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REVIEW PAPER

Emerging Nanofibrous Polycaprolactone Vascular Grafts in Small and Large Animal Models: in vivo and in vitro Analyses

Farnaz Sadat Fattahi

Department of Textile Engineering, Isfahan University of Technology Isfahan, Iran

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ABSTRACT

Over the last decade, engineering the polymeric vascular grafts has been extensively studied. Various types of polymers have been used in this field such as synthetic polymers, natural polymers, and polymer blends. Synthetic polymers, such as Polycaprolactone (PCL), have displayed improved mechanical specifications compared to natural polymers. Polycaprolactone is biodegradable polyester that can be blended with another synthetic polymer or a natural polymer to yield even greater enhanced mechanical properties. The mechanical properties of artificial blood vessels play an important role while the vessels are attached to the native vessels in the animal body. Furthermore, the artificial blood vessels must be adequately strong to resist frequent blood circulation and related pressure. The most significant advantage of engineered vascular tissue implants is their ability to grow, remodel, rebuild, and respond to injury. This article serves as a review of the fabrication, specifications, and benefits of various kinds of polycaprolactone grafts. The primary focus is on the *in vivo* implantation of nanofibrous ones for vascular regeneration in large and small animals. First, the subject of the study was thoroughly investigated, then the search was conducted with a combination of index and text terms. Finally, a number of articles, scientific books, patents, manuals, and university theses were selected and studied, and the obtained data were analyzed, categorized, and edited. PCL polymer has been the most sought-after biodegradable polymer for use as a vascular tissue engineering material.

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INTRODUCTION

Polycaprolactone (PCL)

Polycaprolactone is a biodegradable polyester having a low melting point of about 60 °C and a glass transition temperature of about −60 °C[1-3]. The most widespread public usage of PCL is in the manufacture of specialty polyurethanes (Table 1) [4-6].

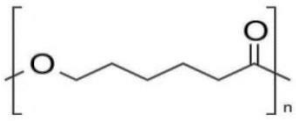
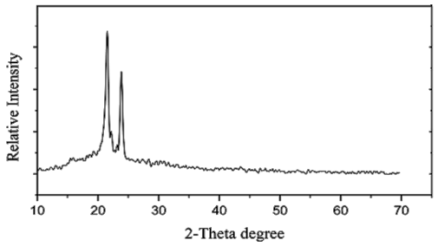
Vascular Tissue Engineering

Vascular tissue damages resulting from defects, accidents, wounds or other kinds of injuries poses a significant challenge to human health [10].

* Corresponding Author Email: *fattahi_farnaz@yahoo.com*

However, in current years, the use of tissue engineering methods has become increasingly important in advancing the field of cardio-vascular biology and improving patient care [11-15]. The objective of vascular tissue engineering is to produce neo-vessels and neo-organ tissue using autologous cells through a biodegradable polymer like *polycaprolactone* (PCL) as a scaffold [16-18]. Fabrication of scaffolds with improved mechanical properties and promising cellular compatibility is essential for many tissue engineering applications [8,19-20]. Favorable scaffolds can be prepared via reinforcement with nanoparticles and hydrogels [21-23].

Table 1: Specifications of Polycaprolactone [7-9].

Melting point	Density	Chemical Formula	Chemical Structure	XRD Pattern
60 °C (140 °F)	1.145 g/cm^3	$(C_6H_{10}O_2)_n$		

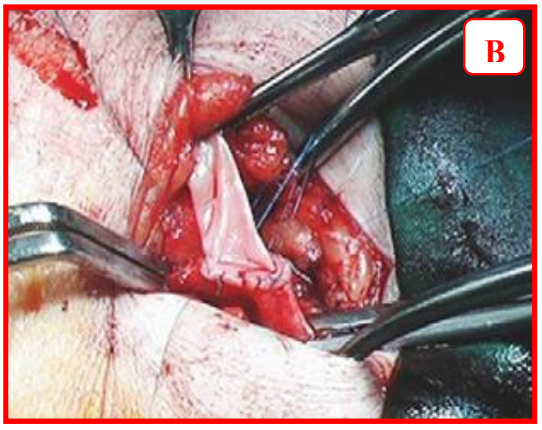


Fig. 1: in vivo implantation of vascular grafts : (A) Tissue engineered blood vessels; (B) Tissue engineered graft was implanted amongst the axillary vein and the humeral artery as an arterial venous shunt [11].

A proper vascular graft must reproduce the biomechanical specifications of blood vessels, as serving like a platform for cell attachment and proliferation [24-26]. It must exhibit nonthrombogenic, nonimmunogenic, biocompatible, and hemocompatible properties; biodegradability, suitable pore size, and elasticity are also important factors [27-29]. Therefore, this graft must aid the *in vivo* regeneration of a tissue-engineered vascular material after being implanted in a suitable location (Fig. 1)[30-32].

Application of PCL Nanofibrous Grafts in the Vascular Regeneration

PCL nano-fibrous scaffolds possess substantial surface area–to-volume ratios and porosity that resemble the structure of protein fibers in native ECM [33-35]. The versatilities of polymer components, fiber structures, and functionalization have made feasible the fabrication of PCL nanofibrous scaffolds with appropriate mechanical strength, transparency, and biological specifications for vascular tissue engineering [17, 36].

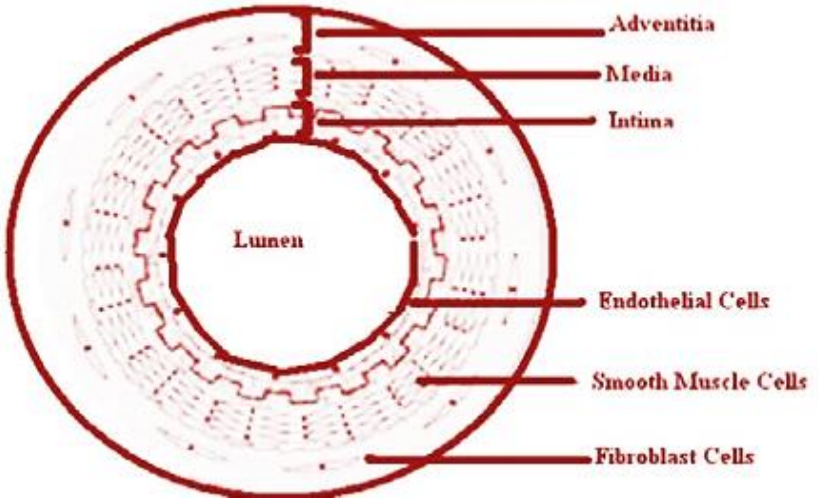


Fig. 2: Schematic illustration of an artery.

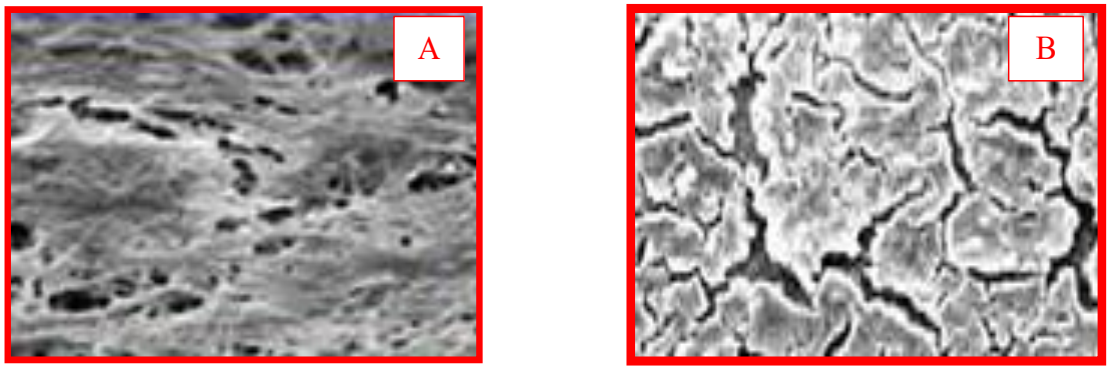


Fig. 3. SEM images of different cells cultured on the PCL scaffolds: A) HCEC-B4G12 cells cultured on SF-P(LLA-CL) nano-fibrous scaffold after 1 week; B) HCEC—B4G12 cells cultured on SF—P(LLA—CL) 50:50 nano—fibrous scaffolds after 1 week[15, 26].

Implantation of PCL Vascular Grafts

The fabrication of PCL nanofibrous scaffolds for cell cultivating serves as an important process for vascular tissue engineering method. Subsequently, implanting the PCL scaffold-cell matrix in an animal body is a main stage for vascular regeneration. One of the primary benefits of vascular engineered implants is that these tissues can grow, remodel, rebuild, and respond to damage [14, 37].

Implantation of PCL Scaffolds in the Blood Vessels

A blood vessel consists of three covers: intima (internal layer), media (central layer), and adventitia (external layer) (Fig. 2).

In the process of blood vessel tissue engineering, effective phases include cell sources, cell culture, scaffolds, vessel bio-reactors, and implantation. Non immunogenic autologous endothelium cells and smooth muscle cells (tunica media area) are isolated from patients. These cells are optimal choices for vessel tissue engineering [15, 38].

Table 2 presents the results of **PCL** vascular implantation surgery in the blood vessels (abdominal aorta, carotid artery) of various animals (Rat, Rabbit, Sheep, Canine).

SEM OBSERVATION

Scanning electron microscopy (SEM), an easily acquired and widely applied image acquisition and analysis method [52, 53], has rarely been used to study the structure of PCL scaffolds after cell culture process. **Fig. 3** exhibits the SEM images of cultured cells on PCL scaffolds for vascular regeneration.

Table 2 : *in vivo* assays of PCL vascular grafts in small and large animal models.

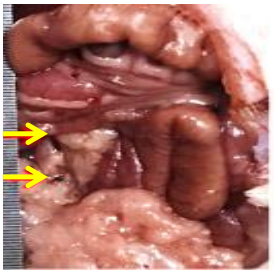
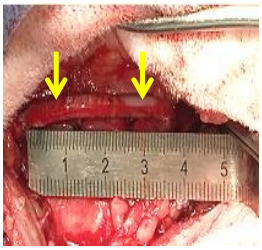
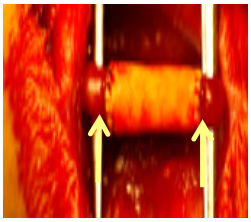
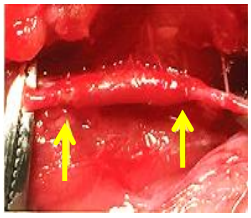
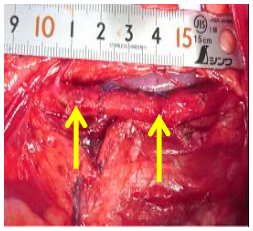
Chemical Composition	Synthesis method	Physical state		Implantation site	Macroscopic pictures after 3 monthss transplantation (The sites of implants are marked with yellow arrows)	Code of Ethics**	Ref.
		Physical shape	Porosity* (%)				
PCL + Fibrin	Electro-spinning	Tubular	75%	Rat's abdominal aorta		Protocol n^0 U-141039/ 110411	[39]
PCL	Electro-spinning	4 cm-long small diameter tube	60%	Sheep's carotid		Protocol n^0 S-20160181	[40]
PCL+ S-nitrosylated keratin	Electro-spinning	Small-diameter grafts	45%	Rabbit's carotid artery		Protocol n^0 I-150201-01089	[41]
Poly(glycerol sebacate)+ PCL	Electro-spinning	---	61%	Rat's common carotid arteries		Protocol n^0 Y-FC11041 01	[42]
Heparin modified PCL	Electro-spinning + "erosion-graft" strategy	Small diameter vascular graft	87%	Canine's abdominal aorta		Protocol n^0 B-86609EE C	[43]

Table 2 : *in vivo* assays of PCL vascular grafts in small and large animal models (Continued).

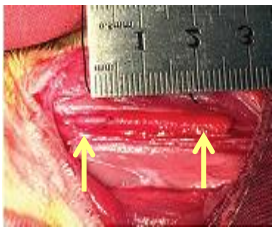
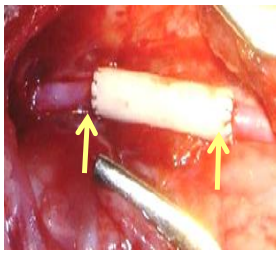
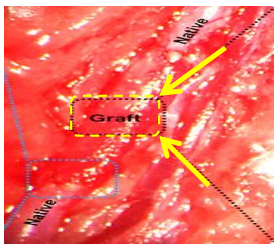
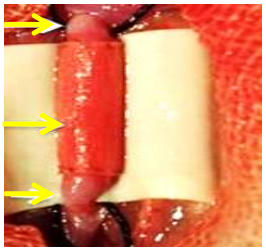
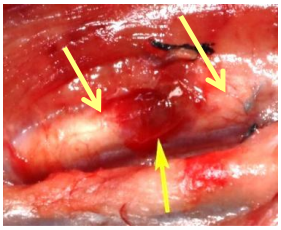
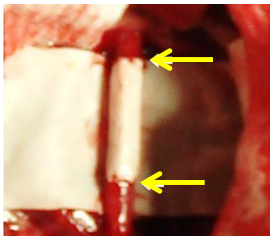
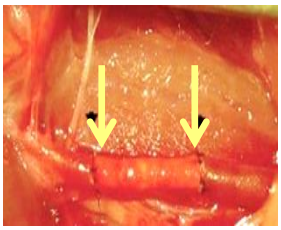
Chemical Composition	Synthesis method	Physical state		Implantation site	Macroscopic pictures after 3 monthss transplantation (The sites of implants are marked with yellow arrows)	Code of Ethics**	Ref.
		Physical shape	Porosity* (%)				
Heparin End-Capped PCL	Electro-spinning	Double-layer small diameter (ID <6 mm) GRAFT	95%	Rabbit's Carotid Artery		Protocol n^0 G-31400833	[44]
PCL + Elastin	Electro-spinning	---	71%	Rabbit's Carotid		Protocol n^0 K-FKT006	[11]
Gamma-Irradiated and Heparin-Immobilized Small-Diameter Polycaprolactone	custom-designed electrospinning	Small-diameter vascular graft	69%	Aged Rats		Protocol n^0 T-1903164	[45]
PCL	Electro-spinning	2.0 mm Inner diameter grafts	75%	Diabetic rat's abdominal aorta		Protocol n^0 S-81901874	[46]
PCL + Chitosan	Electro-spinning	Small Diameter	80%	Sheep's carotid artery		Protocol n^0 UH-54HL11981001	[47]

Table 2 : *in vivo* assays of PCL vascular grafts in small and large animal models (Continued).

Chemical Composition	Synthesis method	Physical state		Implantation site	Macroscopic pictures after 3 monthss transplantation (The sites of implants are marked with yellow arrows)	Code of Ethics**	Ref.
		Physical shape	Porosity* (%)				
Poly(ether urethane)+PCL	Electro-spinning	Bi-layered artificial blood vessels (d = 2.5 mm)	86%	Rabbit's carotid artery		Protocol n^0 Y-JSCX201 905Z	[2]
PCL	Electro-spinning	2 mm Inner diameter vascular prosthesis	75%	Rat's abdominal aorta		Protocol n^0 I-07250950	[48]
PCL + CAG peptide	Electro-spinning	---	65%	Rat's carotid		Protocol n^0 C-13JCYBJ C39300	[11]

CONCLUSIONS

In recent years, adapting tissue engineering methods is crucial for advancing the field of cardiovascular biology and providing better patient care. PCL polymer has drawn significant attention amongst the biodegradable polymers as an appropriate vascular tissue engineering material. The authors propose an alternative strategy, namely "Ultraviolet/O_3 Irradiation," on the PCL nanofibers (for increasing of cell adhesion on the scaffolds). This strategy is expected to improve the success of scaffold implantation.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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