Numerical Optimization of Scaffold Properties for Tissue Engineered Venous Grafts
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Introduction: Tissue engineered vascular grafts have shown great promise as off-the-shelf conduits for use in cardiovascular surgery, particularly in pediatrics and palliative procedures such as Fontan. Nevertheless, these implants exhibit long-term complications due to excessive matrix production and consequent narrowing of the vessel [1]. Recent advances in material science and fabrication techniques allow greater control of scaffold geometries and properties for a greater range of materials. Because of this versatility, computational biomechanical models have been developed to predict growth and remodeling (G&R) outcomes for particular combinations of scaffold properties [2]. While parametric studies are illustrative and increase intuition as to improved designs, truly optimal scaffold designs require identification of quantitative metrics for comparison of outcomes and the coupling of growth and remodeling simulations with an optimization framework. The Surrogate Management Framework (SMF) has been shown to be an effective parameter estimation and optimization method in previous cardiovascular studies [3]. The goal of the coupled simulations presented herein was to identify potentially optimal parameter values from a predetermined set, including scaffold porosity, stiffness, and mass degradation rate, which play key roles in the body’s response to implanted constructs [4].

Methods: A detailed review of the G&R framework for a cylindrical tube has been described previously [2]. In brief, the graft constituents, including polymer, collagen, and smooth muscle cells, were modeled using constrained mixture theory. Rates of inflammation-mediated tissue production and degradation were prescribed based on phenomenological relationships with the scaffold microstructure. The polymer was assumed to have a sigmoidal degradation profile described by a rate-like parameter and an offset. Additionally, mechano-mediated tissue production was assumed to depend on differences in circumferential stress and wall shear stress from homeostatic values for the native vein. The SMF interfaced with iterative G&R simulations to determine optimal parameter values with an objective function based on the difference in linearized stiffness between the graft and native vein. The objective function acts as a quantitative marker for graft performance, and linearized stiffness of vessels has been shown as a key marker of vascular health [5].

Results and Discussion: The coupled simulations revealed the importance of initial parameter choice on graft outcome, while also indicating preferable parameter sets for future experimental testing. Due to the low pressure within the venous circulation, polymers with stiffness values on the order of 1 MPa were predicted to prevent graft dilatation upon loading while limiting mechano-mediated matrix production due to circumferential stresses on the order of those experienced in the native vein. Scaffold porosities of 50% prevented excessive production of inflammatory related matrix components, which have higher stiffnesses than normal matrix materials. Rapid degradation of the polymer, on the order of 2 weeks, was determined to reduce the duration of the inflammatory response and prevent excessive graft thickening. Together, these results highlight the importance of controlling inflammation to prevent stiffening and the associated narrowing of venous vascular grafts.

Translational Impact: This coupled biomechanical – optimization modeling technique reduces the need for costly and time consuming animal procedures to eliminate poor graft designs, especially when scaffold parameters are initially far from optimal. These principles can be applied in similar tissue engineering design problems to reduce the experimental burden and accelerate new device development.

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