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Effect of working environment and procedural strategies on mechanical performance of bioresorbable vascular scaffolds

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Abstract

Polymeric bioresorbable scaffolds (BRS), at their early stages of invention, were considered as a promising revolution in interventional cardiology. However, they failed dramatically compared to metal stents showing substantially higher incidence of device failure and clinical events, especially thrombosis. One problem is that use of paradigms inherited from metal stents ignores dependency of polymer material properties on working environment and manufacturing/deployment steps. Unlike metals, polymeric material characterization experiments cannot be considered identical under dry and submerged conditions at varying paces.

We demonstrated different material behaviors associated with variable testing environment and parameters. We, then, have employed extracted material models, which are verified by computational methods, to assess the performance of a full-scale BRS in different working condition and under varying procedural strategies. Our results confirm the accepted notion that slower pace of manufacturing/deployment phases (i.e. crimping/inflation) can potentially reduce stress concentrations and thus reduce localized damages. However, we reveal that using a universal set of material properties derived from a benchtop experiment conducted regardless of working environment and procedural variability may lead to a significant error in estimation of stress-induced damages and overestimation of benefits procedural updates might offer. We conclude that, for polymeric devices, microstructural damages and localized loss of structural integrity should complement former macroscopic performance-assessment measures (fracture and recoil). Though, to precisely capture localized stress concentration and microstructural damages, context-related testing environment and clinically-relevant procedural scenarios should be devised in preliminary experiments of polymeric resorbable devices to enhance their efficacy and avoid unpredicted clinical events.

Key words: Bioresorbable scaffolds | Polymer characterization | Finite element analysis | Working environment | Microstructural damages

1. Introduction

Stent angioplasty has become the golden standard in treating coronary artery diseases mainly because of its minimally-invasive nature and universally-accepted performance scaffolding narrowed vessels, and restoring physiological blood flow. Most state-of-the-art stents currently in the market are made of metal alloys, such as cobalt-chromium, to provide stable radial support to the arterial wall while maintaining a thin profile to flexibly adapt high vessel tortuosity, bear cyclic loadings from the motion of the heart, and minimize hemodynamics disruption and vascular injury [1]. However, these permanent foreign objects residing inside living arteries may interfere with vascular repair and lead to vessel caging, limited re-intervention, altered vasomotor tone, induced strut malapposition, vessel rupture from strut fracture [2-5], and bleeding or thrombosis in the face of obligate anti-platelet therapy [6-8]. Although various approaches have been investigated to improve the performance of this device [9,10], fundamental limitations associated with metal stents drove the community toward bioresorbable scaffolds (BRS). The emergence of BRS extended the innovation of minimally-invasive angioplasty, allowing for implants to be inserted and then degrade over time, leaving an intact vessel.

Poly-l-lactic acid (pLLA) is the most commonly used material for BRS due to its fairly abundant supply, high strength and modulus, and, more importantly, non-toxic degradation by-products through simple mechanisms such as hydrolysis [11]. However, pLLA is fundamentally different from metals, in terms of its dynamic properties, material behavior, and heterogeneous microstructures [12]. These unique structural features require distinct research paradigms that cannot be assumed to mimic metal devices. Ignoring such differences and simply inheriting evaluation strategies from other durable materials might well bring catastrophic clinical outcomes, and may be why mounting clinical evidences show increased rate of thrombosis and myocardial infarctions with BRS [13,14].

Coronary stents undergo a 2-3 fold radial reduction at crimping and equal expansion at implantation, and are exposed to cyclical asymmetric strain from each heartbeat. Rigorous benchtop experiments, from material level tests such as stress-strain analysis using dog-bone specimens, to durability analysis on simplified geometries, and to device level tests such as crush resistance test, radial expansion/compression test, and longitudinal tensile/compression test, are thus enforced to provide thorough mechanical characterizations on these devices [15-17]. In addition, the irregular and complex structural design of stents relies increasingly on finite element (FE) analysis drawing on material mechanical responses characterized from benchtop stress-strain tests [18,19]. Radial strength, stress distribution, recoil percentage, dog-boning effect, and stent-artery interactions have been reported using both implicit and explicit strategies [18,20,21]. Yet, the accuracy of FE analysis highly depends on benchtop mechanical characterization.

Unlike metals which possess relatively stable mechanical properties under physiological conditions, mechanical responses of polymer materials, such as pLLA, vary largely due to their high sensitivity in testing environment. We hereby emphasize that material behavior would critically change depending on the operation environment. The fact that endovascular implants are designed and tested in dry test room condition, and then implanted in continuous contact to blood flow may cast serious doubt on accuracy of preliminary design steps when material characterization might not comply with realistic material behavior in situ. Differences in yield strain, stiffness, strain at break and ultimate tensile strength have been found when tested in air and in submerged conditions [15] while majority of studies relied on one condition ignoring the implications of the other in terms of more comprehensive material characterization. Furthermore, limited studies have appreciated this critical concept specifically while modeling the device performance and treatment efficacy. According to the operation environment of endovascular implants, as the crimping procedure of BRS is done in air while the inflation is performed when BRS is inserted into the artery and in contact with blood, the design analysis and structural modeling should accordingly consider material properties tested under both scenarios instead of a single universal model for all.

In addition to distinguishing the environment the device is exposed to, the pace of operation may also alter the device mechanical properties due to viscosity [19]. There has been a strict implantation instruction devised by BRS manufacturers for physicians to follow in terms of designated deployment pace, substantially slower compared to metal stents, to prevent acute fractures or reduce recoil during/after implantation [22]. Yet, no explicit limit has been set to specify the optimal pace. One important circumstance that has also been ignored thus far is the fact that crimping, as well, creates microstructural deformations which can develop into more severe structural failures in the future [12]. Proper investigation of crimping and inflation pace is required to minimize microstructural failures and ensure optimal practice in clinics. This fundamental aspect of endovascular implant design has been the central scope of this research, then, to characterize the device with respect to the environment and later assess its performance in the context of intervention. We conducted uniaxial tensile tests on dog-bone samples obtained through laser cutting clinical grade pLLA tubes. Tests were performed in both air and submerged conditions at different velocities. FE analysis was then performed with material properties derived from both conditions to help compare stress distribution and recoil percentage (%recoil) to verify the efficacy of device. This extensive approach of material characterization and device performance assessment may shed further light on the mechanistic knowledge of how the BRS would behave in physiological settings to not only delineate clinical events observed for BRS but also provide design teams with insights to upgrade medical devices for enhanced clinical treatments.

2. Material and Methods

2.1 Material Preparation

pLLA dog-bone specimens and fully resorbable pLLA scaffold systems generously provided by the Boston Scientific Corporation were used in all experimental conditions unless otherwise specified. All units tested were prototypes under development and not commercially available. Scaffolds are 16 mm in length, 3.0 mm in inner diameter before crimping, and have a wall thickness of 105 µm (Figure 1A). Dog-bone specimens were obtained through laser-cutting using the same extruded tubes used to generate scaffolds (Figure 1B), and then flattened with weights prior to experiments. All specimens were carefully extracted having the loading axis aligned with the longitudinal axis of the extruded PLLA tube. Scaffolds and dog-bone specimens were stored at 4 ºC prior to experiments.

2.2 Uniaxial tensile test on pLLA dog bone specimens

Mechanical properties of the material were predominantly characterized by the uniaxial tensile test. The hardening curve resulted from the experiment described evolution of the yield stress during the deformation. The experimental setup (Figure 1C) included a water chamber to allow the specimens being stretched in a submerged condition. A dog-bone specimen was mounted onto two clamps, and immersed in water at room temperature and then stretched by the presented testing machine. The axial load cell signals were recorded in real time and compiled by a computer-based data acquisition system. Experiments were accomplished in the range of quasi-static to dynamic stretching condition with three constant cross-head velocities, 0.001, 0.01, and 0.1 mm/sec, until fracture. It is safe to assume the slowest velocity, 0.001 mm/sec, as a quasi-static condition.

Deformations were observed and recorded by the Digital Image Correlation (DIC) method. This non-contact and material-independent optical measuring system is extensively being used to monitor the displacement history and strain distribution in mechanical applications [23, 24]. All experiments – in dry and submerged conditions – were monitored with a high resolution digital camera. Front surfaces of all specimens were speckle-painted using an airbrush leaving behind randomly patterned black points. The resulted images including the entire experiment up to fracture were then imported to the DIC software VIC-2D (Correlated Solutions) to quantify the displacement field and the planar surface strains. Effective strain distribution of uniaxial tensile samples subjected to different stretching velocities before fracture were assessed for both dry and submerged conditions (Figure 2).

2.3 Material Parameters Calibration

Material parameters for the numerical analysis were extracted from the true stress – true strain experimental curves. The Young's modulus was calculated based on the elastic region of the experiment. Abaqus/Standard 2017 (Dassault Systèmes, Providence, RI, USA) was used as finite element software. Johnson-Cook plasticity model was employed to capture the non-linear material hardening behavior after yielding and the strong dependency on testing velocities. The temperature dependence of the model was deactivated as the tests were conducted under the glass transition temperature and at a constant temperature setting. The yield stress $\bar{\sigma}$ is reported hereinafter:

$$\bar{\sigma} = \left[C_1 + C_2 \left(\bar{\varepsilon}^{pl} \right)^n \right] \left[1 + C_3 \ln \left(\dot{\bar{\varepsilon}}^{pl} / \dot{\bar{\varepsilon}}^0 \right) \right]$$

where $\bar{\varepsilon}^{pl}$ is the equivalent plastic strain, C_1, C_2, n and $\dot{\bar{\varepsilon}}^0$ are material parameters of the model and $\dot{\bar{\varepsilon}}^{pl}$ is the equivalent plastic strain rate. The parameters for both dry and submerged scenarios were identified by enforcing the exact match of the analytically calculated curves over the experimental ones obtained at three different velocities.

2.4 Verification of Material Properties

A dog-bone shaped 3D model was implemented in Abaqus/Standard to numerically replicate the experimental uniaxial tensile tests, wherein all dimensions and parameters accurately traced the experimental settings. A dynamic/implicit solver was used to simulation all six scenarios with parameters identified above. Displacements in all directions were constrained ($U_1 = U_2 = U_3 = 0$) on one end of the specimen while a uniaxial displacement ($U_1 \neq 0$) was applied in a fixed time span (ΔT) on the other, duplicating the experiment. The model was discretized by means of 8-node linear brick reduced integration elements (C3D8R). A sensitivity analysis on the refinement was conducted up to an element size of about 0.05 mm. The applied displacement and the reaction force were extracted and compared in a force-displacement plot to the experimental counterparts (Table I)

Table I. Displacements and test duration applied in finite element set-up to replicate experiment

	Fast	Moderate	Slow
Submerged	U_1=4.18 mm ΔT=46 sec	U_1=5.13 mm ΔT=517 sec	U_1=5.92 mm ΔT=5960 sec
Dry	U_1=4.00 mm ΔT=43 sec	U_1=4.67 mm ΔT=480 sec	U_1=5.90 mm ΔT=5950 sec

2.5 3D Validation by scaffold geometry

A longitudinal tensile and a lateral crush resistance test were conducted on real scaffolds to validate the robustness of both the material and geometrical numerical descriptions. In the longitudinal tensile test, scaffolds were fixed onto a tensile tester (Figure 3A) and stretched at a constant velocity of 0.1 mm/sec for 70 seconds. In the lateral crush resistance test, scaffolds were placed in the middle of two flat plates (Figure 3C) and compressed at a constant velocity of 0.1 mm/s up to a displacement of 2 mm. These conventional tests were chosen due to their simplicity and similarity to in-vivo loads experienced by BRS.

A 3D finite element model of the scaffold was constructed in Abaqus/Implicit to validate the material model (Figure 3B&D). The mesh of 8-node linear brick, incompatible modes elements (C3D8I) was created by Hypermesh (Altair Hyperworks). Incompatible modes elements were chosen based on their accepted performances in describing bending-dominated problems such as the one occurring in scaffold deformation during crimping and inflation. The total number of elements is 242785, with four elements designated across strut thickness.

The numerical models were implemented in a dynamic/Implicit simulation, exactly replicating the geometries, applied boundary conditions, and duration of the experiments. Material properties derived from submerged conditions were used in this analysis since experiments were conducted in water. The elastic modulus was set to 1.4 GPa. In the longitudinal tensile test (Figure 3B), both ends of the scaffold were linked to two multipoint constraints (MPCs); one end was fixed ($U_1 = U_2 = U_3 = UR_1 = UR_2 = UR_3 = 0$) while the other was under axial tension ($U_3 = 7$ mm). The total step time was set to 74 seconds in chorus to the experiment. In the lateral crush resistance test (Figure 3D), an unconstrained scaffold was positioned between two identical plane rigid surfaces (quadrilateral surface element with reduced integration, SFM3D4R, 341 elements). The bottom surface was constrained as fixed ($U_1 = U_2 = U_3 = UR_1 = UR_2 = UR_3 = 0$) while the top surface vertically moved ($U_2 = 2$ mm) to impact, impacting the lateral surface of the scaffold with compression forces. The contact was defined as "hard contact" with a friction coefficient of 0.2 between the surfaces and the scaffold. The total step time was set to 20 seconds according to the experiment. In both cases, the applied displacement and the reaction force were extracted and compared in a force-displacement plot to the experimental counterparts.

2.6 FE analysis of scaffold crimping and inflation

Employing Abaqus/Explicit, crimping and inflation were solved incorporating two sets of material properties, dry and submerged, for a scaffold with the same geometrical design as in previous experiments. The simulation set-up strived to mimic a real clinical intervention scenario. The time scaling factor has been set to 1 with a target time increment of 1×10^{-4}. Interaction between all the surfaces was defined as "general contact" with a friction coefficient of 0.2. The framework of the simulation and its steps could be described as follow:

1. *Crimping*: An unconstrained scaffold (density = 1.4 g/cm^3) was radially compressed by an external rigid cylindrical surface (initial diameter of 3.2 mm, quadrilateral surface element with reduced integration, SFM3D4R, 3952 elements). A radial displacement of 1 mm was applied to all nodes;

2. *Release*: The rigid surface was removed to let the scaffold recoil freely; Step time was set to 10 sec.
3. *Intraluminal positioning*: The crimped scaffold was positioned inside the lumen of a mock vessel. The model consisted of a linear elastic cylinder (density = 1.16 g/cm^3, E = 1.46 MPa, Poisson's ratio = 0.3, internal lumen diameter = 3.0 mm, thickness = 0.5 mm) made of 100500 8-node linear brick, incompatible modes elements (C3D8I).
4. *Inflation*: An internal cylinder (initial diameter = 1.0 mm, with 1400 quadrilateral surface elements with reduced integration, SFM3D4R) radially expanded the scaffold to the final inner diameter of 3.4 mm (about 12% of overexpansion to guarantee the perfect scaffolding at the end of the procedure).
5. *Relaxation*: The internal cylinder was maintained at the expanded state with the step time of 30 sec to allow stress relaxation in the scaffold.
6. *Recoil*: The internal cylinder was reduced to 0.1 mm to allow the scaffold recoil freely.

Three different step times were considered for crimping and inflation (step 1 and 4) to evaluate the effect of operation pace on the scaffold performance (Table II).

Table II. Step duration for step 1 and 4 in each finite element simulation

	Fast	Moderate	Slow
Step 1: Crimping	6 sec	60 sec	600 sec
Step 4: Inflation	10 sec	20 sec	40 sec

Values of the von Mises equivalent stress (MISES) were extracted at the end of the crimping and inflation phases to assess the effect of operation procedural pace on stress concentration. Recoiling percentage (%Recoil) was also calculated for all scenarios using:

$$\%Recoil = (D_1 - D_2)/D_1$$

where D_1 and D_2 are the outer diameter of the scaffold at the end inflation and recoil steps, respectively.

3. Result

3.1 Mechanical Response of pLLA

True stress – true strain curves were plotted to compare dry and submerged samples at three different testing velocities including 0.1 mm/s, 0.01 mm/s and 0.001 mm/s (Figure 4). Similar visco-plastic behavior was observed for all loading conditions, i.e. after passing the yield point, a small amount of stress softening was followed by stress hardening till the sample fractured. The minimum stress evolution was recorded under the quasi-static condition in both dry and submerged conditions. In dry condition (solid lines), lower velocity leads to lower elastic modulus (E), higher yield strain ($\bar{\varepsilon}_y$) and higher fracture strain ($\bar{\varepsilon}_f$) (Table III). Tangent modulus (E_t) is also directly related to the testing velocity. In submerged condition (dash lines), the effect of testing velocity on mechanical responses are not as clear as in dry cases. Although E_t and $\bar{\varepsilon}_f$ in submerged condition have similar trends as in dry condition, the fast and moderate samples show comparable elasticity, which reduces when experiment velocity is the slowest. At a comparable velocity, a clear difference can be seen between dry and submerged conditions, wherein reducing the testing velocity diminishes the observed disparities. This observation emphasizes the necessity to apply proper mechanical properties during FE analysis. In general, submerged samples exhibit less resistance to yielding, higher deformability, and softer behavior compared to dry cases.

Table III: Key mechanical properties from uniaxial tensile test

	Dry			Submerged		
Testing Velocity (mm/sec)	0.1	0.01	0.001	0.1	0.01	0.001
Elastic Modulus (E, GPa)	1.45	1.09	0.94	1.41	1.44	1.19
Yield Strain ($\bar{\varepsilon}_y$)	0.05	0.06	0.07	0.06	0.04	0.04
Fracture Strain ($\bar{\varepsilon}_f$)	0.50	0.57	0.68	0.55	0.61	0.69
Tangent Modulus (E_t, MPa)	244.30	205.43	128.04	227.02	200.14	124.72

3.2 Verification by the FE model

True stress – true strain curves generated from FE analysis mimicking a uniaxial tensile test on dog-bone specimens were highly correlated to results obtained from benchtop tests in both dry and submerged conditions (Table IV, Figure 5A and 5B). In addition, experimental force – displacement curves for full-scale scaffold tests, including longitudinal tensile test and lateral crush resistance test, were dependably followed by FE results using the same set of parameters (Figure 5C and 5D).

Table IV: Simulation coefficients

	Elastic Modulus (GPa)			Johnson-Cook Plasticity Model				
	0.1 mm/s	0.01 mm/s	0.001 mm/s	C_1 (MPa)	C_2 (MPa)	C_3 (MPa)	n	$\dot{\varepsilon}_0$ (1/s)
Dry	1.5	1.1	0.9	55	270	0.0400	1.525	0.0002
Submerged	1.4	1.4	1.2	57	260	0.0975	1.450	0.0002

3.3 Scaffold performance in procedural scenarios

Stresses concentration was highly correlated to specific design features which caused localized deformations (Figure 6). More specifically, after crimping, deformations were clearly visible in experiments and predicted by numerical simulation at inner peak edges (Figure 6A). However, device inflation promoted deformations at outer peak edges (Figure 6B), wherein development of inner sides' deformations into micro-cracks were observed (Figure 6C). These alterations in structural integrity prior and during scaffold implantation may potentially develop into catastrophic structural failures after implantation in situ and may, in part, explain events observed in clinical trials.

The percentage of elements with von Mises stresses higher than yield stress, 100 MPa and 150 MPa in different procedural phases and operational environment were quantified as a representative measure of regions with a risk of failure (Figure 7). Yield stress represents the start of plastic deformation and indicates permanent microstructural damages. Yield stress for dry specimens at fast, moderate and slow paces are 70

MPa, 65 MPa, and 62 MPa, respectively, while for submerged specimens they were slightly lower (63 MPa, 60 MPa, and 59 MPa, respectively at fast, moderate and slow paces) (Figure 4). 150 MPa was chosen because it was about the value of the ultimate tensile stress indicating fracture, while 100 MPa was an intermediate stress intentionally selected between yielding and fracture phases to represent the credibility of FE simulation to capture stress distribution consistency. Crimping the dry samples at fast, moderate, and slow rates, we found that more than half of elements experienced stresses higher than their yield criteria (69%, 61% and 59%, respectively) (Figure 7A). While in submerged samples, lower number of elements yield at similar paces, i.e. 60%, 59%, and 49% when crimping at fast, moderate and slow pace, respectively (Figure 7 B). Inflation of the device exerts critical stresses to higher number of device elements in both dry and submerged conditions (Figure 7 C and D). Comparing the submerged and dry samples, reducing the operational pace considerably drops percentage of elements experiencing the yield in the latter. In general, low, yet concerning proportion of elements experience stresses beyond the fracture point, with higher values for dried samples. In addition, in both operational environment, %recoil were within the range of 8 to 10, which is in accordance with what has been reported in clinics for this viscoelastic-plastic device. Overall, the percentage of elements experiencing extreme levels of stresses decrease as the operation slows down regardless of the environment the specimen is exposed to. This implies that slow procedural pace may potentially reduce stress concentration, and thus lower potential damages caused by deformations.

4. Discussion

Stents experience excessive values of stresses and large deformations while being crimped or inflated, which is even before they serve scaffolding diseased vessels under cyclic asymmetric loadings. This may increase the likelihood of failure for BRS since they are weaker in strength compared to their metallic counterparts, and thus entreats designers to conduct more rigorous tests to achieve comprehensive understandings on device performances. Simply inheriting design paradigms of metal stents to develop BRS, in which the environment and procedural effects on device performances have often been ignored, might lead to incorrect assessment of mechanical stressors the device faces. Most studies have relied on employing a single set of material properties derived from benchtop experiments, usually uniaxial tensile tests, conducted under one testing environment, i.e. in air or in submerged environment, to feed higher-level analyses of device performance, e.g. crimping, inflation and load bearing capability [15,25]. However, viscoelastic-plastic polymers, such as pLLA, consist of heterogeneous microstructural compartments including crystal domains, where molecules are differentially aligned and packed, and amorphous regions where they are randomly oriented. Macroscopic properties of such materials, e.g. mechanical strength, deformability, and yield resistance, greatly depend on their microscopic characteristics such as molecular orientation and degree of crystallinity. This dependency leads to completely different mechanical responses when tested in diverse environment, e.g. in a submerged condition akin to vessel lumen, with lower yielding resistance, higher deformability and softer behaviors (Figure 4 and 5). This observed difference is due to the alterations in crystallinity and molecular orientation caused by re-crystallization and swelling as materials absorb water molecules [12,26]. We suspect that water molecules within the polymeric matrix act as a resisting buffer damping the deforming forces and alleviating the effect of procedural paces. This dependency of material properties on working environment is, thus, importance considering the varying environment BRS are exposed to. In practice, BRS crimping is usually performed, as a step in the manufacturing possess, in air with 37 ^{o}C or higher degrees to reduce material stiffness and prevent micro-cracks. Whereas, BRS inflation is routinely performed in clinics within 10 minutes after balloon-mounted devices are inserted in a submerged environment at body temperature. Such significant disparities in operation environment mandate engineers and designer to conduct device characterization in corresponding realistic scenarios, and if ignored, it can lead to unreliable regulatory tests and eventually unpredictable clinical behaviors. Lack of thorough understandings on BRS mechanical behaviors due to incomprehensive research and unrealistic experiments has already resulted in a disastrous failure in predicting clinical consequences [10, 27-29].

Tragically, to reduce the rate of clinical failures, corrective strategies have been more focused on refining existing implantation techniques of vessel preparation [22]. In addition, clinicians have been advised with a strict implantation instruction to inflate these devices at a much slower pace compared to their metallic counterparts to prevent acute fracture, reduce recoil, and diminish risk of clinical events during/after implantation [22]. However, not only there is no clear-cut measure on what the optimal pace should be, but also proper criteria specifically designed for BRS to determine optimal pace are still missing. Designers and regulatory officers keep on using criteria inherited from metal stent guidelines, which mainly include preventing acute fracture and reducing %recoil.

Due to the differences in elastic modulus, yield strain and tangent modulus when being characterized in dry and submerged conditions (Figure 4), different behaviors in stress concentration have been noticed with FE analysis on crimping and inflation. Crimping the scaffold at a slower pace could reduce the risk of exposing large percentage of elements to high stresses (Figure 7). However, in depth analysis of our results to witness a higher percent of elements underwent high stresses in dry conditions compared to submerged conditions raised the concern that one may underestimate the severity of stress concentration during the crimping process and miss potential modes of failure in case crimping simulation in preliminary steps of design is fed by a material model derived from characterization in submerged condition. On the other side, in a similar scenario, if an inflation modeling is supported by a material model derived from dry sample characterization, the procedural effect of inflation time on reducing stress concentration could be noticeably overestimated, i.e. reducing inflation time from 20 to 40 seconds can reduce the number of elements at stresses above their yield stress by 13% in dry condition (Figure 7C), while it is less than half of this value in submerged condition (Figure 7D). This indicates that optimizing implantation techniques via inflating at a slow pace will not significantly reduce the risk of clinical failures. To obtain a more comprehensive understanding and a more accurate prediction on device performances, one material model to simulate all device-level performances should be corrected.

It is accepted that %recoil and acute macro-structural fractures are the two most important criteria when assessing the performance of stent implantation. However, as we noticed in our FE analysis, inflating at slower pace seems to have very limited effect on preventing recoil (2% difference in %recoil between fast and slow scenarios), as long as clinicians follow the instruction by holding the scaffold at the end of inflation for at least 30 sec. Thus, procedural factors might alleviate/exacerbate structural responses and consequently alter the performance measures such as recoil due to their direct influence on material properties. However, the material behavior change, as a result of interventional procedure alteration, is extremely nonlinear. Corrective strategies merely focused on procedural parameters without noticing their complex effect in material modulation are, thus, misleading as they basically rely on performance measures inherited from metallic counterparts. In addition, it has been proved via several in vitro and in vivo experiments that acute macro-structural fractures could be majorly avoided in case slow inflation (around 2sec/atm) is warranted. Yet, the catastrophic clinical events linger in clinical trials with a higher failure rate compared to metal stents during acute time settings. As a result, continuing to use %recoil and acute macro-structural fracture as mere criteria to assess the device efficacy is no longer a reliable approach nor an accurate prediction tool for future research in BRS evolution. Instead, we hypothesize that it is the microstructural composition of such a heterogeneous material and its evolution over the rigorous interventional procedure and exposure to dynamic biological environment within the body that determines the device performance. Heterogeneities in BRS material properties induce microstructural damages at certain design features (Figure 6) during manufacturing/clinical routines which may potentially develop into catastrophic failures in macro-structures, such as malapposition, large recoil, and fracture leading to reported clinical events [12,30]. Performing the present work, we have further highlighted the importance of incorporating micro-structural damages such as localized deformation and micro-cracks as device evaluation criteria, wherein updates on procedural strategies (reducing pace for instance) may successfully reduce the risk of microstructural damages (reducing the stress concentration in certain spatial locations). However, ignoring the effect environment in which the device operates on material characteristics, and consequently preliminary design simulations, may result in exaggeration of this benefit.

5. Conclusion

Multiple instances of failure reported for the first generation BRS has warranted the necessity of closing the gap between preliminary benchtop predictions and clinical observations. Research paradigms inherited from metal stents should not be applied to BRS due to their substantial differences in material characteristics, which may mislead designers to seek problem sources at erroneous timeframe. Accurate material models warrant realistic inputs into, and thus reliable outcome out of, high-level design analyses of crimping, inflation, and load bearing capability, which entails including the effect of working environment and procedural strategies on mechanical responses to enhance mechanistic understanding of material behaviors of BRS and predict potential clinical failures. Applying a universal set of material properties to study the device performance in different phases of manufacturing/implantation may result in inaccurate assessment of stress concentration and unpredictable device failure. Similarly, for polymeric devices, microstructural damage should be considered as a criterion to assess structural integrity and device efficacy rather than previously-perceived acute fractures and recoil percentage.

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Author Contributions

PJ.W., M.G.B., F.R.N, and E.R.E conceived the ideas and directed the research. PJ.W. and M.G.B. conducted the benchtop tests. PJ.W., M.G.B., and F.B. conducted the FE simulation under guidance of L.P, T.W, and F.M. PJ.W., M.G.B., F.R.N., and F.B. designed the experiments and participated in the analysis and interpretation of the data. PJ.W., M.G.B., F.R.N, F.B. and E.R.E wrote the manuscript. L.P., T.W., and F.M. provided critical revision on the manuscript.

Disclosure

The authors declare that there are no conflict of interests regarding the publication of this article.

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