. Silva-Cunha A, Fialho SL, Naud MC, Behar-Cohen F. Poly-epsilon-caprolactone intravitreal devices: an in vivo study. *Invest Ophthalmol Vis Sci* 2009;50:2312. [PubMed: 19117927]
25. James NR, Philip J, Jayakrishnan A. Polyurethanes with radiopaque properties. *Biomaterials* 2006;27:160. [PubMed: 16026821]
26. Kowligi RR, von Maltzahn WW, Eberhart RC. Fabrication and characterization of small-diameter vascular prostheses. *J Biomed Mater Res* 1988;22:245. [PubMed: 3235462]
27. Guignot C, Betz N, Legendre B, Le Moel A, Yagoubi N. Degradation of segmented poly(etherurethane) Tecoflex (R) induced by electron beam irradiation: Characterization and evaluation. *Nuclear Instruments & Methods in Physics Research Section B-Beam Interactions with Materials and Atoms* 2001;185:100.
28. Muller BP, Ensslen S, Dott W, Hollender J. Improved sample preparation of biomaterials for in vitro genotoxicity testing using reference materials. *J Biomed Mater Res* 2002;61:83. [PubMed: 12001250]
29. Skarja GA, Woodhouse KA. In vitro degradation and erosion of degradable, segmented polyurethanes containing an amino acid-based chain extender. *J Biomater Sci Polym Ed* 2001;12:851. [PubMed: 11718481]
30. Fromstein JD, Woodhouse KA. Elastomeric biodegradable polyurethane blends for soft tissue applications. *J Biomater Sci Polym Ed* 2002;13:391. [PubMed: 12160300]
31. Tsuji H, Horikawa G. Porous biodegradable blends of poly(L-lactic poly(epsilon-caprolactone): polyester acid) and physical properties, morphology, and biodegradation. *Polymer International* 2007;56:258.
32. Lam CX, Savalani MM, Teoh SH, Hutmacher DW. Dynamics of in vitro polymer degradation of polycaprolactone-based scaffolds: accelerated versus simulated physiological conditions. *Biomed Mater* 2008;3:034108. [PubMed: 18689929]
33. Li S, Liu L, Garreau H, Vert M. Lipase-catalyzed biodegradation of poly(epsilon-caprolactone) blended with various polylactide-based polymers. *Biomacromolecules* 2003;4:372. [PubMed: 12625734]
34. Vande Geest JP, Sacks MS, Vorp DA. The effects of aneurysm on the biaxial mechanical behavior of human abdominal aorta. *J Biomech* 2006;39:1324. [PubMed: 15885699]
35. Haskett D, Johnson G, Zhou A, Utzinger U, Vande Geest J. Microstructural and biomechanical alterations of the human aorta as a function of age and location. *Biomech Model Mechanobiol*.
36. Vande Geest JP, Sacks MS, Vorp DA. A planar biaxial constitutive relation for the luminal layer of intra-luminal thrombus in abdominal aortic aneurysms. *J Biomech* 2006;39:2347. [PubMed: 16872617]
37. Lacoulonche F, Gamisans F, Chauvet A, Garcia ML, Espina M, Egea MA. Stability and in vitro drug release of flurbiprofen-loaded poly-epsilon-caprolactone nanospheres. *Drug Dev Ind Pharm* 1999;25:983. [PubMed: 10518238]
38. Masson V, Maurin F, Devissaguet JP, Fessi H. Stability of poly (epsilon caprolacton) nanospheres in sterile aqueous media. *International Journal of Pharmaceutics* 1996;139:113.
39. Gan ZH, Liang QZ, Zhang J, Jing XB. Enzymatic degradation of poly(epsilon-caprolactone) film in phosphate buffer solution containing lipases. *Polymer Degradation and Stability* 1997;56:209.
40. Liu L, Li S, Garreau H, Vert M. Selective enzymatic degradations of poly(L-lactide) and poly(epsilon-caprolactone) blend films. *Biomacromolecules* 2000;1:350. [PubMed: 11710123]
41. Small, Wt; Gjersing, E.; Herberg, JL.; Wilson, TS.; Maitland, DJ. Magnetic resonance flow velocity and temperature mapping of a shape memory polymer foam device. *Biomed Eng Online* 2009;8:42. [PubMed: 20043833]
42. Baer GM, Small Wt, Wilson TS, Benett WJ, Matthews DL, Hartman J, Maitland DJ. Fabrication and in vitro deployment of a laser-activated shape memory polymer vascular stent. *Biomed Eng Online* 2007;6:43. [PubMed: 18042294]

43. Ortega J, Maitland D, Wilson T, Tsai W, Savas O, Saloner D. Vascular dynamics of a shape memory polymer foam aneurysm treatment technique. *Ann Biomed Eng* 2007;35:1870. [PubMed: 17676399]
44. Buller CE, Culp SC, Sketch MH Jr, Phillips HR, Virmani R, Stack RS. Thermal-perfusion balloon coronary angioplasty: in vivo evaluation. *Am Heart J* 1993;125:226. [PubMed: 8417522]
45. Brasselet C, Durand E, Addad F, Vitry F, Chatellier G, Demerens C, Lemitre M, Garnotel R, Urbain D, Bruneval P, Lafont A. Effect of local heating on restenosis and in-stent neointimal hyperplasia in the atherosclerotic rabbit model: a dose-ranging study. *Eur Heart J* 2008;29:402. [PubMed: 18212388]
46. Ayyalasomayajula A, Polk A, Basudhar A, Missoum S, Nissim L, Vande Geest JP. Three dimensional active contours for the reconstruction of abdominal aortic aneurysms. *Ann Biomed Eng* 38:164. [PubMed: 19902358]

Figure 1.
Attachment of polymer blends for delamination testing.

Figure 2. Tangential modulus of abdominal aorta (AA) and abdominal aortic aneurysm (AAA) at a stress of 0.64 MPa with upper and lower 95% confidence intervals.

Figure 3. Tangential modulus of regular (R) and thermoformed (T) PCL/PU blends. X and Y specify direction, where Y is the direction of thermoforming (n=9).

Figure 4. Stiffness comparison between regular (R) and thermoformed (T) blends and aorta tissue. Directions were averaged together.

Figure 5.
Tube diameter expansion vs. blend ratio and heating temperature (n=1 for each blend at each temperature).

Figure 6.
Model vs. data for thermoforming tests.

Figure 7.
Delamination force of blends with linear fits ($n=1$ for each blend at each temperature).

Figure 8.
Mass loss of square (left) and tube (right) specimens in lipase solution (with standard error).
R and T refer to regular and thermoformed, respectively (squares n=9, tubes n=8).

Figure 9.

Tangential modulus of regular (R), lipase degraded (L), and combined thermoformed and lipase degraded (TL) PCL/PU blends. X and Y specify direction, where Y is the direction of thermoforming (n=9 except n=7 for 50/50-L).

Figure 10.
AFM Images of PCL (left), PCL/PU 40/60 (middle), and PU (right).

Figure 11.
SEM Images of PCL (left), PCL/PU 40/60 (middle), and PU (right).

Figure 12.
Porcine aorta before (left) and after (right) PEAP.