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Degree of bioresorbable vascular scaffold expansion modulates loss of essential function

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Abstract

Drug-eluting bioresorbable vascular scaffolds (BVSs) have the potential to restore lumen patency, enable recovery of the native vascular environment, and circumvent late complications associated with permanent endovascular devices. To ensure therapeutic effects persist for sufficient times prior to scaffold resorption and resultant functional loss, many factors dictating BVS performance must be identified, characterized and optimized. While some factors relate to BVS design and manufacturing, others depend on device deployment and intrinsic vascular properties. Importantly, these factors interact and cannot be considered in isolation. The objective of this study is to quantify the extent to which degree of radial expansion modulates BVS performance, specifically in the context of modifying device erosion kinetics and evolution of structural mechanics and local drug elution. We systematically varied degree of radial expansion in model BVS constructs composed of poly DL-lactide-glycolide and generated in-vitro metrics of device microstructure, degradation, erosion, mechanics and drug release. Experimental data permitted development of computational models that predicted transient concentrations of scaffold-derived soluble species and drug in the arterial wall, thus enabling speculation on the short- and long-term effects of differential expansion. We demonstrate degree of expansion significantly affects scaffold properties critical to functionality, underscoring its relevance in BVS design and optimization.

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Keywords

Bioresorbable vascular scaffolds; Radial expansion; Drug delivery; Computational modeling

1 Introduction

Drug-eluting bioresorbable vascular scaffolds (BVSs) have the potential to displace metallic drug-eluting stents (DESs) as the principal technology for restoring luminal patency via percutaneous coronary intervention. As with metallic stents, BVSs provide mechanical support to prevent acute vessel closure and recoil, as well a vehicle for controlled local delivery of antiproliferative drugs to counteract adverse arterial remodeling [1, 2]. By virtue of undergoing complete in-situ resorption, BVSs can also circumvent many classical limitations of permanent endovascular devices as exemplified by DESs [3, 4]. Yet, clinical introduction of BVSs is predicated on demonstrating non-inferior efficacy over DESs and thorough demonstration of device safety that addresses the unique risks inherent to bioerodible implants [5, 6].

Current understanding dictates that polymer-based BVSs provide intrinsically less mechanical support than metallic DES. Also due to the relatively high mechanical compliance, the radial expansion conferred upon deployment can be more variable than with current devices [7, 8]. Expansion is in part a procedural-specific factor, as the plaque and target arterial geometries will dictate the geometry required for ideal BVS deployment. The significant variation in arterial dimensions among individuals, e.g. the coronary artery diameter ranges from about 2-5 mm [9], as well as the range of lumen geometries manifested during various stages of disease progression, necessitate patient-specific assessment of vascular dimensions, appropriate BVS selection, and proper deployment [2, 6, 10]. Geometrical measurements are typically performed via quantitative coronary angiography and do limit instances of extreme over- and under-expansion, but cannot fully eliminate patient-specific variation in optimal deployment [6, 11]. We hypothesized such variability in initial degree of radial expansion plays a significant role in determining dynamic BVS performance over time. The pore structure of constituent polymeric networks will likely vary with expansion, and as a result impact the rates of key kinetic resorptive processes and thus loss of essential BVS function. In addition to ongoing vascular remodeling, evolution in scaffold mechanical properties and pharmacokinetics complicate prediction of how differential expansion modulates device efficacy. The imparted degree of expansion partially defines the initial state from which device evolution proceeds, and thus may be a deterministic factor in long term performance.

To better understand the potential impact of expansion on device performance, we systematically varied the degree of radial expansion of BVS constructs composed of poly-DL-lactide-glycolide (PLGA) and generated in-vitro metrics of degradation, erosion, mechanics, structure, and drug release kinetics. Experimental data were used to construct a finite element computational model to predict transient concentrations of released drug and degradation byproducts in the arterial wall. Our findings suggest that the imparted expansion can potentially alter BVS clinical performance, most notably in terms of structural

mechanics, supporting the need to account for and control this parameter in device design, optimization, and deployment.

2 Methods

2.1 Preparation of resorbable scaffolds

A previously described solution casting method was adopted to prepare PLGA-based resorbable scaffolds [12]. Homogenized polymer solutions of ester terminated 50:50 PLGA with an inherent viscosity of 0.82 dL/g (LACTEL Absorbable Polymers, AL, USA) were created by dissolving PLGA pellets in dichloromethane (Fisher Scientific, NH, USA) followed by stirring for 24 hours at room temperature. The polymer solution was poured on a glass panel and a casting knife with a tunable clearance was moved over the solution to yield uniform wet film with a thickness of 600 μm . To enhance evaporation of residual dichloromethane from the wet film, the glass plate was placed in a fume-hood at ambient conditions for 24 hours and then in a vacuum oven at 50°C for one week. Dry film thickness was tuned through manipulating the polymer concentration and wet film thickness, resulting in a dry film thickness of 150 $\pm$ 20 μm (akin to current BVS technologies) [11].

Dried films were cut into rectangular strips of 70 $\times$ 2 mm and wound onto polytetrafluoroethylene (PTFE) rods (2 mm diameter). Wound films were kept at room temperature for 24 hours and then heated at 37°C for 24 hours to form helical scaffolds. A balloon catheter was used to expand the scaffolds to prescribed radial dimensions of 2 mm, 4 mm, and 6 mm that simulate different degrees of radial expansion E-1, E-2, and E-3, respectively. Deformed scaffolds were acclimated at 37°C for 24 hours to achieve the polymer microstructure that would initially manifest in an implant scenario (Figure 1). Drug containing scaffolds (3% w/w) were prepared by homogenization of the polymer solution with 99.5% pure Paclitaxel (LC Laboratories, MA, USA) prior to film formation.

2.2 Morphological characterization

Scaffold surface morphology was analyzed using a variable pressure scanning electron microscope (SEM) (Tescan Vega-3 SBU, TESCAN USA Inc., PA) at accelerating voltage of 20 kV. Prior to image acquisition, segments of dried scaffolds were coated (Denton Vacuum Desk II Gold Sputter, NJ, USA) for 60 s at 35 mA current and chamber pressure $P < 100$ mTorr. Scaffold porosities were calculated from obtained SEM images using ImageJ (NIH, MD, USA). A modified IsoData threshold method was used to adjust the captured 16-bit images from SEM. Constant lower threshold value of 281 and upper threshold value of 18000 were used for all the images.

2.3 In-vitro hydration, erosion and degradation studies

Dried scaffolds were weighed (W_0) and then immersed into phosphate buffered saline (PBS) maintained at 37°C. The medium was replaced periodically to maintain pH levels, which is critical as PLGA polymer degradation is a pH-sensitive process [13]. At predetermined times, samples were weighed after gently removing unabsorbed PBS from the scaffold surface (W_{wet}). Samples were then rinsed with deionized water, dried at 37°C for one week,

and weighed (W_{dry}). Scaffold water absorption and erosion/weight loss were calculated as follows.

$$\text{Water absorption}(\%) = \frac{W_{\text{wet}} - W_{\text{dry}}}{W_{\text{dry}}} \times 100\% \quad (1)$$

$$\text{Erosion}(\%) = \frac{W_0 - W_{\text{dry}}}{W_0} \times 100\% \quad (2)$$

Gel permeation chromatography (GPC) (Polymer Laboratories) was used to analyze the weight-average molecular weight (MW_w) and polydispersity index (PDI) of dried scaffolds. A linear MW_w profile ($R^2 = 0.99$) of polystyrene (Polymer Standards Service, MA, USA) was used as standards to calibrate the GPC system. Samples were dissolved in high performance liquid chromatography (HPLC)-grade anhydrous tetrahydrofuran (Fisher Scientific, NH, USA) at a concentration between 10-15 mg/mL, which was also the solvent for the GPC mobile phase (flow rate = 1 mL/min, injection volume = 200 μ L/sample). Oven conditions were set at temperature of 30°C and pressure of 5 MPa.

2.4 Mechanical testing

A mechanical testing system (Bose ElectroForce® 3200, MN, USA) was used to measure the radial stiffness of dried scaffolds following an established protocol [14]. Briefly, samples were placed between two flat compression plates and subjected to a ramped uniaxial compressive displacement of 0.5 mm at 0.005 mm/s. Sample force and displacement data were continuously recorded at an acquisition rate of 20 points/s using a system integrated software (Wintest®, MN, USA). These experiments were performed on dry rather than hydrated scaffolds to promote sample stability throughout the applied compression.

2.5 In-vitro drug release

Individual PTFE tubes containing drug-loaded dried scaffolds (4.4 μ g Paclitaxel/ mm^2) were completely immersed in glass vials containing 50 mL of PBS (pH of 7.4) and 10% (v/v) dimethyl sulfoxide (DMSO) (Fisher Scientific, NH, USA). PTFE tubes were used to mimic the arterial wall condition and retain the scaffold shape, whereas glass vials were used to contain both the PTFE tube (with scaffold inside) and static media. The absence of bubbles inside the PTFE tubes ensured that the scaffold was in perfect contact with the PBS solution. DMSO (Paclitaxel solubility limit of 200 mg/mL) was used to enhance Paclitaxel solubility in PBS and restrict drug adherence to the glass walls [15]. A perfect sink condition was maintained and all glass vials were kept in the incubator at 37°C throughout the release study. At predetermined time points, aliquots were withdrawn and Paclitaxel concentrations were quantified. Following 28 days of submersion, the scaffolds were withdrawn, dried and dissolved in acetone to measure remaining (unreleased) drug content. At all time points, Paclitaxel concentration was quantified by an Agilent Series 1100 HPLC (Agilent Technologies, CA, USA) equipped with a 4.6 $\times$ 150 mm LiChrospher RP-18 (particle size: 5 μ m) [16]. The mobile phase consisted of 60% (v/v) HPLC grade acetonitrile (Sigma-Aldrich, MO, USA) and 40% (v/v) deionized water with a flow rate 1 mL/min. The injection

volume was 100 μL and UV detection was performed at 227 nm with the column oven temperature at 30°C. Paclitaxel retention time was approximately 5 min. A linear concentration profile ($R^2 = 0.99$) of 0.1–100 μM Paclitaxel was used as a standard for calibration.

2.6 Computational model

A two-dimensional finite element model was developed to investigate the effect of radial expansion on scaffold degradation by-product and drug pharmacokinetics within the arterial wall. The computational domain comprised of a cross-section of an arterial wall with 1 mm thickness, and a single, fully-embedded, square shaped scaffold strut of dimensions 2.0×0.15 mm. Degradation was modeled as a random scission process of ester bonds between monomers, while bulk erosion was modeled as the release of soluble species from the strut domain [17]. Concentrations of insoluble species were modeled by the following reaction equations:

$$\frac{dC_n^s}{dt} = -nkC_n^sA \quad (3)$$

$$\frac{dC_i^s}{ds} = -iC_i^sA + 2\sum_{m=i+1}^n kC_m^sA \quad (4)$$

where n , C_n^s , k , and A are respectively the number of ester bonds, concentration of the largest species, hydrolytic degradation rate and autocatalytic factor; C_i^s , i , and C_m^s are respectively the insoluble species concentration, number of ester bonds and insoluble species concentrations with the number of ester bonds between n and $i+1$. Concentrations of soluble species (small oligomers and monomers) within the scaffold (C_0^s) were modeled by the diffusion-reaction equation [18]:

$$\frac{\partial C_0^s}{\partial t} = \nabla \cdot (D_0^s \nabla C_0^s) + 2\sum_{m=1}^n kC_m^sA \quad (5)$$

where D_0^s is the diffusion coefficient of soluble species in the scaffold that was modeled as a function of current scaffold MW_w . Concentrations of soluble species in the arterial wall (C_0^w) were modeled using the diffusion-reaction equation:

$$\frac{\partial C_0^w}{\partial t} = \nabla \cdot (D_0^w \nabla C_0^w) - k_m C_0^w \quad (6)$$

where D_0^w and $k_m = 10^{-5} \text{ m}^2/\text{s}$ are the diffusion coefficient and metabolism rate of soluble species in the arterial wall, respectively. Paclitaxel concentration within the scaffold C_p^s was modeled by the diffusion equation:

$$\frac{\partial C_p^s}{\partial t} = \nabla \cdot (D_p^s \nabla C_p^s) \quad (7)$$

where D_p^s is the degradation-dependent transient bulk diffusion coefficient of Paclitaxel in the scaffold, modeled by the following equation:

$$D_p^s = D_0^s \exp(\alpha t) \quad (8)$$

where D_0^s is the Paclitaxel initial bulk diffusion coefficient in the scaffold and α is the diffusion coefficient change rate. Assuming diffusion as the dominant transport mechanism for drug within the arterial tissue and reversible binding to nonspecific tissue sites, the concentration kinetics of Paclitaxel in the arterial wall was modeled by the following equations [19]:

$$\frac{\partial C_{p,f}^w}{\partial t} = \nabla \cdot (D_p^w \nabla C_p^w) - \frac{dC_{p,b}^w}{dt} \quad (9)$$

$$\frac{dC_{p,b}^w}{dt} = k_a C_{p,f}^w (B_M - C_{p,b}^w) - k_d C_{p,b}^w \quad (10)$$

where $C_{p,f}^w$ and $C_{p,b}^w$ are respectively the concentrations of free and bound Paclitaxel in the arterial wall; $D_p^w = 5.71 \times 10^{-10} \text{ m}^2/\text{s}$ and $B_M = 13 \text{ mol/m}^3$ are respectively the Paclitaxel diffusivity and net tissue-binding capacity; $k_a = 21.97 \text{ mol/m}^3\text{-s}$ and $k_d = 2.99 \text{ 1/s}$ are respectively the Paclitaxel association and dissociation rate constants [20].

Based on molecule retention profiles from GPC, the initial scaffold molecular weight distribution (MWD) was prescribed to yield $MW_w = 55.757 \text{ kDa}$ and $PDI = 1.24$. An open boundary condition was imposed both at the intramural interface and perivascular wall. Continuity of soluble species concentrations was assumed at the scaffold-arterial wall interface. For drug transport, all Paclitaxel was assumed to be within the scaffold at the initial stage, i.e. zero initial free and bound Paclitaxel concentrations in the arterial wall were imposed [21]. Continuation of Paclitaxel concentration was assumed for the free drug at the scaffold-arterial wall interface. For the free drug, an open concentration condition was applied at the perivascular wall whereas a zero flux boundary condition was assumed at the intramural interface due to hydrophobicity of Paclitaxel and high resistance provided by the intima [22, 23]. For the bound drug, zero flux boundary condition was assigned at mural interface, scaffold-arterial wall interface and the perivascular wall.

All transient simulations were solved using a standard finite element based software package (COMSOL Multiphysics™, Comsol, Inc, MA, USA). A boundary layer mesh with maximum intensity of elements adjacent to the scaffold strut was used, whereas the Delaunay triangular scheme was used to mesh the remaining computational domain. Iterative mesh refinement was performed until the relative error tolerance reached 10^{-5} . The

numerical solution was deemed to be mesh-independent when the relative change in average arterial wall soluble species and Paclitaxel (free and bound) concentrations was less than 1% for successive mesh refinements. The resultant mesh was comprised of 8912 triangular and 3712 quadrilateral elements and was used for all subsequent simulations.

2.7 Statistical analysis

Results are presented as the average and standard errors of at least 3 independent samples at each time point. Considering incubation time and degree of expansion as independent variables, statistical analyses were performed using both one-way and two-way ANOVA followed by Tukey's post-hoc multi-comparison test. Experimental differences were considered statistically significant at $p < 0.05$. The coefficient of determination (R^2) and Pearson product-moment correlation coefficient (r) were computed to respectively assess the goodness-of-fit of linear regression and strength of correlation between the independent variables and performance metrics.

3 Results

3.1 Scaffold porosity

Scaffold porosity significantly increased with degradation time ($p < 0.001$) and degree of expansion ($p < 0.001$), although no differences were observed among the scaffolds immediately after expansion (Figure 2 and 3A). The imposed degree of expansion had a dramatic effect on polymer microstructure at increased incubation times with the most expanded construct (E-3) exhibiting a near 4-fold increase in porosity compared to the least expanded construct (E-1) at two weeks. Individual pore size and connectivity were similar in all cases, suggesting that differences in porosity emerge as a consequence of increased pore density as opposed to the growth of existing pores.

3.2 Scaffold hydration, degradation and erosion

All scaffolds were initially glassy and flexible, and transformed to whitish and brittle within one week of submersion in PBS. Following this period, reduced structural integrity of the scaffolds was evident in a manner that increased with degree of radial expansion. Water rapidly permeated into all scaffolds upon submersion in PBS (Figure 3B), resulting in significant weight increase over time ($p < 0.001$). Water uptake was significantly affected by degree of expansion ($p < 0.01$), with E-3 exhibiting a 40% higher water uptake compared to E-1 in the first week.

Differences in water uptake were associated with differential rates of ester bond scission and loss of MW_w . Greatest divergence among scaffold variants was seen over the second week of submersion (Figure 3C). The scaffold degradation half-life ($t_{deg}^{1/2}$), defined as the time at which the initial MW_w is reduced by 50%, was less than one week in all cases and was accelerated at higher expansions ($p < 0.005$). Despite differences in early degradation rates, all scaffolds retained less than 10 % of the initial MW_w by four weeks in this rapidly eroding material system.

Although degradation studies revealed that generation of soluble species is a rapid process following scaffold submersion in PBS, protracted diffusion within the bulk polymer resulted in a temporal shift between degradation (dissolution of polymer to smaller species) and erosion (loss of scaffold mass). While mass loss was negligible over the first 2 weeks for all degrees of scaffold expansion (less than 5%), dramatic and differential changes were observed at later stages (Figure 3D). The scaffold erosion half-life ($t_{\text{ero}}^{1/2}$), defined as the time at which W_0 is reduced by 50%, exceeded the 4-week period over which the study was conducted, underscoring the temporal shift between degradation and erosion. While the overall erosion curves among samples were similar, ($p>0.1$), they diverged significantly at later times with E-3 losing 38% more mass than E-1 by 4-weeks ($p<0.05$).

3.3 Scaffold mechanical properties

Radial compression testing was used to characterize scaffold structural mechanics as a function of imposed expansion and incubation time. All recorded forces were normalized by the scaffold length to reflect structural stiffness in the radial direction (Figure 4A). Data were further processed to compute the scaffold compressive modulus (E_c), which was the slope of the force-displacement curves over the range of low displacements (0-0.3 mm) (Figure 4B). While radial expansion caused an initial reduction in stiffness, scaffolds were mechanically equivalent after 1 week ($p>0.05$). Non-uniformities were generated within the scaffold at extended incubation times and as a result mechanical studies were only possible over a 1-week period.

3.4 In-vitro drug release kinetics

Initial Paclitaxel release from all scaffolds was moderate, with less than 10% of loaded drug released within 2 weeks (Figure 4C). Accelerated release kinetics occurred over the next 2 weeks, cumulating in approximately 50% drug release by all scaffold variants over the study period. The imposed degree of radial expansion significantly affected cumulative Paclitaxel release kinetics over four weeks ($p<0.001$), with the most notable differences emerging at later time points (14 – 28 days).

3.5 Computational predictions of degradation by-product and drug distribution

Model-based predictions of scaffold degradation profiles showed excellent correlation ($R^2 = 0.99$) with experimental findings under static conditions (Supplemental Figure 1), enabling estimation of global initial soluble species diffusion coefficient and variable hydrolytic degradation rates for E-1, E-2 and E-3 (Table 1). Isotropic diffusion and a homogeneous initial distribution of soluble species inside the scaffold yielded maximal soluble species concentration at the core of the strut (Figure 5A). Generated degradation by-products, including lactic acid, accumulated in the arterial wall at early times (< 30 days), suggesting a period over which the rate of species release from the scaffold exceeds the local clearance capacity. Increased expansion influenced arterial wall soluble species concentration at later times, specifically by reducing the time to and increasing the extent of maximal by-product accumulation (Figure 5B).

The initial Paclitaxel bulk diffusion coefficient and diffusion coefficient changes rate for E-1, E-2 and E-3 were estimated using obtained experimental release data and a representative simulation of static in-vitro drug release (Table 1, Supplemental Figure 2). Identified parameters were then incorporated into the described 2-D simulation of drug release within the arterial wall, permitting evaluation on how differential expansion impacts drug delivery from implanted BVSS (Figure 5C). Throughout the simulated time period (75 days) the majority of drug within the arterial wall was in the bound form irrespective of expansion, with a consistently order-of-magnitude higher concentration of bound (Figure 5D) compared to free (Figure 5E) drug. The competing kinetics of Paclitaxel release and clearance led to peak concentrations in surrounding tissue which were similar in magnitude across the degrees of radial expansion and occurred around 4 weeks in all cases.

Using the model of drug release from BVS, two hypothetical extreme scenarios were simulated to further characterize the limiting effects of scaffold erosion on arterial wall Paclitaxel pharmacokinetics: 1) “fast erosion” and 2) “slow erosion” (Figure 5F). In case of “fast erosion”, the Paclitaxel diffusion coefficient inside the scaffold was assumed identical to that in the arterial wall ($5.71 \times 10^{-10} \text{ m}^2/\text{s}$), whereas for “slow erosion” it was held at its initial (minimal) value ($3.50 \times 10^{-19} \text{ m}^2/\text{s}$). Comparison to the “normal erosion” case (i.e. predictions for E-2), in which the diffusion coefficient is an increasing function of time, demonstrates the significant potential range in BVS drug delivery characteristics. In our model, order-of-magnitude variations in both the time course and amount of Paclitaxel delivery to the arterial wall were observed for these limiting scenarios.

4 Discussion

BVSS have been heralded as the fourth revolution in percutaneous coronary interventional (PCI) treatment, owing to their inherent potential to treat acute coronary lesions while mitigating long term risk associated with permanent DES [4, 7]. The notion of temporary scaffolding following PCI is attractive, although the optimal lifetime and performance characteristics of erodible endovascular implants remain open questions. Several engineering criteria must be met and clinical endpoints confirmed to ensure these devices are both safe and effective. In this paper, we demonstrate that degree of radial expansion plays an important role in modulating the evolution of BVS performance following implantation, particularly at longer times as the scaffold materially degrades then structurally erodes. Using PLGA as an exemplary polymer, we show that the microstructural network varies with expansion, in turn impacting key performance metrics for vascular scaffolding in relation to mechanical and drug delivery properties. Computational models were constructed based on a subset of generated in-vitro data to predict the concentrations of drug and degradation by-products in the arterial wall, thus providing additional insight into how expansion is linked to BVS performance.

Together, our in-vitro data suggest that scaffold elution of Paclitaxel is initially a diffusion-mediated process, whereas at later times becomes dominated by erosion. Despite rapid scaffold hydration, diffusion of hydrophobic Paclitaxel within the hydrophobic scaffold remains relatively slow. With onset of erosion, drug release rate increases markedly – a trend we would expect to persist with any hydrophobic compound. Radial strength of the

scaffold was found to depend on the degree of expansion and linearly vary with the MW_w within the first week, suggesting a causal relationship that can be exploited in the BVS design process for longer operating times (Figure 6A). Moreover, a linear correlation was observed between the percent of released drug and scaffold mass loss ($R^2 = 0.92$), underscoring the significant interplay of these processes and providing a secondary metric by which drug release rates can be indirectly tuned or inadvertently imposed (Figure 6B). These correlations more generally relate key transient scaffold properties to degradation and erosion processes, which themselves occur at different rates and have different sensitivities to radial expansion. Clearly, further modulation of drug release from BVSs can be achieved through tuning of strut geometry and the incorporation of coatings.

The rate of MW_w decrease is higher than the rate of water absorption, suggesting that in addition to simple hydrolysis, ester bond scission is enhanced by autocatalysis. Water absorption kinetics eclipsed erosion in all BVS variants, suggesting a bulk rather than surface process underlies scaffold erosion. Bulk erosion was indeed qualitatively observed and expected, as the thickness of the scaffolds was below the critical thickness identified for PLGA erosion mechanisms [24]. Various strategies for tuning BVS $t_{ero}^{1/2}$ and $t_{deg}^{1/2}$ have been previously identified, including base polymer selection and control of initial MW_w , additive inclusion, end-group capping, porosity and degree of crystallinity [16, 17, 25]. Our results suggest that these methods also can be leveraged to control transient drug release and radial strength properties in BVS applications.

Scaffold pore formation was increased by expansion, which in turn led to increased water penetration and accelerated degradation kinetics. While the precise mechanism by which expansion enhances pore formation is not explored in our work, it is likely that existing pores and diffusion channels within the polymeric network are extended in concert with bulk material expansion [26, 27]. As a consequence of enhanced degradation, mechanical stiffness of the scaffold is rapidly compromised. Such effects can promote likelihood of early scaffold fracture which has emerged as a recognized risk factor for BVS restenosis clinically [28]. Indeed, BVS over-expansion and otherwise inappropriate deployment has been shown to enhance early fracture rates [29]. Material selection and fabrication protocols can be tuned to promote requisite mechanical strength for the intended functional lifetime of the device [7, 13]. Still, irrespective of the specific base polymer and manufacturing technique, a given BVS will be limited by a maximum attainable degree of expansion prior to the onset of mechanical failure. It is important to recognize that BVS under-expansion, similar to DES [30], may also increase risk of deleterious arterial remodeling and clotting due to disturbed blood flow patterns [31]. Previous findings suggest that the risk attributed to BVS over-expansion (above the critical 0.5 mm tolerance) exceeds that of under-expansion [29]. However, the limited number of clinical trials and restrictive patient population prevent drawing definitive conclusion with regards to how the degree of expansion affects clinical outcomes.

Our in-vitro findings suggest that BVS pharmacokinetics are mildly impacted by expansion, and computational results demonstrate that arterial wall drug transport is relatively insensitive to the observed variations in release. Taken together, these findings suggest that

transport mechanisms within the arterial wall as opposed to marginally differential release kinetics determine bound Paclitaxel wall concentrations. Results also indicate that arterial wall drug levels are initially diffusion-controlled but become erosion-dependent at later times. We expect that the predicted interplay among erosion, drug release, and degree of radial expansion to persist at least qualitatively across candidate BVSs, and play an increasingly important role in cases where time scales of drug release exceed that of erosion (see limiting case of fast erosion; Figure 5F). Numerous polymer synthesis strategies could be used to protract BVS erosion kinetics (i.e. increased polymer molecular weight, cross-linking, and solid content), control drug release rates (i.e. addition of coatings, tuning of strut surface area) and thus tune local wall drug concentrations [17]. Computational modeling provides critical insight into relations among these phenomena and a basis for reducing the experiential design space for development and evaluation of clinical-grade devices.

The generation and fate of degradation by-products (soluble species) are themselves critical determinants of BVS safety. Excessive accumulation of acidic by-products such as lactic acid lowers the local pH and potentially induces tissue necrosis. While in-vitro/in-vivo tracking of degradation by-products is difficult to experimentally realize, computational models can readily provide insight into soluble species kinetics and help identify qualitative trends. Our results suggest that increased expansion elevates the risk for local by-product accumulation and thus alteration of local pH.

Study limitations

A rapidly degrading polymer with low MW_w was used in this study, as opposed to clinically-viable polymers with high MW_w and lifetimes of up to 2 years. We expect that the presented scaffold response to differential expansion can be qualitatively related to other BVS formulations and designs (zip-lock or slotted-type) through correlation with MW_w and mass loss kinetics. Moreover, a wide (3-fold) range of radial expansion was examined using our experimental BVSs. Although such variance will likely extend beyond the operating specifications of clinically approved devices, our study is the first-step in understanding the importance of radial expansion in BVS deployment. Here again our findings retain qualitative relevance, as the sensitivity among clinically-viable scaffolds to expansion will undoubtedly vary among products and necessitate device-specific characterization. Finally, our computational framework did not account for the impact of the local mechanical environment of the arterial wall on BVS degradation and drug release kinetics, both of which exhibit strain-sensitivity in other polymeric systems [32]. Overall, our findings provide phenomenological insight into the role of radial expansion in determining scaffold performance and underscore the need to carefully consider its potential variation in BVS design and clinical translation.

5 Conclusion

BVS technologies are undergoing rapid development and emerging devices have the potential to transform management of coronary heart disease owing to effective treatment of short term vessel closure while avoiding long term consequence. Yet optimizing BVS efficacy and safety is predicated on understanding performance – a complex task given the

inseparable link between device resorption and imposed evolution in device function. While device design and manufacturing processes can affect intrinsic resorption rate and hence function, we here demonstrate that deployment itself, independent of design, is important to consider. When devices are over-expanded relative to design specifications, degradation and erosion accelerate, thereby modulating loss of structural integrity and drug release. Understanding such dynamics is critical to robust BVS design and safe use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. A schematic of the employed BVS synthesis procedure

Three scaffold variants with an increasing degree of radial expansion (E-1, E-2, or E-3) were created for subsequent studies. Constant surface area was maintained for all scaffolds, implying a variation in length in the expanded states.

Figure 2. SEM images of scaffold microstructure

SEM images were used to assess the morphology of the scaffold surface as a function of in-vitro incubation time and the imposed degree of radial expansion.

Figure 3. Evolution in scaffold structure and composition

The degree of radial expansion modulates in-vitro scaffold (A) porosity, (B) water absorption kinetics, (C) degradation kinetics as indicated by loss of weight-average molecular weight (MW_w), and (D) erosion kinetics as indicated by mass loss. The total amount of absorbed water, MW_w , and mass loss at any point are normalized with respect to the scaffolds concurrent dry mass, initial MW_w , and initial dry mass, respectively. *indicates statistically significant differences between groups ($p < 0.05$).

Figure 4. Evolution in scaffold function

The degree of radial expansion modulates in-vitro scaffold (A) compressive force response and (B) linearized compressive moduli. Compressive force vs. displacement curves correspond to the 4 day incubation time point. Forces are normalized with respect to the corresponding scaffolds length. (C) The degree of radial expansion also affects in-vitro release kinetics of Paclitaxel in PBS solution at 37°C. The drug release amount is normalized with respect to the initial drug content.* indicates statistically significant differences between groups ($p < 0.05$).

Figure 5. Computational predictions of arterial wall concentrations

(A) A representative surface plot of the soluble degradation species concentration (after 30 days degradation for expansion case E-2) predicted by a two-dimensional computational model consisting of a square scaffold strut fully-embedded in the arterial wall. (B) Computational predictions indicate that peak arterial wall soluble species concentration is influenced by the degree of radial expansion. Initial soluble species diffusion coefficient of $1 \times 10^{-13} \text{ m}^2/\text{s}$ and hydrolytic degradation rate of $4.0 \times 10^{-8} \text{ m}^3/\text{mol} - \text{s}$, $4.3 \times 10^{-8} \text{ m}^3/\text{mol} - \text{s}$, and $4.6 \times 10^{-8} \text{ m}^3/\text{mol} - \text{s}$ were used for E-1, E-2, and E-3, respectively. Color bars represent soluble species concentrations in corresponding domains. (C) A representative Paclitaxel concentration surface plot (after 30 days degradation for expansion case E-2). Color bars represent Paclitaxel concentrations in corresponding domains. Computational predictions indicate that average arterial wall (D) bound and (E) free paclitaxel concentrations kinetics are largely independent of radial expansion. Paclitaxel initial bulk diffusion coefficient in the scaffold of $3.5 \times 10^{-19} \text{ m}^2/\text{s}$ and the diffusion coefficient change rate of $3.75 \times 10^{-6} \text{ m}^2/\text{s}$, $4.00 \times 10^{-6} \text{ m}^2/\text{s}$, and $4.05 \times 10^{-6} \text{ m}^2/\text{s}$ were used for E-1, E-2, and E-3, respectively. Arterial wall Paclitaxel diffusivity of $5.71 \times 10^{-10} \text{ m}^2/\text{s}$, net tissue-binding capacity of $13 \text{ mol}/\text{m}^3$, association and dissociation rate constants of $21.97 \text{ mol}/\text{m}^3 - \text{s}$ and 2.98798 1/s , respectively were used for all illustrated simulated results. (F) Scaffold erosion affects arterial wall Paclitaxel pharmacokinetics. Paclitaxel bulk diffusion coefficient in the scaffold of $5.71 \times 10^{-10} \text{ m}^2/\text{s}$ and $3.5 \times 10^{-19} \text{ m}^2/\text{s}$ were considered for limiting (extreme) cases of scaffold erosion.

Figure 6. Scaled-evolution in scaffold function

(A) For a given degree of expansion, scaffold compressive modulus exhibits linear correlation ($R^2 = 0.99, 0.79, 0.99$ for E – 1, E – 2, E – 3, respectively) with normalized MW_w.

(B) For all degrees of expansion, the fraction of cumulative Paclitaxel release from the scaffold exhibits linear correlation ($R^2 = 0.92$) with scaffolds mass loss (A)

Table 1
Model parameters for computational simulation

Parameter values were estimated based on best-fit with experimental results. Representative transient simulations that mimicked static in-vitro experiments were performed to predict kinetic parameters for scaffold MW_w loss and drug release.

		Degree of radial expansion		
		E-1	E-2	E-3
Initial soluble species diffusion coefficient	D^w_0 [m^2s^{-1}]	1×10^{-13}	1×10^{-13}	1×10^{-13}
Hydrolytic degradation rate	K [$m^3mol^{-1}s^{-1}$]	4.0×10^{-8}	4.3×10^{-8}	4.6×10^{-8}
Drug bulk diffusivity $D=D_0 \exp(\beta t)$	D_0 [m^2s^{-1}]	3.5×10^{-19}	3.5×10^{-19}	3.5×10^{-19}
	α [s^{-1}]	3.75×10^{-6}	4.0×10^{-6}	4.05×10^{-6}