Bioinspired Vascular Grafts

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Contents

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Abstract

A durable, synthetic small-caliber bypass graft has not been identified for revascularization of vessels less than 6 mm in diameter, and there exists limited availability of autologous conduits suitable for transplant. Consequently, alternative approaches have focused on designing arterial prostheses through the mimicry of some or all of the characteristics of the arterial wall. Notwithstanding early reports of promising results, important limitations remain associated with tissue engineering strategies, and the design of a living arterial substitute remains elusive. This chapter aims to describe the structural, mechanical, and biological properties of blood vessels and discuss the design considerations that must be implemented to realize the promise of bioinspired vascular grafts.

1 Introduction

Cardiovascular disease (CVD) affects over 80 million adults in the United States and represents a leading cause of death globally (Benjamin et al. 2019). CVD is most often due to progressive atherosclerosis, which may lead to plaque rupture and arterial occlusion with attendant clinical consequences of myocardial infarction, stroke, or amputation. While mild to moderate CVD can often be treated with modification in diet and lifestyle, as well as medications that limit the progression of atherosclerosis or risk of thrombosis, surgical and catheter-based interventions remain a mainstay of treatment, particularly for symptomatic disease. Catheter-based procedures, such as angioplasty, stenting, and atherectomy are commonly used to treat stenotic vessels or obstructive lesions (DeRubertis et al. 2007; Mwipatayi et al. 2008; McKinsey et al. 2008). Nonetheless, over 500,000 surgical bypass procedures, using a synthetic or autologous conduit, are performed annually in the United States (Go et al. 2013). Despite advances in minimally invasive, catheter-based interventions, including drug-coated stents and balloons, bypass surgery continues to be required for many patients and represents an optimal choice for durable long-term revascularization (Weintraub et al. 2012).

Despite a role for both synthetic and autologous conduits, their clinical performance remains suboptimal. The reconstruction of a large diameter vessel (>6 mm), such as the aorta, can be successfully performed using a synthetic prosthesis (Brewster 1997; Qu and Chaikof 2010). However, synthetic polymeric grafts display limited long-term patency when used in the femoral-popliteal position and exhibit very poor patency for tibial revascularization (Pereira et al. 2006; Van Der Slegt et al. 2014). The 1-year patency of synthetic polymeric conduits in the femoral-popliteal position is approximately 70% (Johnson and Lee 2000; Piffaretti et al. 2018). In general, a durable small-caliber synthetic bypass graft has not been identified for revascularization of vessels that are less than 6 mm in diameter, such as the coronary arteries.

Autologous grafts display higher patency rates than synthetic conduits but also suffer from a number of limitations (Klinkert et al. 2004; Goldman et al. 2004).

When used for coronary artery bypass graft (CABG) surgery, internal mammary artery (IMA) grafts exhibit patency as high as 93% at 10 years, (Loop et al. 1986; Berger et al. 2004; Taggart et al. 2019), and radial artery (RA) grafts have likewise been associated with low rates of stenosis and graft failure (Gaudino et al. 2018). However, the availability and length of IMA and RA conduits are limited. For this reason, saphenous vein grafts continue to be widely used, especially for multi-vessel revascularization. However, vein graft patency is less durable than one might expect, with failure of at least one vein graft commonly occurring within 12 to 18 months after CABG surgery (Mehta et al. 2011; Hess et al. 2014) and the occurrence of a hemodynamically significant stenosis or graft occlusion in 40% of vein grafts 1 year after lower extremity bypass surgery (Conte et al. 2006). Moreover, a suitable venous conduit is often unavailable in many older adults that have had prior surgery or who present with additional comorbid conditions (Kumar et al. 2011).

Vein graft failure has typically been attributed to intimal hyperplasia, which, when hemodynamically significant, leads to acute graft thrombosis (Sottiurai et al. 1983; Motwani and Topol 1998). Factors at the time of initial harvest of a vein graft that contribute to the development of intimal hyperplasia include ischemia-reperfusion injury of the vein wall that may cause endothelial and smooth muscle cell damage with release of pro-inflammatory factors, uncontrolled smooth muscle cell (SMC) proliferation, and extracellular matrix (ECM) production, particularly at the site of venous valves (Clowes 1993; Lemson et al. 2000; De Vries et al. 2016). A number of reports have also demonstrated that a mismatch in mechanical compliance between synthetic polymeric vascular conduits (0.2–1.9%/100 mmHg), autologous vein grafts (0.5–3%/100 mmHg), and native artery (5–15%/100 mmHg) can also initiate maladaptive biological responses that contribute to anastomotic intimal hyperplasia and subsequent graft failure (Abbott et al. 1987; Ballyk et al. 1997). Additional limitations of polymeric grafts include their susceptibility to bacterial colonization and infection and an inability of the synthetic conduit to grow in pediatric patients necessitating subsequent surgical intervention. Thus, there remains a critical need to address these shortcomings.

A current perspective held in tissue engineering is that an ideal vascular conduit would reproduce both the structure of a native artery and its related biological and mechanical characteristics (Fig. 1). In this chapter, we summarize past and current

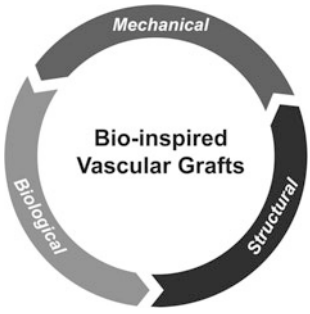

Fig. 1 Bioinspired vascular grafts should aim to recapitulate the structural, mechanical, and biological characteristics of native arteries

approaches to engineer a living blood vessel; the ability of each of these strategies to recapitulate the structural, mechanical, and biological characteristics of a native artery; and the existing shortcomings of these schemes.

2 Structural Considerations

The arterial wall, like many tissues in the body, can be represented as a reinforced composite of structural proteins that protect and orient living cells. It is characterized by a well-defined muscular layer that is responsible for providing strength, controlling vascular tone, and determining overall biomechanical responses. For this reason, the design of a bioinspired vascular conduit must be informed by (1) identifying the key cellular and acellular components responsible for the functional properties of a blood vessel (Fig. 2) and (2) an understanding of the architecture and organization of each component within the vessel wall (Table 1).

2.1 Structural Proteins: Collagen and Elastin

Collagen represents 20% to 50% of the dry weight of the arterial wall, present in the basement membrane and the interstitial matrix, and plays a crucial role in cell

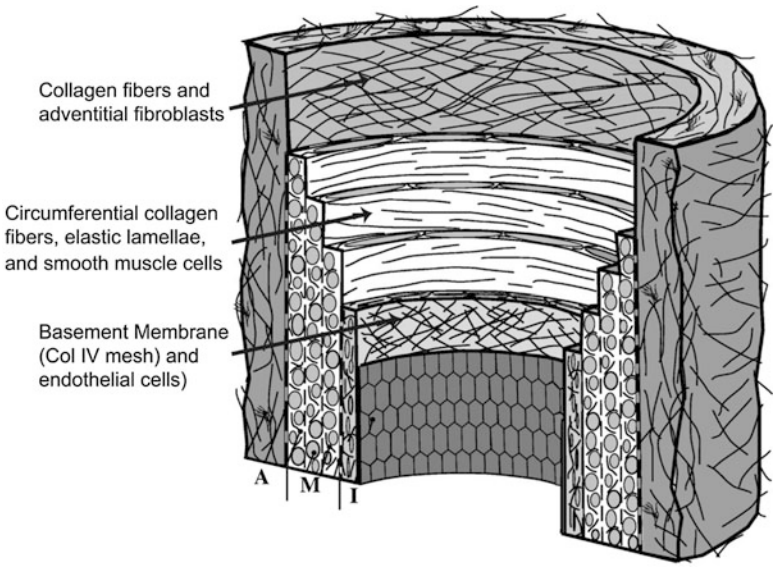

Fig. 2 *Histological representation of a native artery.* The Intima (I) consists of a monolayer of endothelial cells, and a basement membrane, a mesh-like substrate of type IV collagen. The Media is composed of networks of elastin (elastic lamellae) and circumferentially aligned smooth muscle cells and crimped collagen fibers (Col I and III). The Adventitia (A) consists of randomly aligned collagen fibers (Col I and III) and fibroblasts. (Modified with permission from Gasser et al. 2006)

Table 1 Structural components of the arterial wall

	Source	Location	Function	Organization
Collagen (I, III, IV)	Fibroblasts and SMCs	Tunica intima, media, adventitia	Provides mechanical support and strength and influences cell function through mechanotransduction pathways	Col I, III: Circumferentially aligned, crimped fibers Col IV: Mesh-like structure
Elastin	SMCs	Tunica media (elastic lamellae)	Component of arterial ECM that provides elasticity/recoil and allows interlamellar communication	Concentric 3 μm thick lamellae
Endothelial cells	Mesoderm	Luminal side of tunica intima	Regulates thrombotic and inflammatory responses	Monolayer of polygonal shaped cells
Smooth muscle cells	Ectoderm, Mesoderm	Tunica media	ECM production, vaso-responsiveness, and regulates inflammatory responses	Circumferential orientation
Fibroblasts	Mesoderm	Tunica adventitia	ECM production and vessel wall regulation	Isotropic alignment

behavior and vessel wall biomechanics (Linsenmayer 1991; Shoulders and Raines 2009). Closest to the luminal side, the subendothelial basement membrane, comprised mainly of type IV collagen, serves as a mesh-like physical barrier that protects and regulates normal endothelial function (Sand et al. 2016). The interstitial matrix is composed of type I and III collagens in the medial and adventitial layers (Shekhonin et al. 1985). As opposed to type IV, collagens I and III are structured into circumferentially aligned bundles of collagen fibers, with a characteristic 10 to 200 μm crimped or undulating morphology, which is an important determinant of passive and active biomechanical responses (Rezakhaniha et al. 2012; Robertson and Watton 2013). Genetic defects of either fibril-forming collagen can affect vascular wall strength and increases the likelihood of aneurysm formation, as in the case of Ehlers-Danlos syndrome (Sasaki et al. 1987).

Elastin is the second most common structural protein in the arterial wall and is secreted by vascular smooth muscle cells as tropoelastin, which undergoes post-translational modifications to form cross-linked, mature fibers (Parks et al. 1993). Elastin fibers are 1000 times more flexible than collagen and are found in high abundance in the aorta, where it comprises approximately 30% of the dry weight of the vessel wall (Debelle and Tamburro 1999). Elastin forms unique structures known as elastic lamellae, which consists of fibers arranged in 3 μm thick concentric fenestrated lamellae that confer elastic recoil and resilience to the arterial wall, and permits transmural delivery of nutrients and electrolytes (Mithieux and Weiss 2005).

2.2 Cellular Components: Endothelial Cells, Smooth Muscle Cells, and Adventitial Fibroblasts

Endothelial cells (ECs) populate the innermost layer of the arterial wall, where they are in direct contact with blood. This mesoderm-derived specialized epithelium is organized into a semipermeable monolayer that adheres to the basal lamina. Within the native artery, endothelial cell morphology is defined by polygonal-shaped cells, elongated in the direction of blood flow, measuring 12 to 25 μm in length (Garipcan et al. 2011). ECs are a unique cellular subset, due to the presence of tight intercellular and adherens junctions, which serve to regulate cell permeability and membrane polarity, as well as modulate endothelial cell growth through contact inhibition (Bazzoni and Dejana 2004; Lampugnani 2012). As the blood-contacting surface in the arterial wall, endothelial cells have been found to express various molecules that regulate blood homeostasis (Sumpio et al. 2002; Esmon 2005). For example, thrombomodulin, found in the membrane of ECs, inhibits blood coagulation by catalyzing thrombin-induced activation of the protein C pathway (Esmon 1989; Stearns-Kurosawa et al. 1996). Similarly, heparan sulfate is a surface proteoglycan on the luminal aspect of the endothelium, which contains a unique pentasaccharide motif that is recognized by antithrombin III (ATIII), binds to factor IIa (thrombin) and factor Xa, and inhibits clot formation (Bernfield et al. 1999; Rabenstein 2002). Heparan sulfate also facilitates leukocyte adhesion and diapedesis (Parish 2006).

Vascular smooth muscle cells (SMCs) are contractile, bi- or multinucleated cells, with a spindle-shaped morphology that populate the arterial tunica media. Most SMCs have been reported to be mesoderm derived; however, those that populate the aorta and pulmonary arteries are derived from neural crest cells (Le Lièvre and Le Douarin 1975). Within the arterial wall, SMCs are tightly packed in a circumferentially aligned manner, and, unlike endothelial cells, each cell is surrounded by a 40 to 80 nm thick basal lamina suspended in a collagen fibril matrix with alternating rings of elastic lamellae (Rhodin 1979; Clark and Glagov 1985). In healthy adults, SMCs are non-proliferative, are metabolically quiescent, and are not actively migrating or proliferating (Bacakova et al. 2018). As the primary cellular component of the arterial media, SMCs regulate arterial tone and local tissue oxygen delivery through vasomotor control. SMCs are vaso-responsive to Ca^{2+}, myogenic stretch, as well as endothelin, nitric oxide, and prostacyclin secreted by endothelial cells (Wilson 2011).

Adventitial fibroblasts populate the outer most layer of the arterial wall, where they regulate production and organization of undulated collagen fibers that serve to limit vessel overdistension (Stenmark et al. 2013). For years, the adventitia was commonly considered a supporting tissue. However, recent studies have identified adventitial fibroblasts as key regulators of the vessel wall response to hormonal, inflammatory, and environmental stresses, such as hypoxia, ischemia, or hypertension (Stenmark et al. 2011). Activated adventitial fibroblasts have been found to proliferate and upregulate the release of chemokines leading to adventitial remodeling and neointimal hyperplasia (Shi et al. 1996; Sartore et al. 2001). Overall, adventitial fibroblasts are capable of regulating vascular structure and function

through the secretion of growth factors, cytokines, and chemokines that serve to communicate with adventitial neural cells, circulating inflammatory cells, and neighboring SMCs and ECs (Sorrell and Caplan 2009).

2.3 Structural Considerations in Vascular Grafts

In 1986, Crispin Weinberg and Eugene Bell published the first report of "a blood vessel model" for the replacement of small-caliber vessels. They encapsulated fibroblasts and smooth muscle cells in casted collagen tubes, supported with a Dacron mesh, lined with endothelial cells (Weinberg and Bell 1986). Although the end result was a weak construct that "grossly resembled a muscular artery," this work motivated further investigations aimed at engineered vessels that mimicked the structure of native arteries.

Buijtenhuijs et al. subsequently developed a semi-aligned, porous scaffold consisting of collagen and elastin fibers and seeded it with vascular smooth muscle cells (Buijtenhuijs et al. 2004). They were among the first to explore strategies for controlling structural protein morphology and orientation within a vessel wall by tuning the freeze-drying of a suspension of insoluble type I collagen and elastin. Since then, electrospinning and wet-spinning have also been used to control the organization of collagen and elastin fibers (Buttafoco et al. 2006; McClure et al. 2010; Huang et al. 2013; Ahn et al. 2015). These modalities consist of the continuous formation of polymer filaments by either mechanical extrusion into coagulation baths or electrostatic repulsion between polymer solutions and charged surfaces (Miranda-Nieves and Chaikof 2017). As an example, Caves et al. developed a continuous wet-spinning system for the extrusion of synthetic collagen fibers into a 10 wt% polyethylene glycol bath and, after embedding within a recombinant elastin-like protein matrix, generated a vascular graft that resembled the reinforced composite structure of the arterial wall and the circumferential alignment of collagen fibers within the tunica media (Caves et al. 2010a, b).

Approximating the crimped morphology of native collagen fibrils has been possible through molding and chemical treatment (Caves et al. 2010c; Liu et al. 2015). For example, Naik et al. developed a MEMS-based micromolding approach capable of producing in-plane crimped microfibers with a crimp-periodicity of about 100 μm (Naik et al. 2014), and Kumar et al. used excimer-laser technology to ablate collagen lamellae without protein denaturing (Kumar et al. 2014). In both cases, sheets of crimped collagen fibrils were generated, which exhibited orthotropic tensile properties.

On another hand, various groups have focused on recapitulating the structure of native vessels through an approach driven by cellular engineering. For example, vascular conduits have been produced by rolling sheets of fibroblasts or smooth muscle cells produced over a 3- to 7-week period (L'Heureux et al. 1998, 2006). Cell-sheet engineered grafts have shown to recapitulate the lamellar structure of

arteries and the position of vascular cells. Complementary strategies, such as patterned polydimethylsiloxane (PDMS) substrates and dynamic mechanical stimulation, have been successfully employed to guide cell sheet alignment during growth or after maturation, in order to better approximate the arterial microstructure (Xing et al. 2017; Rim et al. 2018). For instance, Isenberg et al. cultured smooth muscle cells on gelatin-coated, micropatterned PDMS and produced cell sheets with alignment in the same direction as the pattern (Isenberg et al. 2012). Similarly, Gauvin et al. reported that mechanical stimulation of 10% strain at a frequency of 1 Hz for 3 days significantly enhanced fibroblasts cell sheet alignment (Gauvin et al. 2011).

Other approaches have leveraged advances in polymer science to generate synthetic, biodegradable scaffolds for direct implantation or ex-vivo cell seeding and mechanical preconditioning (Roh et al. 2009; Dahl et al. 2011; Syedain et al. 2016). The goal of these approaches is to rely upon cell-mediated synthesis of ECM, with a number of strategies applied to control ECM composition, organization, and architecture. Successful strategies have included the use of perfusion bioreactors with control over pulse rate and cyclic distension to increase production of structural proteins (Solan et al. 2003; Syedain et al. 2008); culture medium supplementation with organic and inorganic compounds that enhance matrix remodeling and crosslinking (Neidert et al. 2002; Dahl et al. 2005); and controlled release of growth factors and recombinant chemokines in order to modulate inflammation and promote cellular migration (Wu et al. 2012; Yu et al. 2012). As an example, Huang et al. discovered that biaxial preconditioning of SMC-seeded, polyglycolic acid (PGA)-based scaffolds enhances the formation of mature elastin fiber and undulated collagen fibrils (Huang et al. 2015, 2016). Similarly, Roh et al. reported that the release of monocyte chemoattractant protein-1 (MCP-1) modulated monocyte recruitment, promoted migration and proliferation of adjacent vascular wall cells, and overall resulted in the in situ remodeling of poly(L-lactide-co-caprolactone) [PLCL] scaffolds (Roh et al. 2010).

Notwithstanding reports of promising results (McAllister et al. 2009; Syedain et al. 2017; Kirkton et al. 2019), cell-based strategies remain limited by the absence of protocols for the rapid and scalable production of patient-specific vascular wall cells and need for decellularization before implantation (Wystrychowski et al. 2014; Lawson et al. 2016). More specifically, studies have revealed feasibility challenges when using cells isolated from the intended patient population (>65 years old), or allogeneic sources, including reduced proliferation and ECM production due to telomere shortening (Poh et al. 2005), and immune rejection associated with HLA mismatching. Recent reports have sought to address these limitations by deriving SMCs and ECs from patient-specific human induced pluripotent stem cells (hiPSCs), which have unlimited proliferation capacity (Wang et al. 2014; Patsch et al. 2015; Gui et al. 2016; Luo et al. 2017). Similarly, multiplex genome editing has been employed to selectively ablate HLA class I and II molecules and introduce immunoregulatory factors in order to evade both the adaptive and innate immune mechanisms of immune rejection (Deuse et al. 2019; Xu et al. 2019; Han et al. 2019). However, the scalability and efficacy of these approaches remains uncertain.

3 Mechanical Considerations

The biomechanical characterization of engineered arterial substitutes has been largely limited to evaluating burst pressure and suture retention, with the goal of matching these discrete values to those reported for arteries or saphenous vein. Although important metrics, these parameters provide relatively limited insight into the biomechanical properties of the engineered conduit, which influence cellular responses, tissue remodeling, and long-term conduit durability. In this section, we will discuss (1) the mechanical behavior of native arteries and (2) unique mechanical considerations in the design of an engineered living blood vessel that influence both early and late performance characteristics of the conduit.

3.1 Hyperelasticity and Compliance

Arteries are constantly subject to cyclic mechanical stress and can compensate for alterations in intravascular blood volume with minimal changes in pressure through modulating vascular tone. Collagen and elastin, and their unique structural organization, are responsible for the nonlinear responses of arteries to loading forces (Wagenseil and Mecham 2009). At low radial stretch, less than 10% of collagen fibers are engaged and aligned with unfolding of elastic lamellae dictating mechanical behavior. Large radial changes result in marginal increases in pressure. Beyond the range of physiological pressure (80 to 120 mmHg), collagen bears the load with the recruitment, circumferential alignment, and straightening of undulated fibers, leading to marginal radius changes with increasing pressure (Fig. 3). Recent studies have shown that elastic stretching and architecture, as well as collagen fibril recruitment and straightening varies within the arterial wall, in order to compensate the

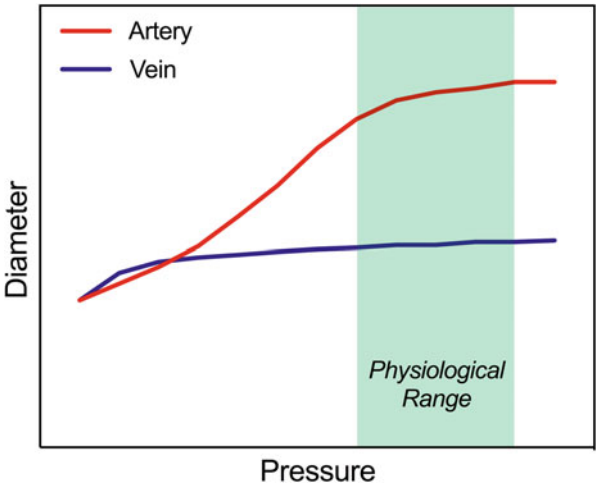

Fig. 3 *Pressure-diameter curves comparing murine carotid artery and murine inferior vena cava*. Values were recorded using pressure myograph

circumferential stretch experienced during radial distension (Zeinali-Davarani et al. 2015; Yu et al. 2018a, b).

When arteries are pressurized, they are subjected to distention in all directions. Many constitutive models have been used to calculate the stress-strain response of the arterial wall from pressure-diameter curves (Başar and Weichert 2000). The most commonly used formulation is the hyperelasticity model in which the vessel is treated as an orthotropic, cylindrical body in which all net strains are oriented along the circumferential, longitudinal, and radial directions (Dorbin 1978; Gasser et al. 2006). Longitudinal and circumferential stresses *(σ)* are calculated as:

$$\sigma = \frac{P\lambda}{ALt} \tag{1}$$

where P is the inflation pressure, λ is the stretch, L is the initial length, t is the thickness of the tissue, and A is the cross-sectional area of the cylinder. Similarly, strain *(E)* can be defined by:

$$E = \frac{1}{2}\left(\lambda^2 - 1\right) \tag{2}$$

Compliance mismatch is an important failure mode, which can be characterized through the arterial pressure-diameter relationship. Compliance *(c)* represents the percent change in diameter over a physiologic range of pressure and is calculated as:

$$\mathrm{c} = \frac{\mathrm{d}_{120} - \mathrm{d}_{80}}{\mathrm{d}_{80}\left(\mathrm{P}_{120} - \mathrm{P}_{80}\right)} \times 10^4 \tag{3}$$

where d is diameter and P is inflation pressure (Robertson and Watton 2013). Arterial compliance (%/100 mmHg) varies with vessel type and location, ranging from 8.0 to 17.0, 6.5 to 12.0, and 6.0 to 14.1%/100 mmHg, for coronary, internal thoracic, and the femoral arteries, respectively (Kumar et al. 2011). Precise methodologies, such as laser micrometry and pressure myography, should be employed to accurately measure outer diameter and pressure and successfully quantify compliance in the 80 to 120 mmHg pressure range. Laser micrometry uses a laser to scan a field, and by detecting the time during which the laser path is obstructed, the dimensions of any sample can be calculated (Syedain et al. 2011). Pressure myography relies upon recording changes in diameter using a high-resolution camera placed over a conduit that is mounted onto small cannulae during the course of pressurization (Schjørring et al. 2015).

The pressure-diameter, stress-strain, and compliance characteristics of a saphenous vein are significantly different than those responses measured for arterial blood vessels (Li 2018). Due to reduced elastin content and a lower number of elastic lamellae, stiffening occurs at lower pressures (Fig. 3), with the saphenous vein exhibiting a significantly lower compliance (0.7–2.6%/100 mmHg) (Lee et al. 2013). For this reason, when used as an arterial substitute, elevated arterial pressure induces increased stress in the vein wall, promotes smooth muscle cell proliferation

and matrix production, and, as a consequence, increases the risk of intimal hyperplasia (Li 2018).

3.2 Residual Stress

In the 1960s, Bergel performed an experiment in which he prepared cross-sectional rings of excised, intact, unloaded arteries, and noted that when cut radially "an artery will unroll itself" (Bergel 1960). This was the first report of stress in an artery even when there is no distending pressure. The cut ring "opens" to minimize stored strain-energy, as the inner wall is in compression and the outer wall in tension (Humphrey 2002). This residual stress is the result of differences in the waviness of the elastic lamellae between the inner and outer wall (Yu et al. 2018a). Direct quantification of residual stress (Λ) is not a simple task. Thus, surrogate measures of residual strain have been employed, such as measurements of the opening angle after a radial cut (Matsumoto et al. 2015).

$$\Lambda = \frac{\pi\left(R_a^2 - R_i^2\right)}{\Theta\left(r_a^2 - r_i^2\right)} \tag{4}$$

where R is the adventitial or intimal radius prior to cutting, Θ is the observed opening angle, and r is the adventitial or intimal radius after cutting. Residual stress provides an indirect measurement of arterial wall stress and the mechanical microenvironment within the vessel wall.

3.3 Mechanical Considerations in Vascular Grafts

Reports of engineered arterial substitutes have focused almost entirely on optimizing burst pressure and suture retention strength while lacking attention to many critical biomechanical parameters discussed in this chapter. Nonetheless, some reports have identified these limitations and proposed modified design strategies (Dahl et al. 2007). For instance, failure to match the hyperelastic behavior of native tissues due to inferior collagen and elastin organization has been addressed by tuning initial polymer concentration (Cummings et al. 2004; Lai et al. 2012) and establishing fabrication protocols with increased control over ECM composition, organization, and architecture (Hall et al. 2016; Xing et al. 2017; Yokoyama et al. 2017). In particular, construct fabricated with pre-stretch, electrospun PLCL fibers at various orientations recapitulated the nonlinear stress-strain behavior of native arteries (Niu et al. 2019).

Variations in polymer composition, organization, and architecture, as well as cyclic pre-conditioning, have proven tunable strategies for designing constructs with control over compliance and residual stress (Niklason et al. 2001; Huang et al. 2016; Niu et al. 2019). For example, McClure et al. reported that altering

combinations of collagen, elastin, and synthetic polymers in electrospun grafts allowed precise control over the compliance of the conduits (McClure et al. 2010). Caves et al. employed a fabrication scheme in which a range of collagen fiber orientation and volume fractions were investigated, and reported compliance from 2.8 to 8.4%/100 mmHg, matching values reported for major arteries of interest (Caves et al. 2010a). Huang et al. fabricated constructs through biaxial preconditioning of cell-seeded PGA scaffolds with increased conduit compliance due to the formation of mature elastin fiber and crimped collagen fibrils (Huang et al. 2015, 2016).

Noteworthy, the capacity for biomechanical properties to vary post-implantation has also been reported. In a clinical study, 25 patients were enrolled in an arteriovenous (A-V) shunt safety trial, and the compliance 6-month post-implantation increased approximately threefold (L'Heureux et al. 2007; Konig et al. 2009), suggesting that consideration should also be given to the role of in vivo remodeling in the long-term performance of vascular grafts.

4 Biological Considerations

The biological characterization of engineered living arterial grafts has almost exclusively been focused on evaluating cell infiltration and stem cell differentiation. Limited insight has been obtained surrounding the phenotypic variations of cellular components within vascular grafts. In this section, we will discuss (1) the key phenotypic biomarkers of vascular smooth muscle cells, endothelial cells, and adventitial fibroblasts and (2) biological considerations in the design of living blood vessels.

4.1 Smooth Muscle Cell Phenotype

Smooth muscle cells are a highly specialized and differentiated cell. Under normal conditions, SMCs are elongated, spindle-shaped, non-proliferative, metabolically quiesced, and functionally contractile (Rensen et al. 2007). They are associated with elevated expression of contractile apparatus proteins, such as α-smooth muscle actin (α-SMA), calponin, smoothelin, and smooth muscle myosin heavy chain (SM-MHC) (Owens 1995). However, SMCs are remarkably plastic and can shift phenotype in order to adapt to fluctuating environmental cues, physical stressors, and biochemical alterations. In response to vessel injury, SMCs have been documented to proliferate, migrate, and over-secrete EMC molecules, in particular fibronectin (Gomez and Owens 2012). This de-differentiated synthetic state is associated with loss of contractile proteins, a rhomboid morphology, and expression of proteolytic enzymes and inflammatory cytokines, such as MCP-1 (Bennett et al. 2016). Overall, human arteries may contain a heterogeneous mixture of contractile and synthetic functions (Hao et al. 2003).

4.2 Endothelial Cell Phenotype

Mechanical forces, soluble growth factors, and cytokines, as well as contact with tissue-based cells and ECM protein, regulate endothelial cell phenotype. Under normal conditions, ECs are quiescent, anticoagulant, anti-inflammatory, anti-oxidative, and non-angiogenic with a low replicative capacity (Cines et al. 1998). Quiescent ECs exhibit cobblestone morphology and express markers such as VE-cadherin, PECAM-1, CD34, and CD36 (Lin et al. 2000). However, in response to physical and biological stressors, endothelial cells can de-differentiate into an activated, pro-inflammatory state (Liao 2013). Activated ECs are associated with loss of vascular integrity, causing efflux of fluid into the extravascular space; expression of leucocyte adhesion molecules, such as selectins, ICAM-1, and VCAM-1; prothrombogenicity, due to loss of surface expressed thrombomodulin; and increased cytokine production, such as IL-6, IL-8, and MCP-1 (Hunt and Jurd 1998).

4.3 Adventitial Fibroblast Phenotype

The principal function of adventitial fibroblasts is the deposition of isotropic collagen bundles that provide support and prevent overdistension. However, in response to hormonal, inflammatory, and environmental stresses such as hypoxia, ischemia, or hypertension, adventitial fibroblasts undergo phenotypic switching into myofibroblasts, characterized by the expression of contractile proteins, in particular α-SMA; secretion of pro-inflammatory cytokines, such as TGF- β; increased proliferation and synthetic activity; as well as enhanced migration and functional contractility (Strauss and Rabinovitch 2000; Maiellaro and Taylor 2007). Adventitial fibroblast activation significantly alters the vessel wall microstructure, with the over-accumulation of ECM proteins, such as collagen, elastin, and fibronectin, influencing vessel elasticity and flow dynamics (Desmoulière et al. 2005), and increased cell migration associated with neointimal hyperplasia (Kalra et al. 2000; Misra et al. 2010).

4.4 Biological Considerations in Vascular Grafts

For most reports of tissue engineered vascular grafts, the extent of biological characterization has been limited to identifying post-implant cell infiltration or assessing stem cells differentiation in pre-seeded scaffolds (Koobatian et al. 2016; Syedain et al. 2017; Kirkton et al. 2019). Although an indication of tissue remodeling, such information provides relatively limited insight into the late performance characteristics of vascular conduits. A recent viewpoint in the tissue engineering of living blood vessels is that cellular phenotype should be a key consideration when selecting design strategies. More specifically, fabrication approaches should aim to generate constructs that induce contractile SMCs,

quiescent ECs, and inactivated fibroblasts. As an example, Yokoyama et al. fabricated arterial grafts by varying hydrostatic pressure and evaluated expression levels of SMC markers, such as fibronectin, collagen, and elastin, to identify the ideal conditions that resulted in a contractile phenotype (Yokoyama et al. 2017). Similarly, iPSC-derived SMCs were examined for an array of biomarkers, including α-SMA, calponin, smoothelin, SM-MHC, collagen, and elastin, in order to determine serum and growth factor concentrations optimal for cell maturation (Wanjare et al. 2013, 2014).

5 Conclusions

Surgical revascularization of small diameter vessels remains a clinical challenge given limited availability of suitable arterial conduits. Synthetic and autologous grafts exhibit poor 1-year patency rates and are often constrained by availability and length. These challenges have motivated the development of tissue-engineering strategies. Preclinical and early clinical reports describe the use of vascular grafts produced by cellular engineering or from a variety of natural and synthetic biodegradable scaffolds with the potential for ex vivo preconditioning or direct in vivo implantation. Likewise, polymer- and cellular-based approaches have been explored to better recapitulate properties of the arterial wall. However, the design of a durable synthetic small-caliber bypass graft remains elusive.

A current perspective in blood vessel engineering suggests that an ideal living arterial conduit should reproduce both the structure of a native artery and its related biological and mechanical characteristics. In this chapter, we have summarized the characteristics of native arteries and discussed approaches to engineer living blood vessels that replicate these features. It has been noted that many published fabrication schemes lack a holistic view of the native artery as a unique structure that dictates overall biomechanical properties and influences cellular responses, tissue remodeling, and long-term conduit durability. For this reason, we conclude that future design strategies should be informed by the structural, mechanical, and biological considerations discussed herein.

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