Published in final edited form as:

J Biomech. 2014 June 27; 47(9): 2080–2087. doi:10.1016/j.jbiomech.2013.10.009.

Computational Model of the In Vivo Development of a Tissue Engineered Vein from an Implanted Polymeric Construct

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Abstract

Advances in vascular tissue engineering have been tremendous over the past 15 years, yet there remains a need to optimize current constructs to achieve vessels having true growth potential. Toward this end, it has been suggested that computational models may help hasten this process by enabling time-efficient parametric studies that can reduce the experimental search space. In this paper, we present a first generation computational model for describing the in vivo development of a tissue engineered vein from an implanted polymeric scaffold. The model was motivated by our recent data on the evolution of mechanical properties and microstructural composition over 24 weeks in a mouse inferior vena cava interposition graft. It is shown that these data can be captured well by including both an early inflammatory-mediated and a subsequent mechano-mediated production of extracellular matrix. There remains a pressing need, however, for more data to inform the development of next generation models, particularly the precise transition from the inflammatory to the mechanobiological dominated production of matrix having functional capability.

Keywords

tissue engineering; interposition graft; mouse model; constrained mixture theory; inflammation; mechanosensing

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Disclosures

CB receives grant support from Gunze Limited and the Pall Corporation. The authors do not have any professional or financial conflict of interest.

1 Introduction

There have been tremendous advances in the development of tissue engineered vascular grafts (TEVGs), particularly since publication of the seminal paper by Niklason et al. (1999). Such grafts have been successfully implanted in children for the treatment of congenital defects (cf. Hibino et al., 2010), and other first in human trials are underway for diverse applications (e.g., L'Heureux et al., 2007). Most of the related advances have been realized by trial-and-error, however, mainly from the painstaking empirical evaluation of a multitude of different construct biomaterials, cell sources, culture conditions, and so forth. Notwithstanding the remarkable successes to date, there has been a call for a more rational design of TEVGs (Hibino et al., 2011), and computational biomechanical models promise to aid in this pursuit (Niklason et al., 2010).

During this same period, there has also been a call in vascular mechanics for computational models of the growth and remodeling (G&R) capability of blood vessels in response to altered hemodynamics or diverse diseases (cf. Humphrey and Taylor, 2008). Fundamental to developing such models is an understanding of cellular responses to the associated bio-chemo-mechanical stimuli and, in particular, how cells establish, maintain, remodel, or repair the extracellular matrix that dictates the overall structural integrity of the vessel as well as the microenvironment in which the intramural cells must function. Although much remains to be discovered regarding mechanisms, data have been sufficient to develop microstructurally motivated phenomenological models of vascular G&R that capture salient observations (e.g., Valentin et al., 2009; 2011).

In this paper, we extend a prior G&R model for native vessels to develop a first generation computational model of the in vivo development of a tissue engineered vein from an implanted polymeric scaffold. Model development was informed by longitudinal data on cell biological, histological, and mechanical changes in an inferior vena cava interposition TEVG in mice that were studied for up to 24 weeks (Naito et al., 2012; 2013). Briefly, the evolving graft remained patent without stenosis or aneurysm, and its compliance became similar to the native vein by 24 weeks. Three prominent features of the development of this TEVG were an early critical role of macrophage mediated inflammation, degradation of the polymer scaffold over a period of just a few weeks, and significant accumulation of fibrillar collagen. Hence, the primary extensions to the prior G&R model were the incorporation of the monotonic loss of the load bearing capability of the polymer scaffold, inclusion of an inflammatory-mediated production of collagen that was followed by a mechano-mediated production, and the evolution of collagen properties following deposition within the evolving graft. Results demonstrated that salient features of the evolving biomechanical behavior of the TEVG were captured reasonably well.

2 Methods

2.1 General Approach

Details on the original motivation and theoretical framework for our G&R approach can be found elsewhere (Humphrey and Rajagopal, 2002; Valentin et al., 2009). Briefly, it is assumed that $a = 1, \dots, n$ structurally significant constituents can exhibit different material

properties, rates of production and removal, and stress-free configurations, yet they are constrained to deform with the bulk material. It is thus straightforward to quantify deformations experienced by individual constituents (via the deformation gradient $\mathbf{F}_{n(\tau)}^\alpha(s)$, where $n(\tau)$ denotes the constituent-specific stress-free, or natural, configuration and $\tau \in [0, s]$ is the G&R time of deposition) if one knows the gross deformation of the composite vessel and deformations associated with the deposition of the constituent within the extant matrix. In this way, the energy stored in the vessel due to gross deformations can be assumed to equal the sum of the energy stored in each constituent, which in turn depends upon its individual deformation. That is, the total energy $W(s) = \sum W^\alpha(s)$ at any G&R time s , where the constituent-specific energies are given by

$$W^\alpha(s) = \frac{\rho^\alpha(0) Q^\alpha(s)}{\rho(s)} W^\alpha(\mathbf{F}_{n(0)}^\alpha(s)) + \int_0^s \frac{m^\alpha(\tau)}{\rho(s)} q^\alpha(s-\tau) W^\alpha(\mathbf{F}_{n(\tau)}^\alpha(s)) d\tau.$$

Here, $\rho^\alpha(0)$ is the initial constituent-specific mass density (i.e., at G&R time $s = 0$), $\rho(s)$ is the current overall mass density, $Q^\alpha(s) \in [0,1]$ is the fraction of the constituent present at time 0 that survives to the current time s , $m^\alpha(\tau)$ is the rate of new mass density production, and $q^\alpha(s-\tau) \in [0,1]$ is the fraction of the constituent produced at time $\tau \in [0,s]$ that survives to time s . An advantage of this framework is that one can use this “rule-of-mixtures” constitutive relation within classical formulations of vascular wall mechanics, namely equilibrium and stress constitutive (Humphrey, 2002)

$$\text{div} \mathbf{t} = 0, \quad \mathbf{t} = \frac{2}{\det \mathbf{F}} \mathbf{F} \frac{\partial W}{\partial \mathbf{C}} \mathbf{F}^T$$

where $\mathbf{t}$ is the overall Cauchy stress and $\mathbf{C} = \mathbf{F}^T \mathbf{F}$ is the overall right Cauchy-Green tensor. Most important here, however, is that this framework requires three classes of constituent-specific constitutive relations: the rate of production $m^\alpha(\tau)$, the rate of removal $q^\alpha(s-\tau)$,

and the stored energy $W^\alpha(\mathbf{F}_{n(\tau)}^\alpha(s))$. As demonstrated by Valentin et al. (2009), salient features of arterial G&R have been captured by assuming that production depends on changes in intramural and wall shear stresses from homeostatic targets, that removal tends to follow a first order kinetic decay with a stress-dependent rate parameter, and that constituent behaviors can be described with classical neo-Hookean or Fung exponential models.

2.2 Parameter Classification

Such constrained mixture models of G&R involve several classes of constitutive and geometric parameters (cf. Valentin and Humphrey 2009a,b; Valentin et al., 2009). The functional forms and parameter values chosen herein were motivated by both reported observations and hypothesized behaviors. Tables 1 to 4 classify the specific functional forms (Table 1) and parameter values (Tables 2 to 4) by level of consensus and function. In particular, Table 2 addresses initial graft geometry, polymer degradation, and native inferior vena cava properties that have been measured previously (Roh et al., 2008; Sokolis, 2012; Naito et al., 2013; Lee et al., 2013). Table 3 lists parameters that were motivated by experimental results and observations, though without quantifiable data to validate the

parameter values (e.g., peak time of macrophage infiltration was estimated, not known, from immunohistochemistry in Hibino et al., 2011). Table 4 shows values for quantities that were less well known but amenable to parametric study (e.g., stretch at which constituents are incorporated within extant matrix, changing rates of production for inflammation, and changing collagen parameters in response to polymer), several of which are described more below. Note, too, that parametric studies were performed for cases with less certainty within known physiologically-relevant bounds.

2.3 Illustrative Constitutive Relations

Consider first the polymeric scaffold (i.e., $\alpha = p$). Because the TEVG consists solely of polymer at the time of implantation, $\rho^p(0) = \rho$ with all other initial apparent mass densities 0. Thereafter, $m^p(\tau) \equiv 0$ (i.e., polymer is not produced in vivo) and we simply need to model loss of the polymer. Based on qualitative information on the degradation kinetics (cf. Fig. 2 in Naito et al., 2013), we let $Q^p(s) \equiv \phi^p(0) \left(1 + e^{k_q^p(s - Offset^p)}\right)^{-1}$, a sigmoidal loss, with $k_q^p \equiv 0.12 \text{ day}^{-1}$ and $Offset^p \equiv 24 \text{ days}$ to capture the near complete loss of polymer by 12 weeks. Although the mechanical behavior of the scaffold has not been quantified rigorously, we assumed a standard neo-Hookean form in terms of principal stretches, thus

$$W^p(\mathbf{F}_0^p(s)) = c^p \left((\lambda_\theta^p)^2 + (\lambda_z^p)^2 + \frac{1}{(\lambda_\theta^p \lambda_z^p)^2} - 3 \right),$$

where $c^p = 20.4 \text{ kPa}$ based on pilot studies. It appears, however, that the structural integrity of the polymeric scaffold is lost prior to its complete degradation (i.e., non-load bearing fragments persist for some time), hence we let $c^p(s) = c^p(0) - \xi^p(s - 7)$ with a 7 day offset to account for observed degradation of the P(CL/LA) coating, and $\xi^p = 0.60 \text{ kPa/day}$.

Next, consider the role of inflammation. Despite observations of the early presence, then decline, of macrophages within the implanted polymeric scaffold (Roh et al., 2010; Hibino et al., 2011) and the similar (and likely directly associated) early increases, then decreases in matrix metalloproteinase-9 (MMP-9) activity and collagen production (Naito et al., 2012, 2013), data are not sufficient to build a mechanistic model of the inflammation-mediated turnover of matrix. Hence, we used a gamma distribution function to model phenomenologically this contribution to the production of collagen (due to a foreign body response) and an exponential decay to capture its removal. Specifically, we let

$m_{infl}^k(\tau) \equiv K_{infl} \left(\alpha \tau e^{1 - \alpha \tau} \right)$, where k = passive smooth muscle and the four families of collagen fibers, with increases in the synthetic capability of the TEVG given by the rate parameter $K_{infl} \equiv 45$ and where the inflammatory-mediated response peaks at time $\alpha^{-1} \equiv 10 \text{ days}$ (representing the time of highest measured macrophage infiltration; Roh et al., 2010, Hibino et al., 2011). Note that these parameters allow the inflammation-mediated production of collagen to cease following the near complete degradation of polymer (i.e., loss of the foreign body).

Finally, it was assumed that once the (stiff) polymer no longer carried load, the intramural synthetic cells would begin to sense mechanical stresses and turnover matrix accordingly. Hence, following prior work on arteries (cf. Valentin et al., 2009), we let a mechanical stress-mediated production of collagen, $m_{strs}^k(\tau) \equiv K_{strs}^k \Delta \sigma^k(\tau)$, with $\sigma^k(\tau)$ a normalized difference in intramural stress from a target value and K_{strs}^k a gain-type parameter. At this point it is important to note two things regarding the collagen production. First, the scaffold was implanted without embedded synthetic cells, hence collagen production could not begin until host synthetic cells invaded the construct. This delay was modeled using a function $(1 - e^{-\tau})$ to premultiply that term which described the two mechanisms of production. Second, we assumed that in the long-term, the TEVG will reach a basal rate m_B^c of collagen production, which could thus be introduced as a premultiplier. Hence the total production term was given by,

$$m^k(\tau) = m_B^k (1 - e^{-\tau}) (m_{infl}^k(\tau) + m_{strs}^k(\tau) + 1),$$

Not knowing whether collagen produced in response to inflammation or mechanical stress has different degradation kinetics, we let $q^k(s, \tau) = \exp(-\int_{\tau}^s k_h^q(t) dt)$ where $k_h^q(\tau)$ is a rate-type parameter for mass removal with units of days⁻¹. For the collagen produced via inflammation, $k_{infl}^q = \beta_{infl} k_h^q$, where $\beta_{infl} \in [1, \dots, 3]$ decreases the half-life due to increased MMP expression (Table 4). For completeness, we described the mechanical properties of the collagen and passive smooth muscle using,

$$W^k(\mathbf{F}_{n(\tau)}^k(s)) = \frac{c_1^k}{4c_2^k} \left(e^{\left(c_2^k \left(\lambda_{n(\tau)}^k(s)^2 - 1 \right)^2 \right)} - 1 \right),$$

where c_1^k, c_2^k are material parameters. Material properties of the healthy murine inferior vena cava from SCID/bg mice (Table 2) were calculated via nonlinear regression using biaxial data from Lee et al. (2013).

Once produced, via either mechanism, collagen must evolve until it becomes a mature fiber. While the time-course and steps of collagen fibrillogenesis have been studied extensively (Birk et al., 1995, 1989a,b, 1997a,b), data on the evolving mechanical behavior of collagen are not yet sufficient to model mechanistically the microstructural and compositional changes (e.g., lateral and linear fusion of fibrils to form fibers, formation of cross-links and proteoglycan bridges, or the undulation and type I:III ratio). We can glean insights, however, from Ansorge et al. (2011), Miller et al. (2012a,b), and Marturano et al. (2013) to propose a phenomenological approach to capture the evolving mechanical behavior (cf. Fig. 2 in Miller et al., 2012a). We thus modeled the general evolving behavior (e.g., shortened “toe-region” due to loss of undulation and increased organization followed by a progressively stiffer load-dependent response due to changing fiber diameter, type I:III ratio, cross-links, and so forth) by increasing both the parameter and decreasing the ratio $c_1^c : c_2^c$ (Table 3).

Moreover, TEVGs produce aggregating proteoglycans (Keire et al., 2010; Naito et al., 2012), which may increase compressive properties (Table 3).

A parametric study (Table 4) was used to evaluate possible differences in material properties for collagen produced due to inflammation, where $c_1^{c,inf} = \gamma_1^{c,inf} c_1^{c,h}$ and $c_2^{c,inf} = \gamma_2^{c,inf} c_2^{c,h}$, with $\gamma_1^{c,inf} \in [1, 30]$, $\gamma_2^{c,inf} \in [1, 30]$. Similarly, collagen properties were studied for stress-mediated production via the parameters $\gamma_1^{c,sts} \in [1, 20]$, $\gamma_2^{c,sts} \in [1, 20]$, which accounted for potential changes in microstructure due to the lack of elastin and active smooth muscle in the evolving TEVG (Table 4).

3 Results

The material parameters that yielded the best prediction of the evolution of TEVG mechanical behavior and geometry are shown in the third column of Table 4 (best-fit values). Associated predictions of constituent mass density production (normalized to basal production for each constituent) throughout the G&R simulation (168 days) are in Fig. 1. Inflammation-mediated production peaked at 10 days (reflecting the time of highest macrophage infiltration; Hibino et al., 2011) with a 45-fold increase relative to the basal production of each constituent (Fig. 1A). Inflammation-mediated production subsided shortly after the complete loss of polymer (Fig. 1A). Note that the inflammation-mediated production was assumed to be isotropic, hence producing similar fold increases for all four families of collagen fibers in response to the implanted interpositional polymeric scaffold. Stress-mediated production did not begin until the scaffold's load-bearing capability was compromised and the polymer no longer stress-shielded the synthetic cells within the growing TEVG (Fig. 1B). The fold increases in stress-mediated production, relative to basal values, were anisotropic (i.e., different for different families of collagen) because of differences in tensions from homeostatic values in different directions. This anisotropy allowed an appropriate evolution of the organization of collagen in response to the applied loads. Total increases in production (inflammation- and stress-mediated) relative to basal are shown in Fig. 1C for all constituents.

Survival fractions, $q^a(s - \tau) \in [0, 1]$, for a sample constituent deposited at some time $\tau \in [0, s]$ during the simulation are shown in Fig. 2 for a constituent produced via both mechanisms of production. Those produced during the inflammation-mediated period were augmented by the β_{infl} parameter; the best-fit value $\beta_{infl} = 2$ yielded the best predictions and resulted in a lower survival fraction (Figure 2). The survival fractions for the stress-mediated constituents remained at homeostatic values (Table 2; Figure 2).

Tension-stretch relationships for the native SCID/bg IVC (data from Lee et al., 2013) and the predicted polymer graft at day 1 following implantation are shown in Figure 3 (Panels A and B). The predicted mechanical behavior of the evolving TEVG (solid curves) transitioned from that of a stiff PGA-P(CL/LA) scaffold (neo-Hookean) augmented by stiff collagen (higher type I:III ratio) produced via the inflammatory response at 2 weeks (Fig. 3C) to a more compliant (Fung-type exponential) response from 6 to 24 weeks (Fig. 3D-F). This evolving response reflects the decreasing contribution of the polymeric scaffold plus the

transition from an inflammation- to a stress-mediated collagen production (which begins ~4 to 5 weeks after implantation when the scaffold lost integrity). The 6 to 12 week behavior is representative of the co-existence of collagen produced via both mechanisms. At 24 weeks, the more compliant TEVG consisted primarily of collagen produced via stress-mediation. The predicted wall tension-stretch relationship (solid curves) was similar to that observed from experimental biaxial tests (Naito et al., 2013) shown as open circles (Fig. 3; C-F); not surprisingly, there was considerable specimen-to-specimen differences in the experiments, perhaps reflective of biological variability as well as slight differences in construct construction and surgical procedure. Similar to the evolving material response, the predicted pressure-diameter responses revealed a structural response evolving from stiff (Fig. 4C) to compliant (Fig. 4F) consistent with trends in the experimental data (circles) (Naito et al., 2013). These results indicated good agreement between predicted and measured findings (Naito et al., 2013), which suggests that the proposed model can capture salient aspects of collagen deposition via inflammation- and stress-mediated mechanisms in addition to degradation and loss of load-bearing integrity of the polymer scaffold in an inter-positional in vivo application in veins.

Finally, it should be noted that an initial parametric study was used to identify appropriate material properties for collagen produced via the inflammation- and stress-mediated mechanisms. In general, there was a need to increase the c_1^c and c_2^c parameters relative to those for native values for both mechanisms of collagen production. These changes also modified the $c_1^c:c_2^c$ ratio from 2.32 for the native SCID/bg IVC to ~4.64 for the inflammation-mediated production and ~7.73 for stress-mediated production. While estimated bounds for these parameters gave reasonable predictions due to the scatter in the experimental data, the best-fit values are shown in Table 4.

Similarly, the optimal parameter for controlling the rate of degradation, $k_{infl}^q = \beta_{infl} k_h^q$, was determined via a parametric study where $\beta_{infl} \in [1, ..., 3]$. Predicted evolving tension-stretch relationships for $\beta_{infl} = [1, 2, 3]$ are shown in Fig. 5. Note that as the collagen produced via inflammation degraded more quickly, the TEVG became increasingly more compliant (indicative of larger contribution of stress-mediated collagen).

4 Discussion

Early functional requirements of TEVGs, beyond minimal thrombogenicity, included sufficient suture retention strength and adequate burst pressure (cf. Guilak et al., 2003). Given recent advances, however, much more ambitious functionality is now desired – ultimately, the ability of the TEVG to adapt in response to somatic growth and/or changes in hemodynamic loading. There is, therefore, a pressing need to understand better the biochemomechanical mechanisms that govern the development, maintenance, and remodeling of these grafts. Towards this end, we proposed a first generation computational model that eventually can be used to test consequences of competing hypotheses regarding roles of scaffold fabrication, genetic limitations on gene expression, pharmacological support, and so forth. This model combined, for the first time, an early inflammation-mediated production followed by a mechano-mediated production of collagen as the

polymeric scaffold degraded. The former was motivated by an observed early peak in MMP-9 activity (Naito et al., 2013), which may have resulted in large part from an early increase in macrophages (Roh et al., 2010; Hibino et al., 2011), as well as known interactions between MMP activity and collagen production (Strauss et al., 1996). We conjectured that this early inflammatory period was driven largely by a foreign body response, which decreased as the polymer degraded (Fig. 1A). We also conjectured that synthetic smooth muscle cells or fibroblasts were largely stress shielded by the polymer until it lost its mechanical integrity, prior to its ultimate degradation (Fig. 1B). Hence, the model was designed to capture sequential, but likely overlapping, inflammatory- and mechano-mediated matrix production. Figures 3 and 4 show that the model captured the dramatic changes in macroscopic mechanical behavior over a 24-week period. Such findings are encouraging, yet this is but a first generation model and many assumptions need to be evaluated via more complete data.

Toward this end, we suggest that it is not the large number of parameters that enabled a good description of the data. Rather, it is the appropriateness of the underlying hypotheses and associated functions used (cf. Valentin and Humphrey, 2009b); hence, as in systems biology, we must focus on collecting data sufficient for parameter estimation. Advances in optimization theory and uncertainty quantification promise to aid in this regard (cf. Sankaran et al., 2013). We assumed, however, that the mechanical properties of the polymeric scaffold could be described by a neo-Hookean behavior, where the shear modulus decreased linearly following day 7 when the P(CL/LA) coating had degraded. Although consistent with recent work by others (e.g., Vieira et al., 2011), there is still a need for much more data on both the time-course of the loss of structural integrity and the complete removal of polymer (i.e., inflammatory stimulus). The scaffold may also exhibit an evolving compressible behavior due to changes in porosity, which were not considered. We assumed a simple sigmoidal decay for the scaffold, consistent with limited data in Naito et al. (2013). With more complete data, however, it will be possible to exploit more sophisticated constitutive relations on polymer degradation, including stress-mediated effects (cf. Baek and Pence, 2011). Perhaps the greatest need for data relates to the production and removal of collagen and its evolving structural integrity. What are the sources of the synthetic cells and what chemo- or mechano-stimuli are most important at the different times of development? How does scaffold porosity and surface character influence matrix production? How much of the collagen that is synthesized via a foreign body response is lost with the degradation of the polymer? What roles do observed increases in elastic fibers (i.e., fibrillin-1 and elastin) or glycosaminoglycans / proteoglycans, especially versican and decorin, play in the evolving structural integrity of the graft? What is the time course of collagen fibrillogenesis and cross-linking? These and many other questions need to be answered both longitudinally and quantitatively.

In summary, however, we presented the first computational model of in vivo development of a tissue engineered vein from an implanted polymeric scaffold. The process of modeling revealed the need to complement the usual mechano-stimulated production of collagen with an inflammation-mediated production, consistent with empirical observations on these TEVGs. Moreover, the modeling revealed the need to “mature” the deposited collagen over a period of 14 days, a proposed accelerated timeframe for the vasculature, not unlike that in

proposed in tendon and cornea (Birk et al., 1995; Zhang et al., 2005). Indeed, it appears that TEVG development represents a transition from a foreign body response to a mechanobiological-controlled response, and it will likely be important to determine the optimal period of the former to initially promote but not subsequently impede efficient graft development. Herein lies one of the greatest promises of computational models, parametric studies that could possibly reduce the empirical search space and thus render more efficient the search for optimal conditions.

Acknowledgments

This research was supported, in part, by R01-HL098228 (C. Breuer), 5T32-HL098069 (A. Sinusas), and R21-HL107768 (J. Humphrey). The authors would like to acknowledge Conor Grady for data on the polymer mechanical behavior.

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Fig. 1.

Mass density production is shown for each constituent (collagen families 1,2,3,4, and circumferential smooth muscle) throughout the G&R simulation (168 days). (Panel A) Inflammation-mediated production peaked at 10 days (reflecting the time of highest measured macrophage infiltration) with a 45-fold increase relative to basal production for all constituents, then decreased following loss of the polymeric scaffold (by 8 weeks). Increases in inflammation-mediated production were isotropic (i.e., consistent fold increases relative to basal production for all families of collagen fibers). (Panel B) Stress-mediated production

increased following the loss of structural integrity of the polymeric scaffold around 4 weeks. Production increases were anisotropic and remained elevated relative to basal for the remainder of the simulation. (Panel C) Total increases in production relative to basal rates for all constituents. Note the change of scale from previous panels to account for additive effects of all contributing constituents. These results suggest a steady state, but not optimal (relative to native vein), long-term turnover.

Fig. 2.

Time-course of the survival fractions, which range over $[0,1]$, for sample constituents produced at some time τ during the simulation for the inflammation- and stress-mediated mechanisms of production. For the inflammation-mediated collagen (dashed line), $\beta_{infl} = 2$, which resulted in a shorter half-life (smaller survival fraction) compared to the stress-mediated collagen (solid line).

Fig. 3.

Circumferential tension-stretch relationships for the native SCID/bg inferior vena cava (Panel A), simulated polymeric scaffold at time 1 day (Panel B), and both predicted (solid curves) and experimental data (circles) for TEVGs at 2 (Panel C), 6 (Panel D), 12 (Panel E), and 24 weeks (Panel F). Note that the mechanical behavior (predicted and experimental) evolved from a stiff response dominated by polymer and inflammation-mediated collagen (Panel C) to a compliant more vascular-type response due primarily to collagen produced via the stress-mediated phase (Panel F). Note the similarity in the overall predicted behaviors and the experimental results.

Fig. 4.

Pressure-normalized diameter relationships are shown for the native SCID/bg inferior vena cava (Panel A), simulated polymeric scaffold at 1 day (Panel B), and both predicted (solid waves) and experimental data (circles) for TEVGs at 2 (Panel C), 6 (Panel D), 12 (Panel E), and 24 weeks (Panel F). Note the transition from a stiff polymer-dominated response (Panel C) to a more compliant, vascular type response (Panel F) as well as the agreement between the predictions and experimental data.

Fig. 5. Circumferential tension-stretch relationships at 2 (Panel A), 6 (Panel B), 12 (Panel C), and 24 weeks (Panel D) for indicated values of β_{infl} for collagen produced via the inflammation-mediated response. Decreasing the half-life of collagen (increasing β_{infl}) resulted in an increase in TEVG compliance over time. A value of $\beta_{infl} = 2$ yielded the best predictions with respect to the experimental data.

Table 1

Classification of specific functional forms of constitutive relations employed in the constrained mixture model of the evolving TEVG in the venous circulation. “Well accepted” relations represent those for which experimental data have established some level of consensus. Postulated forms represent those for which experimental data is wanting.

Class	Relationship	Form	Reference
Well Accepted	Mass density removal-time (neotissue)	Exponential decay	Niedermuller et al., 1977; Valentin et al., 2009
	Energy density-strain (collagen/muscle)	Fung exponential	Valentin et al., 2009; Nevo et al., 1989
	Energy density-strain (polymer)	neo-Hookean	Niklason et al., 2010
Postulated	Mass density production-stress	Linear	
	Mass density production-inflammation	Gamma	
	Damage function-polymer	Linear after P(CL/LA) coating degrades	
	Mass density removal-time (polymer)	Sigmoidal	

Table 2

Measured or calculated parameters include those reported in the literature. These parameters were obtained via direct measurements, histology, or fits to experimental data. Confidence level for each parameter is reported (H: high, M: medium, L: low).

Measured or Calculated Parameters			
Role	Parameter/Value	Confidence Level	Reference
1. Vessel geometry	Initial Length = 5 mm	H	Naito et al., 2013
	Initial thickness = 150um	H	Roh et al., 2008
	Initial porosity = 78.5%	H	Roh et al., 2008
2. Initial mass fractions	$\phi^p(0) = 1.0$	H	Naito et al., 2013
	$\phi^{f,k}(0)=0.0$		
	$\phi^m(0)=0.0$		
3. Constituent mass fractions for healthy vein	$\phi^p(\infty)=0.0$	H	Silver et al., 2001
	$\phi^f(\infty)=0.70$		
	$\phi^m(\infty)=0.30$		
4. Physical constants	$\rho_s = 1050kg/m^2$	H	Humphrey, 2002
5. Homeostatic kinetics (stress-mediated)	$k_q^{h,m} = \frac{1}{80}day^{-1}$	H	Valentin et al., 2009
	$k_q^{h,c} = \frac{1}{80}day^{-1}$		
6. Polymer kinetics	$k_q^p = 0.12day^{-1}$	H	Naito et al., 2013
	$Offset^p = 24 days$		
7. Elastic parameters for native SCID/bg IVC	$c_1^{c,h} = 2.32 kPa$	M	Calculated from experimental data in Lee et al., 2013
	$c_2^{c,h} = 1.0$		
	$c_1^{m,h} = 0.217 / kPa$		
	$c_2^{m,h} = 0.251$		
8. Distribution of collagen amongst 4 fiber families	$\phi^{f,k}(\infty) = [0.3,0.335,0.1825,0.1825]$	H	Sokolis, 2012
9. Initial polymer elastic parameters	$c^p = 20.4 kPa$	L	Unpublished Pilot Study

Table 3

“Motivated” parameters were inferred or postulated from experimental results or observations but with no direct, quantifiable measurements to validate the chosen parameters. Confidence level for each parameter is reported (H: high, M: medium, L: low).

Motivated by experimental results/observations, no direct measurements			
Role	Parameter/Value	Confidence Level	Reference
10. Timecourse of collagen fibrillogenesis	<u>0-2 days</u>	H	Timecourse: Birk et al., 1989a,b; Birk et al.,1995; Birk et al., 1997a,b
	$c_1^c = 0.25c_1^{c,h}$		
	$c_2^c = 0.25c_2^{c,h}$		
	<u>2-5 days</u>	L-M	
	$c_1^c = c_1^{c,h}$		
	$c_2^c = 0.50c_2^{c,h}$		
	<u>5-14 days</u>		
	$c_1^c = c_1^{c,h}$		
	$c_2^c = 0.75c_2^{c,h}$		
	<u>14+ days</u>		
	$c_1^c = c_1^{c,h}$		
	$c_2^c = c_2^{c,h}$		
11. Peak time of macrophage infiltration	$\frac{1}{a} = 10 \text{ days}$	M	Roh et al., 2010; Hibino et al., 2011
12. Compressive modulus	<u>Homeostatic (vein)</u>	M	Keire et al., 2010; Naito et al., 2012
	$c_{1,c}^c = 0.1c_1^{c,h}$		
	$c_{2,c}^c = 0.1c_2^{c,h}$		
	<u>Fibrillogenesis and TEVG</u>		
	<u>0-5 days</u>		
	$c_{1,c}^c = 0.3c_1^{c,h}$		
	$c_{2,c}^c = 0.3c_2^{c,h}$		
	<u>5+ days</u>		
	$c_{1,c}^c = 0.25c_1^{c,h}$		
	$c_{2,c}^c = 0.25c_2^{c,h}$		

Table 4

“Bounded” parameters are less well-known, but can be prescribed such that the model yields expected biomechanical responses and thicknesses. The inflammation-mediated rate parameter was considered a “free” parameter as there are no data to identify appropriate bounds; a range was identified such that the model yielded biomechanical responses and thicknesses consistent with reported experimental values (Naito et al., 2013). Confidence level for each parameter is reported (H: high, M: medium, L: low).

Bounded and Free Parameters				
Role	Parameter Range	Best-fit Value	Confidence Level	Motivation
13. Target stresses	Calculated from homeostatic elastic parameters		H	Calculated from material parameters from Lee et al., 2013
14. Deposition stretches	$G_h^c \in [1.00, 1.20]$	$G_h^c = 1.08$	M	
	$G_h^m \in [1.00, 1.40]$	$G_h^m = 1.14$		
15. Production kinetics	$K_{strs}^k \in [0.10]$	$K_{strs}^{1,2,3,4} = 1.0$	M	
16. Inflammation-mediated degradation kinetics	$\beta_{infl} \in [1,3]$	$\beta_{infl} = 2$	L	Decrease half-life of neotissue from inflammatory response (Increased MMPs)
		$k_{infl}^q = \beta_{infl} k_h^q$		
17. Inflammation-mediated elastic parameters	$Y_{1,infl} \in [1,50]$ where $c_1^{c,infl} = \gamma_{1,infl} c_1^{c,h}$	$Y_{1,infl} = 20.0$	L	Increased Type I:III ratio, produced via inflammation in response to polymer
18.	$Y_{2,infl} \in [1,50]$; where $c_2^{c,infl} = \gamma_{2,infl} c_2^{c,h}$	$Y_{2,infl} = 10.0$	L	
19. Stress-mediated elastic parameters	$Y_{1,sts} \in [1,25]$; where $c_1^{c,sts} = \gamma_{1,sts} c_1^{c,h}$	$Y_{1,sts} = 5.0$	L	Increased cross-link deposition and/or change in undulation in response to lack of elastin and active smooth muscle
	$Y_{2,sts} \in [1,25]$; where $c_2^{c,sts} = \gamma_{2,sts} c_2^{c,h}$	$Y_{1,sts} = 1.5$		
21. Inflammation-mediated production kinetics	$K_{infl} \in [1,...]$	$K_{infl} = 45$	L	Rapid deposition of neotissue in response to polymer via inflammation-mediated (monocyte/macrophage driven) response
22. Damage parameter	$\xi^p \in [0.50, 0.75] \text{ kPa/day}$	$\xi^p = 0.6 \text{ kPa/day}$	M	Loss of structural integrity of polymer