Review

Electrospinning of Biomaterials for Vascular Regeneration

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Cardiovascular diseases have been the leading cause of morbidity and mortality in the world recently. With the growing aging population accompanied by chronic diseases, such as uremia and diabetes, there is an increasing clinical demand for vascular grafts with proper performance. Although some achievements have been made in the development of tissue-engineered vascular grafts composed of natural and synthetic polymeric materials or decellularized vessels, clinical applications with a diameter of less than 6 mm are still principally derived from autografts, such as autologous saphenous veins. Many challenges remain in antithrombosis, rapid endothelialization, modulating the inflammatory response and inhibition of intimal hyperplasia and calcification. In the review, recent progress in the electrospinning of biodegradable polymers for vascular regeneration are summarized, especially from the view of biomechanical factors. Hybrid vascular grafts consisting of natural and synthetic polymers with multicomponent, di- or tri-layers are focused in order to provide novel experiences in biomaterials for applications in this field.

Keywords Electrospinning; Biodegradable polymer; Vascular graft; Biomechanical factor; Compliance

1 Introduction

Cardiovascular diseases(CVDs) have become a significant cause of death in the world. According to the World Health Organization's data, there are approximately 17.9 million people died from CVDs every year[1]. Vascular replacement or revascularization are the most common surgical procedures, and with the growing aging population accompanied by chronic diseases, such as uremia and diabetes, there is an increasing clinical demand for vascular grafts with long-term patency[2,3]. Although some favorable outcomes in large and middle-diameter(diameter>6 mm) vascular grafts have been achieved, clinical small-diameter vascular grafts(SDVGs) with a diameter smaller than 6 mm are mainly autografts. However, the use of autologous grafts is often limited by vessel harvest and availability, and associated with significant complications[2]. As a result, the development of synthetic SDVGs is a suitable alternative. Significant advances of engineered SDVGs have been made in single-cell layer vessels and tissue-engineered vascular grafts(TEVGs) composed of natural and synthetic polymeric materials over decades, but many challenges still remain in terms of anti-thrombosis, rapid endothelialization, modulating the inflammatory response and inhibition of intimal hyperplasia and calcification[1,4—6]. Therefore, SDVGs require particularly exacting design criteria, and among them the adequate biomaterials with proper mechanical properties to withstand billions of cardiac cycles are necessary consideration[3]. Biomechanical signals play an important role in cell adhesion, growth, differentiation and tissue regeneration. Differences in mechanical properties between the synthetic vascular graft and target natural vessel including tensile strength, Young's modulus, elongation, suture retention, burst pressure and compliance will increase the risk of inducing graft failure finally caused by intimal hyperplasia, aneurysm formation, calcification and so on[7,8]. Specifically, compliance mismatch has been demonstrated to be associated with intimal hyperplasia and vascular occlusion[9].

The techniques for manufacturing vascular grafts commonly include electrospinning, decellularization, lyophilization, and 3D printing and bioprinting, where electrospinning is particularly attractive due to its simplicity and versatility[2—4,10—15]. The electrospun fibrous membranes have a specific surface area, mechanical integrity and fiber continuity, providing a biomimetic extracellular matrix (ECM)[Fig.1(A) and (B)][10,12,15,16]. A variety of natural, synthetic or hybrid materials have been electrospun into tubular constructs for vascular regeneration. Moreover, by adjusting the electrospun parameters, such as polymer concentration, voltage, flow rate and so on, vascular grafts with controlled fiber diameter, porosity, inner diameter, mechanical properties and compositions can be easily obtained[17]. Followed by the modification with biomolecules, biological behaviors can be significantly improved, such as cell adhension and infiltration, and thus facilitating tissue regeneration. Detailed introduction of electrospinning and its application in tissue regeneration have been reviewed

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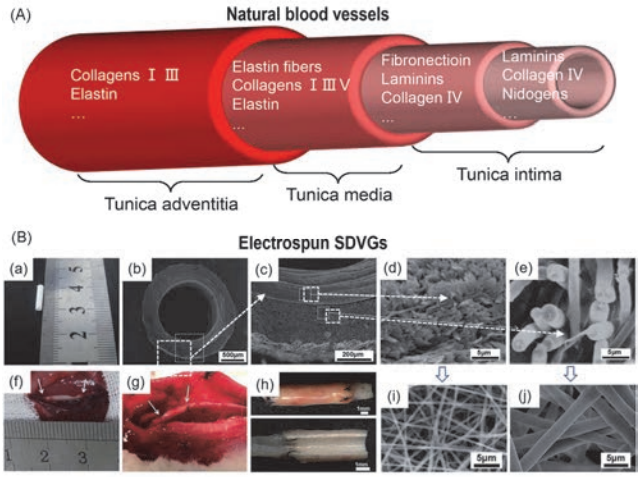

Fig.1 Blood vessel structure and electrospun SDVGs

(A) Schematic natural vascular layers; (B) macroscopic(a), cross-section(b,c,d,e) and fiber morphology(i,j) as well as implanted and explanted images(f,g,h) of a typical bi-layer electrospun SDVG with a thinner-fiber inner layer and a thicker-fiber outer layer.

(A) Redrew according to Ref.[18]; (B) Reprinted with permission from Ref.[21], Copyright 2019, Wiley-VCH.

previously[10]. This review will focus on the recent progress in electrospinning of various polymeric biomaterials for vascular regeneration, including natural and synthetical polymers with biodegradability and biocom-patibility. Mechanical properties of SDVGs, especially compliance, are highlighted based on the effects of biomechanical factors. Hybrid vascular grafts with multicomponent, and di- or tri-layers are involved to provide experiences in biomaterials for applications in this field.

2 Requirements of SDVGs

2.1 Structure of Blood Vessel

A typical blood vessel consists of tunica intima, tunica media and tunica adventitia, showing a tri-layer structure. Fig.1(A) presents the three vascular layers and their associated ECM components[18]. In fact, the tunica intima contains basal lamina and basement membrane, which are composed of endothelial cells(ECs) monolayer, laminins, collagen IV, nidogens, proteoglycans and glycoproteins, playing an important role in biological signaling transductions[19]. In the media, vascular smooth muscle cells(SMCs), elastin lamellae and collagens I, III are the main components, providing mechanical support and vasoactive response. Loose connective tissue fibroblasts and high content of collagens I, III as well as elastin make up the tunica adventitia. It can be seen that collagens I, III and elastin are the major components of tunica media and adventitia[20]. It is supposed that both collagen and elastin, with the triple helical structure and elasticity, respectively, are responsible for providing mechanical stability and integrity of blood vessels[3]. The modulus of collagen is approximately 100 times higher than that of elastin[3].

2.2 Requirements of SDVGs

Generally, an ideal SDVG has the following requirements[1,3]. First, the vascular graft should have adequate mechanical properties for supporting blood flow without rupture or dilation, and suitable suture retention for surgical procedure. Second, a nonthrombogenic and anticoagulant luminal surface is vital for SDVGs, since partial or complete vascular blockage will occur once a thrombus has formed. Third, the grafts should provide a natural ECM mimic microenvironment for supporting cell growth and vascular remodeling. Forth, the prepared SDVGs should be biocompatible for minimizing the risk of immune recognition and inflammation. In short, the overall objective is to get a ready-to-use SDVG that can be remodeled and regenerated by the host. Therefore, graft compliance is a considerable factor as well, since compliance mismatch between SDVGs and natural vessels would lead to some adverse biological responses.

3 Compliance

In the field of vascular tissue engineering, compliance is a critical biomechanical factor for synthetic vascular grafts. Compliance mismatch at the anastomosis sites between vascular grafts and native blood vessels could give rise to the poor long-term patency of SDVGs.

3.1 Outcomes of Compliance Mismatch

There are three hemodynamic flow patterns at the distal anastomosis after a vascular graft is implanted. When the diameter of a graft is larger than that of a native vessel, a convergent blood flow pattern would be observed around the anastomosis. At this point, the wall shear stress increases and may result in platelet activation, endothelial damage and dysfunction[4]. In addition, overhigh compliance also increases the risk of vasodilatation, aneurysms, and graft rupture[7]. As shown in Fig.2, when the graft compliance is lower than that of a native vessel, a divergent blood flow(flow separation) is usually formed. This flow geometry can reduce the mean wall shear stress and slow down the blood flow rate inside the lumen, causing ECs dysfunction[4]. It has been found that the dysfunctional ECs could change the levels of secreted growth factors and cytokines, such as platelet-derived growth factor (PDGF), stimulating SMC-based ECM reconstruction and further thickening the intima[22,23]. Additionally, low wall shear stress will increase the adhesion of monocytes to the endothelial layer, trap platelets and leukocytes, and also promote thrombosis[4]. Besides wall shear stress, wall stress

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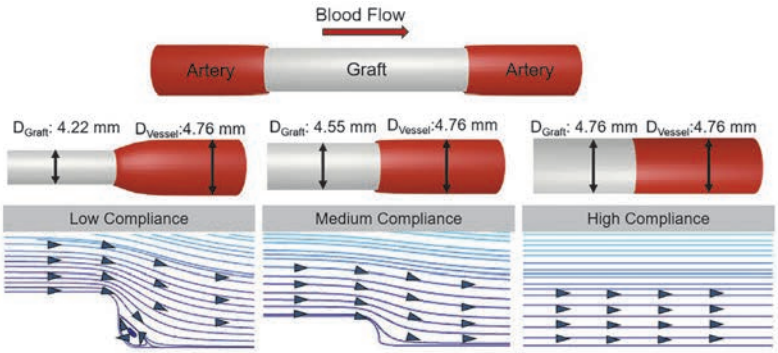

Fig.2 Effect of graft diameters with different compliances on flow patterns at distal anastomosis
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around the anastomoses will increase in the mismatched compliance grafts. High shear stress has been shown to promote the expression of PDGF and matrix metalloproteinase (MMP), as well as SMCs phenotype changes from contractile to proliferative, simulating the proliferation and migration of SMCs and thus promoting intimal hyperplasia formation. Furthermore, compliance mismatch at the anastomosis may also lead to an increased suture stress, which may stretch SMCs and promote their proliferation[9].

Cosgriff-Hernandez's group[22] prepared low, medium and high compliance vascular grafts with different thicknesses, and systematically studied the effect of graft compliance on WSS and histological changes during vascular remodeling. A computational model was first employed and predicted that the diameter difference between low compliance graft and native artery was the largest, which has the greatest impact on blood flow distribution and blood recirculation and low wall shear stress zone have been formed. Further, a pig carotid artery *ex vivo* organ culture model was used to evaluate the behavior of SMCs, ECs and ECM on different compliance grafts and the result presented that the arteries sutured with low and medium compliance grafts showed early markers of intimal hyperplasia and elevated levels of intimal hyperplasia after 2 weeks of culture under physiological conditions[22].

Overall, compliance mismatch between SDVGs and native vessels will result in abnormal hemodynamic behavior around the anastomosis, leading to intimal hyperplasia formation, which has a serious effect on the long-term graft patency.

3.2 Compliance of Electrospun SDVGs

The compliance of SDVGs is defined as the capability of the vascular grafts to expand circumferentially under pulsating pressure, that is, circumferential elasticity[24]. For artificial blood vessels, compliance is calculated by the percentage change of graft diameter under a certain pressure range according to Equation 1[22,25—28].

$$\text{Compliance}(\%)=\frac{\frac{R_{p_2}-R_{p_1}}{R_{p_1}}}{p_2-p_1}\times 10^4 \quad (1)$$

where, p_1 is the diastolic pressure, p_2 is the systolic pressure, R_{p_1} and R_{p_2} stand for the vascular graft diameters under p_1 and p_2, respectively. According to the type of pressure tested, graft compliance has two modes. One is static compliance, where a constant pressure was used to test the diameter change, and another is dynamic compliance, referring to the diameter change under repetitive cyclical pressure similar to the pulsatile pressure of blood circulation[29]. The schematic representations of static and dynamic compliance testing apparatus are shown in Fig.3(A, B), and Fig.3(C) is the

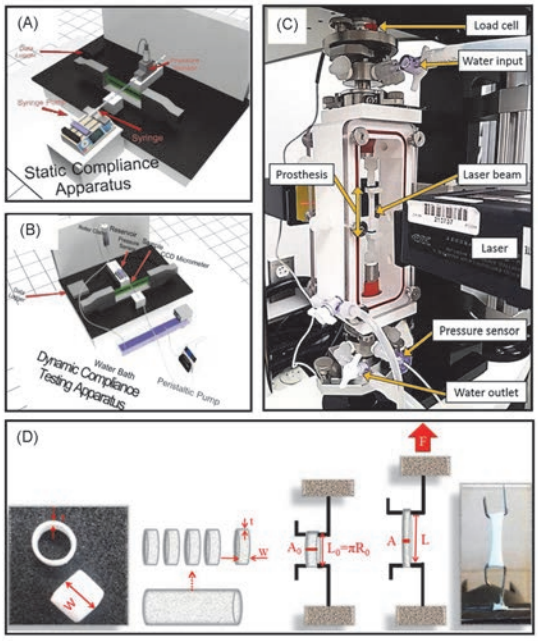

Fig.3 Schematic representation of static(A) and dynamic testing devices(B), compliance testing setup with a TA instrument ElectroForce® 3200(C), schematic diagram of tubular graft testing by a uniaxial tensile system(D)
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photograph of a complete system for testing graft compliance in most cases. Moreover, the compliance of tubular grafts can also be obtained simply through a uniaxial tensile system [Fig.3(D)].

The compliance values of electrospun vascular grafts are summarized in Table 1. Dacron and e-PTFE are most widely used in synthetic materials, but they are comparatively rigid, with e-PTFE grafts showing lower dynamic compliance of (0.26%—1.20%)/100 mmHg(1 mmHg=1.013×10^5 Pa) as compared to approximately (4%—8%)/100 mmHg of native vessels[4,24]. In contrast to commercialized Dacron and e-PTFE, polyurethane(PU) is composed of soft and hard segments held together by hydrogen-bond interactions and van der Waal forces, displaying tunable flexibility and mechanical properties. Therefore, the vascular graft compliance based on PU can be optimized by varying compositions and components of the reactants or adjusting the blending ratio with others, depending on the target host vessels. By changing a triblock copolymer diol as the soft segments, such as poly(δ-valerolactone-co-ε-caprolactone)-b-poly(ethylene glycol)-b-poly(δ-valerolactone-co-ε-caprolactone)(PVCL-PEG-PVCL)[30] or polycaprolactone-b-polytetrahydrofuran-b-polycaprolactone(PCTC)[31], biodegradable PU with a low modulus and high flexibility has been successfully prepared. The dynamic compliance of the tri-layered silk fibroin/PU vascular graft with the formulation of 50% silk fibroin-50% PU is (4.8%±1.0%)/100 mmHg, which is comparable to that of a cephalic vein[(4.3%±0.7%)/100 mmHg] and lower than that of radial artery[(7.8%±0.4%)/100 mmHg], but it tends to increase with the increasing of PU ratio[32].

Owing to the presence of abundant ester bonds, common biodegradable polyesters, such as polycaprolactone(PCL), poly(*L*-lactide)(PLLA), polyglycolide(PGA) and poly(*L*-lactic-co-glycolide)(PLGA) are relatively stiff and have limited flexibility. Generally, these polyesters are used in conjunction with PU or other elastic materials to obtain appropriate mechanical strength and flexibility for vascular replacement[20,24,27,33,34]. For example, a tri-layered vascular graft composed of a PCL inner layer, a PLGA middle layer and a PU outer layer was constructed, taking advantage of the high

Table 1 Summary of compliance of electrospun SDVGs[a]

Graft composition	Mass ratio, *m*/*m*	Thickness/μm	Compliance/ (%•100 mmHg^{-1})	Pressure range tested/mmHg	Native compliance referenced (%•100 mmHg^{-1})	Other information	Ref.
Collagen (Bilayer)		500±140	2.66±0.51 3.06±0.96 2.63±0.45	50—90 80—120 110—150	HA 4.7—17.0 HSV 0.7—3.7	Circular knitting and electrospinning; Collagen type I	[26]
ELR+PCL sheath		30±6(PCL)	4.11	Dynamic	HA 4.5—6.2	Salt leaching/gas foaming and electrospinning	[27]
PCL/fibrin	20/80	300	11.5±1.83(1m); 24.2±3.67(3m); 58.4±2.51(9m)	Dynamic (*in situ*)	—[b]	PCL(M_n=80000)	[34]
SF(i); SF/PU (1/1; m); SF(o)		335±68	4.8±1.0	Dynamic 80—120	CV 4.3±0.7 RA 7.8±0.4	SF(extracted from *B. mori* silk cocoons)	[32]
PCU		84±12	3.19±0.75(0m); 3.72±0.95(6m); 5.0±1.62(12m)	80—120	—	Synthesized from poly(hexamethylene carbonate): HDI: bis(3-hydroxypropyl) carbonate=1:2:1	[35]
PEUU@PEG-Hep		400	8	Dynamic 80—120	HMA 7.8±0.6 HSV 5.0±0.6	Synthesized from PCL diol: HDI:BD=1:2:1; M_n=5.4×10^4	[25]
PET/PCL	3/1 1/1 1/3	424±27 413±36 395±8	2.67±0.54 4.34±1.09 4.19±0.78	80—120	SV 4.4±0.8	PET(M_W=24000); PCL(M_n=80000)	[28]
PET/PU/PCL	50/25/25 25/50/25 25/25/50 33/33/33	452±23 465±20 478±58 390±24	6.45±0.75 4.05±0.21 4.55±0.29 7.09±0.49	Static	—	PCL(M_n=80000); PET(M_n=18000)	[33]
PU/PCL	9/1	145	4.30±0.24 3.60±0.18 3.18±0.10	50—90 80—120 110—150	HCA 7.25	PCL(M_n=80000)	[24]
PCL(i); PLGA(m); PU(o)		197±18(i) 314±28(m) 88±7(o)	2.50±1.60	Static	CA 4.5—6.2 SV 0.7—1.5	PCL(M_n=100000); PLGA (LA:GA=75:25); Electrospinning(i); Freeze-drying(m); Electrospinning(o)	[20]

a. The letters of 'i, m, o' in parenthesis stand for the inner, middle and outer layers, respectively. The HA, HSV, CV, RA, HMA stand for human artery, human saphenous vein, cephalic vein, radial artery and human mammary artery, respectively. *b*. It was not mentioned in the corresponding paper.

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tensile strength and biocompatibility of PCL, porous microarchitecture of PLGA layer for SMCs penetration and mechanical stability and elasticity of PU fibers. Neat PCL layer and PU fibers have also been prepared and possessed compliance of (1.5%±0.7%)/100 mmHg and (5.4%±1.3%)/100 mmHg, respectively, while the compliance value of the tri-layered tubular graft is (2.5%±1.6%)/100 mmHg[20]. Another work based on PET/PU/PCL triad-hybrid SDVGs with different composite ratios also presented a similar trend in the compliance property[33]. Recently, poly(ester urethane)urea (PEUU) has been investigated as a novel synthetic polymer in preparation of artificial SDVGs, which showed a low-initial-modulus and matched compliance characters[25].

The inferior mechanical properties of natural polymers are the most limitations in the TEVG application, but a bi-layered collagen vascular graft with improved mechanical properties was obtained by synergistically employing circular knitting and electrospinning approaches, and its dynamic radical compliance in the pressure range of 80—120 mmHg could reach (3.06%±0.96%)/100 mmHg[26]. In addition to material properties, the compliance of vascular grafts also depends on their dimensional structure and composition including graft diameter, wall thickness, fiber structure and so on. For example, the higher of wall thickness, the lower the compliance. In terms of multilayer electrospun vascular grafts, the compliance could be enhanced by varying the thickness of each layer or increasing the elastic component proportion[20,22,24].

The initial compliance is just a manifestation of the mechanical property of a vascular graft itself. After it was implanted *in vivo*, the graft compliance may be changed with the material degradation and tissue regeneration. In other words, *in situ* remodeling of the implanted graft may lead to the changes in mechanical properties. For example, Zhao *et al*.[34] have systematically studied the *in vivo* performance of PCL/fibrin vascular grafts in the rat abdominal aorta model. The graft compliance was tested *in situ* by an ultra-high resolution ultrasound instrument, and it showed successively increasement after implantation for 1, 3 and 9 months[34]. Owing to bulk degradation and concomitant tissue regeneration, the PCU vascular graft becomes structural thinning, resulting in significantly improved compliance after 12 months of implantation[35]. Therefore, it is important to balance the degradation rate and tissue regeneration in order to obtain suitable compliance during the entire vascular reconstruction process. It is not enough that the intrinsic compliance of the vascular grafts matches their target natural blood vessels, and further *in vivo* compliance testing is necessary.

It is well established that the mechanical integrity and flexibility of vessels are conferred by elastin and collagen components[3]. By modifying with palmitic acid, two kinds of poly(glycerol sebacate)(PGS) derivatives(9-PPGS and 16-PPGS) with reduced degradation rates were successfully prepared and implanted in a rat common carotid artery. After 12 weeks, there was no significant difference in collagen content among the regenerated 9-PPGS, 16-PPGS and PGS graft, but 16-PPGS graft had a higher elastin content that was closest to that of the host artery, resulting in suitable compliance and highest patency, and also implying an important role of elastin in vascular mechanics and stability[36].

Elastin is mainly located in tunica media and tunica adventitia, while collagen shows a high relative content in tunica adventitia(Fig.1), and elastin is more flexible than collagen. As a result, elastin fibers in tunica media will be stretched preferentially under blood pulsation pressure, leading to that the degree of radial deformation does not obey Hook's law in response to luminal pressure change, that is, a non-linear and anisotropic character in natural arterial compliance[18,24]. Also, elastin is responsible for elasticity and compliance of blood vessels, and collagen mainly provides mechanical support[37]. It was demonstrated that elastin-like graft could recapitulate the anisotropic behavior and its dynamic compliance was close to that of native arteries in the whole range of pressures tested[27]. In addition, the compliance of synthetic PU/PCL vascular grafts at different wall thicknesses was tested within the range of normal human physiological blood pressure range(80—120 mmHg). With the increase of pressure, the compliance value decreased, also displaying a non-linear behavior[24].

It can be seen that numerous synthetic vascular grafts could meet the initial compliance requirement through optimization, but how to maintain the graft compliance similar to that of natural vessels during the whole tissue remodeling process is more important.

4 Electrospun SDVGs

The appropriate mechanical properties are the key to achieve long-patency for SDVGs. It is well recognized that mechanical stimulation can promote the contractile phenotype of SMCs and ECM deposition[38,39]. Besides, the mechanical properties of vascular grafts have been demonstrated to have a significant impact on the polarization of macrophage phenotype, which may influence the remodeling process[40]. Generally, vascular grafts should be easy to handle and suture, and resistant to kinking and deformation. The most influencing important factor on the mechanical properties is the material nature. Up to now, there are numerous natural and synthetic polymers or their hybrids that have been widely investigated to construct artificial vascular grafts by electrospinning technique, and here some of them are summarized(Table 2).

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Table 2 Summary of mechanical properties of electrospun SDVGs(1 mmHg=1.013×10^5 Pa)*

Graft composition	Mass ratio *m*/*m*	Thickness/μm	Fiber diameter/nm	Young's modulus/ MPa	Tensile strength/ MPa	Elongation (%)	Burst pressure (mmHg)	Other information	Ref.
SF		486±6	2750±61	10.52±0.90	1.22±0.03	—	1441±41	SF(extracted from *B. mori* silk cocoons)	[41]
Tropoelastin		430±65	580±94	0.15±0.05(R) 0.15±0.03(L)	0.34±0.14 0.38±0.05	79±6 75±5	485±25	Disuccinimidyl suberate as cross-linker	[42]
PLCL/Collagen/ Chitosan	75/20/5	*ca*. 300	409±120	10.30±1.10	16.9±2.9	112±11	3365	PLCL(LA:CL=50:50); Collagen(*ca*.10^5 Da); Chitosan(*ca*.10^6 Da); Glu as cross-linker	[43]
PU/Gelatin/ bivalirudin	2/10/1	120—130	1810±310	0.84±0.20	15.60±0.80	—	14896±304	PU(Tecoflex-80A); Glu as cross-linker	[44]
PU/SF	1/1	164±22	316±121	10.60±1.52	3.35±0.58	127±31	—	PU(Carbothane®Aromatic, AC-4075A); SF(from *B. mori* silk cocoons)	[45]
TPU/SF	1/1	—	1310±620	1.19±0.31	1.61±0.37	166±27	—	SF(from *B. mori* silk cocoons); TPU(Tecoflex SG-80 A)	[46]
PCL-Tropoelastin (Bilayer)		240±46	1800—2350	8.73—13.10(L) 6.43—7.13(R)	2.59—3.50 1.20—2.00	250—381 50—100	—	PCL(M_w=80,000)	[47]
PCL/Collagen(i); PCL/Silica(o)	4/1 4/1	150(i) 300(o)	358±92 239±86	10—20	2—4	69—130	—	PCL(M_n=80,000);	[48]
PTMC/Gelatin	2/3	232±40	400—800	0.40±0.045	0.050±0.001	60±7.5	—	PTMC(M_n=10^5); Gelatin(M_n=5×10^4—10^5)	[49]
PEUU@PEG-Hep		400	400—500	3	7	400	8000	PCL diol:HDI:BD=1:2:1; M_n=5.4×10^4	[25]
PCL-RGD		400—500	730±290	6.43±0.82	4.32±0.48	115±32	—	PCL(M_n=80000)	[50]
PCL		400—500	5590±670	21.00±1.39	8.72±0.84	639±24	—	PCL(M_n=80000)	[51]
PLCL (Trilayer)		18(i) 14(m) 21(o)	1578±298 2473±598 2092±384		30.97±3.95	190±19	—	PLCL(LA:CL=50:50; M_n=450000)	[52]
PEUU-RGD		—	1132	3.8±0.1	8.2±0.3	194±14		(PCL and serinol): HDI:BD=1:2:1	[53]
PCL/PU	100/0 90/10 75/25 50/50 25/75 10/90 0/100	500±32	433±80 411±78 420±75 428±89 436±84 440±86 470±95	4.8±0.11 9.7±0.59 7.2±1.34 5.3±0.45 2.0±0.17 1.7±0.11 1.2±0.39	2.7±0.4 4.7±0.34 3.4±0.6 4.8±0.62 0.34±2.2 4.4±1.90 0.54±3.2	142±17 128±10 112±29 268±22 203±35 309±12 71±321	2560±121 2353±64 2215±73 2017±72 1666±279 1333±36 1156±149	PCL(M_n=80000); PU(APILON 6505)	[54]
PET/PU/PCL	50/25/25 25/50/25 25/25/50 33/33/33	452±23 465±20 478±58 390±24	388±88 547±89 515±97 437±121	16.3±0.45 24.1±2.6 13.0±0.42 39.2±1.98	3.93±0.06 3.88±0.36 3.49±0.56 5.27±0.83	278±36 277±13 140±30 389±99	2332±206 1689±143 2041±105 2167±850	PCL(M_n=80000); PET(M_n=18000)	[33]
PLLA/PCL	20/1 10/1	150	926±215 982±175	67.0±8.7 33.0±7.0	1.9±0.1 1.0±0.1	—	—	PLLA(M_W=100000); PCL(M_W=2000)	[55]
PU/PCL	9/1		523±93	4.8 ±1.3(R) 13.8±4.4(L)	7.4±2.5		2031	PCL(M_n=80000)	[24]
PET/PCL	3/1 1/1 1/3	424±27 413±36 395±8	450±118 494±130 433±114	24.13±2.89 11.41±4.85 8.82±0.77	3.62±0.81 4.66±1.93 9.47±0.7	429±249 374±169 205±51	2953±45 3157±1865 6378±2159	PET(M_W=24000); PCL(M_W=80000)	[28]
PLLA/PCL(i); PU(m); PLLA/PCL(o)	3/7 3/7	15±1(i) 127±2(m) 19±1(o)	—	—	63.40(L) 52.34(R)	266 319	—	PCL(M_W=80000); PLLA(M_W=55000)	[56]
PCL(i); PLGA(m); PU(o)		197±18(i) 314±28(m) 88±7(o)	—	—	8.83±1.20(L) 5.78±1.42(R)	121±38 142±46	2737±583	PCL(M_n=100000); PLGA(LA:GA=75:25)	[20]

* The letters of 'i, m, o' in parenthesis stand for the inner, middle and outer layers, respectively. R and L represent radial and longitudinal mechanical results. PTMC is the polytrimethylene carbonate. Glu, HDI and BD are the short names of glutaraldehyde, hexamethylene diisocyanate and 1,4-butanediamine, respectively.

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4.1 Natural Polymers

Common natural biodegradable polymers including silk fibroin, collagen, elastin, gelatin, chitosan and hyaluronic acid have abundant cell-binding sites with excellent biocompatibility, but the insufficient mechanical strength limits their applications.

Silk fibroin(SF) has a crystalline structure and an amorphous region, and the latter consists of hydrophobic $(GAGAGS)_n$ amino acid sequences, which are responsible for providing the mechanical properties of SF[57]. Alessandrino *et al*.[58] developed a tri-layered SDVG from SF with an intermediate layer and electrospun inner and outer layers. The burst pressure of this SF graft could achieve (2308±88) mmHg, which was sufficient to withstand the physiological blood pressure, but the poor bonding among the three layers leads to discontinuity in mechanical properties, seriously affecting the graft performance.

Collagen is a main structural component of mammalian vascular ECM with biocompatibility, biodegradability and bioactivity, but collagen can trigger platelet adhesion and activation due to its inherent thrombogenicity[4]. It is necessary for collagen-based TEVGs to be incorporated with antithrombogenic materials. An electrospun collagen vascular graft with improved biological properties was constructed by modifying hyaluronic acid oligosaccharides. The glycosylated collagen graft could effectively promote the endothelialization, but the mechanical results were not mentioned in this study[59].

Elastin is also one of the most stable proteins that provides the elasticity of blood vessels, enabling the vessel to prevent permanent deformation under pulsatile cycles. Moreover, elastin also plays an important role in regulating various cellular functions, displaying anti-thrombogenic and anti-inflammatory properties. Nevertheless, natural elastin is highly crosslinked and extremely insoluble with low operability[60]. Hence, many elastin-derived materials, such as soluble recombinant human tropoelastin(rTE) and elastin-like recombinamers are commonly integrated into biomimetic vascular grafts[61]. The rTE vascular graft that was prepared *via* electrospinning and followed by cross-linking of disuccinimidyl suberate, showed an ultimate tensile strength of (0.36±0.05) MPa and a burst pressure of (485±25) mmHg, demonstrating insufficient mechanical properties of rTE[42].

Gelatin, chitosan and hyaluronic acid are the most common non-ECM derived natural materials that used in tissue regeneration. Gelatin contains many integrin-binding sites that promote cell adhesion. Chitosan has remarkable antithrombotic and antibacterial performance as well as modifiable amine group. Hyaluronic acid is a hydrophilic and non-adhesive natural polymer with a relatively rapid degradation rate. The three natural polymers are rarely used alone as vascular graft preparation due to their inferior mechanical properties and fast degradation rate[2,4].

4.2 Synthetic Polymers

Biodegradable synthetic polymer materials have gained particular attention in preparing SDVGs due to their wide availability, easy processability, stable and definite chemical structure, controllable degradation rate and mechanical properties.

Because of the structural integrity, biocompatibility and biodegradability, PCL is considered as the most important synthetic materials in the field of vascular graft engineering. Kong *et al*.[50,51,56,62] have conducted a series of studies focused on PCL electrospun graft for vascular regeneration. The effect of fiber diameter, arrangement and other factors on the vascular graft performance, such as mechanical properties and macrophage phenotype induction have been systematically investigated[51]. For example, both a thicker-fiber graft and a thinner-fiber graft based on PCL were prepared by electrospinning, with the fiber diameter of (5.59±0.67) and (0.69±0.54) μm, respectively. The mechanical results showed that there was a significant increase in elongation of thicker-fiber graft as compared with that of thinner-fiber one, and Young's modulus had a slight increase, but the tensile strength decreased. Besides, the thicker-fiber graft had a larger pore size and porosity, which was more favorable for cell infiltration and migration. Electrospun PCL vascular grafts with thicker-fibers could also enhance the vascular regeneration and remodeling process by mediating macrophage polarization into the M2 phenotype. Moreover, the long-term performance of the macro-porous electrospun PCL vascular graft was further investigated *in vivo*. One year after implantation, no signs of aneurysm, stenosis or calcification were observed, and new vessels were regenerated on the luminal surfaces[62]. It could be also shown that arginine-glycine-aspartate(RGD)-modified PCL vascular graft showed a decreased Young's modulus and an elongation, but an improved tensile strength[50].

Poly(*L*-lactide-co-*ε*-caprolactone)(PLCL) is a biodegradable synthetic copolymer with biocompatibility and appropriate mechanical properties, and the biodegradation rate and mechanical strength can be tuned by varying the molar ratio of *L*-lactide and *ε*-caprolactone in the copolymer[63]. Kong *et al*.[39] prepared a vascular graft based on PLCL microfibers with a circumferentially aligned structure. The tensile strength and elongation were much higher than those of PCL graft, exhibiting a remarkable resistance to deformation. In addition, during vascular remodeling, the number of M2

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type macrophages was found to be much higher than that of M1 type macrophages, indicating the mechanical properties of the graft have a promoting effect on the polarization of the macrophages phenotype. A tri-layered PLCL vascular graft with three different fiber structures on a single electrospun membrane was developed by a new electrospinning technique. The graft showed a suitable tensile strength for vascular reconstruction[49]. Poly(ethylene glycol)-b-poly(*L*-lactide-co-*ε*-caprolactone)(PELCL) is a hydrophilic, biodegradable and flexible copolymer that was synthesized in our group for preparing SDVGs[21,64—67]. Biodegradable PLLA, PGA and their copolymer PLGA are also commonly used in vascular engineering, but it is noted that the acidic degradation products could possibly cause local inflammation[4].

Compared with traditional biodegradable aliphatic polyester, amino acid-based polymers including poly(ester amide)(PEA), poly(ester urea)(PEU), PEUU and so on, have adjustable hydrophilicity/hydrophobicity, anionic/cationic charge, degradation rate and physicochemical properties, and become promising materials for vascular tissue engineering[68—70]. Mo *et al*.[25] prepared an electrospun vascular graft from low-initial modulus PEUU elastomers followed by functionalized with poly(ethylene glycol)(PEG) and heparin. This PEUU@PEG-Hep graft has mechanical properties similar to that of native blood vessels. *In vivo* evaluation indicated that the graft has good biocompatibility. The PEUU modified with acrylamide-terminated glycine-arginine-glycine-aspartic peptide(Ac-GRGD) was also studied, and the results showed that Ac-GRGD peptide immobilized on PEUU nanofiber could be used as a physical cross-linking agent to form a rigid network, which would be beneficial to improving the mechanical properties[53].

In addition, many artificial vascular grafts are prepared from two or more synthetic polymers in order to get superior performance. PCL is a semi-crystalline and relatively stiff polymer with limited flexibility. PU is an elastic and flexible material. As a result, there are many composite PCL/PU vascular grafts prepared by blending PCL with PU in different proportions[24,71]. It was demonstrated that as PCL content increased, the tensile strength first increased and then decreased due to the varied internal bonds and connections, while the Young's modulus had a decreasing trend with the increased addition of PU[54].

The complexity of the vascular wall microarchitecture promoted the development of multi-layer electrospun TEVGs. To better mimic the structure and function of the natural vessels, a three-layered vascular graft was constructed with an inner PLA/PCL layer for rapid endothelialization, middle PU/PCL layer for providing mechanical properties and the outer circumferentially aligned PLA/PCL layer for guiding SMCs[56]. Another bio-inspired tri-layered vascular graft has also been developed from PCL inner layer, porous PLGA middle layer and PU outer layer for endothelialization, SMCs penetration and superior mechanical properties, respectively, and the three layers were bonded by thermal cross-linking to keep the entire tubular structure[20].

4.3 Hybrid Materials

Most synthetic polymers are lack of cell-binding sites owing to their inherent hydrophobicity and limited bioactivity, but they usually have appropriate and tunable mechanical properties. While natural polymers have insufficient mechanical strengths, but excellent biocompatibility and high cell affinity. Therefore, hybrid materials that combined synthetic and natural polymers can compensate for each other, gaining more and more attention.

Electrospun SDVGs made from PLCL/collagen/chitosan in different proportions were prepared and studied. It was shown that when the PLCL/collagen/chitosan ratio was 75:20:5, the hybrid graft had a tensile strength of 16.9 MPa, an elongation of 112%, a Young's modulus of 10.3 MPa and a burst pressure higher than 3365 mmHg[43]. A similar study was found that the optimal mechanical properties were obtained when the mass percentage of PLLA/collagen/chitosan was 10:1:0.5, with a scaffold thickness of (220±30) μm, a tensile strength of 2.13 MPa and a rupture burst pressure of 2593 mmHg[72]. It is evident that hybrid scaffolds with appropriate ratios have potential application in vascular tissue engineering. Gostev *et al*.[46] studied the performance of PU/gelatin SDVG, which had a tensile strength of (15.6±0.8) MPa and a burst pressure of (14896±304) mmHg, exceeding those of natural arteries for 7—8 times[44]. Besides, many other hybrid systems, such as PU/SF, PCL/gelatin have also been studied[45,48].

In addition, to hybridize synthetic polymers with natural polymers, bioactive molecules can also be incorporated to improve the performance of vascular grafts. For instance, heparin has a famous anti-clotting ability, thus playing an important role in anti-thrombosis and improving the patency in SDVGs[25]. Gallic acid is known for its antioxidant effect[73]. Bioactive peptides, such as YIGSR(Tyr-Lle-Gly-Ser-Arg), RGD(Arg-Gly-Asp) and REDV(Arg-Glu-Asp-Val) can effectively promote cell adhesion and proliferation, thus improving the endothelialization rate[74]. Nitric oxide(NO) has good antioxidant and antibacterial properties, and it can also promote the production of vascular endothelial growth factor from ECs, so endogenous NO donor, such as *S*-nitrosoglutathione can be applied in vascular tissue engineering[75]. Our results demonstrated that microRNA-126 and microRNA-145 in the fibrous inner and outer or middle layers could modulate ECs and SMCs, respectively, promoting normal ECM formation[21,64,65].

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5 Summary and Outlook

Electrospinning technique provides an effective way to prepare vascular grafts with various diameters, thicknesses, material compositions and so on. This review described recent advances on biomechanical properties of electrospun SDVGs based on natural, synthetic polymers and hybrid materials, in which graft compliance is a necessary consideration. It is more important how to keep long-term mechanical integrity and adequate compliance for the SDVGs that developed from biodegradable polymers during the post-implantation by balancing the graft degradation and ECM remodeling process. Here, *in vivo* and long-term compliance evaluation methodology needs further improvement to ensure consistency among the various vascular grafts.

Generally, ester groups provide biodegradability, while strong intermolecular hydrogen bonding interactions exist between amide groups, endowing thermal and mechanical stability. It is assumed that the polymers containing both ester and amide moieties, such as PEUU and PEA have adjustable biodegradability, mechanical properties and flexibility, showing great potential for the development of mechanically long-lasting SDVGs. However, due to that synthetic polymers inherently lack cell binding sites, hybrid materials consisting of bioactive substances, such as elastin-like recombinamers or growth factors and mechanically supporting synthetic polymers may be a candidate for the preparation of biomimetic vascular graft. Indeed, progresses in various polymers and their copolymers or blends with optimal mechanical properties have been made in the last decade, but the biological and mechanical complexity in natural blood vessels remain the driving force for further developing clinically viable SDVGs with novel structure and biomaterials.

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Conflicts of Interest

The authors declare no conflicts of interest.

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