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# Tissue Engineering for Cardiovascular Regeneration: Brief Review on Scaffold Fabrication

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**Abstract:**
Tissue engineering is the combination of engineering and fundamental sciences to develop an artificial organ that derived from the tissue human sources. It involves the construction of three main pillars include cell sources, scaffold materials and biological factors. These three important elements are necessary to be incorporated and integrated well, to construct a functional artificial tissue engineering product. Few applications can be associated with the expansion of tissue engineering where cardiovascular regeneration is one of the targets of tissue engineering. Among the fabrication techniques, electrospinning, three-dimensional printing, molding and decellularization, are four engineering methods that are commonly used in fabricating scaffolds for cardiovascular tissue engineering. One of the purposes of the emerging of cardiovascular tissue engineering is the limitation of current commercialized patches or membranes that often cause post-complications following the cardiovascular treatments. This review paper covering a brief introduction on the tissue engineering for cardiovascular regeneration, focusing on the scaffold fabrication.
**Keywords:** Tissue engineering; Cardiovascular; Scaffold; Fabrication technique

## 1. INTRODUCTION

Tissue engineering is defined as an interdisciplinary field that uses the concept of biology and engineering towards the development of biological replacements that restore, maintain, or improve damaged tissues. This concept has been defined by Langer and Vacanti in the early 1990s (1). The main approach of tissue engineering on the restoration of damaged tissues is based on the construction of substitutes with suitable combination of cells, appropriate matrices and biomolecules. Figure 1 illustrates the concept of tissue engineering.

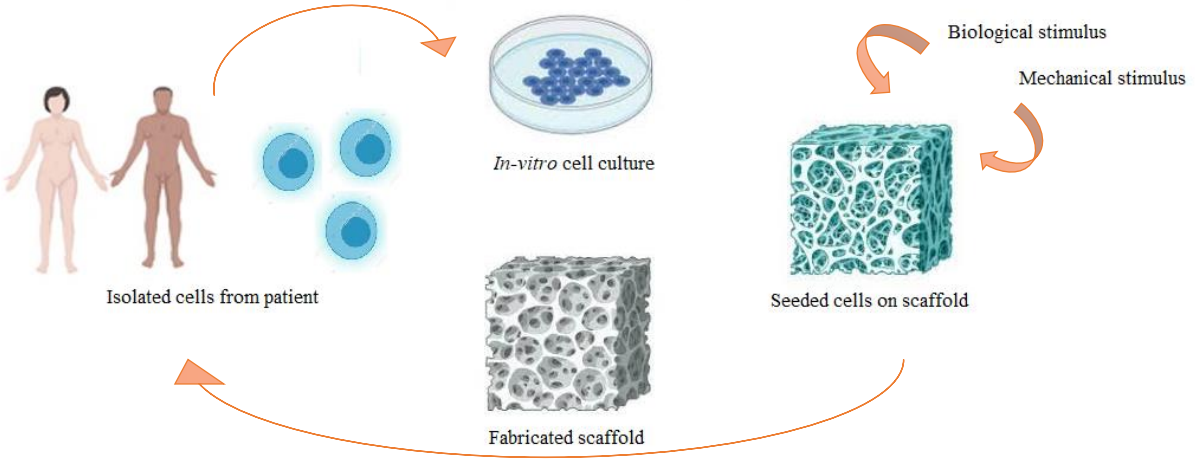


Figure 1. Concept of tissue engineering.



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The concept is associated with the use of living cells, seeded on natural or synthetic materials to create implantable grafts. The process involves the implantation of isolated cells or cell substitutes into the body, delivering of tissue-inducing substances such as growth factors and the placement of cells on different matrices with suitable physical stimulus (2). Understanding the structural and functional functions of each native tissue counterpart is essential for the successful development of tissue equivalents, as is carefully selecting the range of features required to accurately recapitulate the unique properties of native tissues for each application (3).

Cardiovascular tissue engineering is focused on the restoration of cardiac tissues. It is mainly intended on overcoming difficulties found in surgical treatment. The greatest limitations are to find compatible tissues and the complication of immune rejection. Moreover, some patients might depend on lifelong immunosuppressant drugs (4). Therefore, tissue engineering provides a better option as it involves vascular construction that overcomes the drawbacks mentioned earlier.

## 2. CONCEPT OF TISSUE ENGINEERING IN CARDIOVASCULAR APPLICATION

### 2.1 Sources of Cells

Cell sources are tissue specified cells that are seeded in the scaffold. The seeded cells will synthesize a mass of tissue matrix and form interconnected links with the native tissues. Tissue engineering faces challenges and considerations regarding choices of cells as there are various types of cells available for vascular construct. Choosing appropriate cell type is very crucial for an effective cardiac regeneration (4). There are several criteria on choosing optimal cell source such as easily harvestable cells, highly proliferative and immunogenic. Importantly, the cells need to have the right phenotype for easy cell differentiation into mature and functional cardiomyocytes (4,5).

Cardiac fibroblasts (CF) are one of the most abundant cells present in the cardiovascular system which is mainly associated with the formation and maintenance of connective tissues (6). These cells are available in large numbers and phenotypically plastic, they are particularly useful for cell therapy and tissue engineering. These cells play roles in pathogenic remodeling during hypertension, myocardial ischemia and heart failure and also take part in scar formation which make them crucial for tissue repair after the treatment of cardiovascular diseases.

Fibroblasts secrete cytokines that can trigger proliferation in cultured cardiomyocytes, and the structural proteins that are produced by them controls cardiomyocyte cell-cycle activity by regulating the stiffness of extracellular matrices (ECM), thus developing a flexible scaffold. These cells are able to produce induced-pluripotent stem cells and capable to induce cardiac progenitor cells, which then can differentiate into vascular cells. These cells generate growth factors and other signaling molecules that directly modulate cardiomyocyte function and also influence ECM formation and degradation (5,6).

### 2.2 Scaffold

Scaffolds are solid biomaterials with three-dimensional pores that are designed to provide structural support to facilitate cellular growth and tissue regeneration (7). Apart from the choice of cells, the selection of appropriate biomaterial is another crucial component for the development of successful scaffold. The criteria for a good biomaterial selection are the biomaterial should encourage cell-biomaterial interaction, cell adhesion and ECM deposition. It should also allow enough gas, nutrient and regulatory factors to be transported, to support cell survival, proliferation and differentiation. The biomaterials need to be biodegradable at a suitable degradation rate which associated with the type of native tissues at the point of interest. The materials mainly should possess the least amount of toxicity or inflammation upon grafting (2).

Tissue engineered 3D scaffolds can be made up of natural and synthetic materials. The best natural scaffold should be the ECM of the target tissue in its native state. It is difficult to mimic the complex structure and function of ECM completely, but many on-going studies have built scaffolds that are at least partially similar with the ECM properties (7). Natural biomaterials are constructed from the naturally available materials such as ECM from allograft and xenograft or other natural polymers such as proteins, polysaccharides, lipids and polynucleotides. While synthetic materials mainly consist of inorganic substance and organic synthetic polymers. Natural biomaterials are highly biocompatible, but lack of physical and mechanical stability compared to synthetic polymers. Therefore, it is necessary to understand the conditions specific for treatment to create suitable scaffolds.

### 2.3 Biological Factor

Another pillar for tissue engineering is the biological factor that will support tissue growth in the human physiological environment. It involves the saturation of growth factors, protein, mechanical stimulation, genetic phenotype and many others. The process to support seeded scaffolds into a complete cardiovascular tissue engineering product is often conducted in a biology reactor.

## 3. SCAFFOLD FABRICATION IN CARDIOVASCULAR TISSUE ENGINEERING

### 3.1 Fabrication Techniques

Fabrication techniques are used to build scaffold materials where these scaffolds should act as a template for regeneration of tissues and organs. Since 1980, a variety of fabrication techniques have been explored by many researchers to intricate polymers with desired characteristics and complex architecture for tissue engineering applications. The chemical and surface properties of the chosen biomaterial and intended area of scaffold application determine which fabrication method needs to be employed. Some of the approaches for creating vascular structures include electrospinning, molding, three-dimensional printing, sheet rolling and decellularization (8).

Each of these techniques has its own advantages and disadvantages depending on the processes where some methods involve the application of heat and pressure or the addition of organic solvents to dissolve the polymers in order to fabricate vascular membranes into desired properties. Therefore, the selection of appropriate technique is crucial for the success of vascular substitute implantation. The advantages and disadvantages of some fabrication approaches are described in Table 1.

Table 1. List of vascular membrane fabrication techniques (9,10).

| Fabrication technique | Description | Advantages | Disadvantages |
|---|---|---|---|
| Electrospinning | High voltage is applied to a polymer solution to form a spinning fibre jet. | High surface-area-to-pore-volume ratio, nanofibrous structure mimics native ECM, incorporation of bioactive materials. | Low mechanical stability. |
| 3D printing | A sequential layer by layer deposition of material commanded by a computer design. | Cost effective, automatic process with predesigned structure. | Creating microvessels is difficult due to low resolution, low cell viability due to shear damage from ink extrusion. |
| Decellularization | Extraction of ECM scaffold after removal of cellular components by chemical or physical agents. | Preserve native architecture of native ECM, similar biomechanical properties of blood vessel. | Potential immune response, long production time. |
| Molding | Casting a polymer solution in a mold with desired shape. | Large range of shape possible, simple device setup. | Use of toxic solvent. |

### 3.2 Commercialized Vascular Membrane

Polymer synthetic vascular membranes are the option to treat cardiovascular diseases since they have been commercially available since 1970s. There are many characteristics of scaffold need to be considered to make it as a successful graft. Some of the properties are strength, viscoelasticity, biocompatibility, blood compatibility and biostability (11). The materials used for cardiovascular graft should be biostable to provide excellent mechanical strength for long term implantation. Expanded polytetrafluoroethylene (e-PTFE) and (PET) biostable prostheses are the only clinically accepted solution, alternate to autologous grafts for revascularization procedures (12).

Polytetrafluoroethylene is a linear thermoplastic polymer which is fully fluorinated by the polymerization process of tetrafluoroethylene (13). Polytetrafluoroethylenes are inert fluorocarbons, crystalline material and have high chemical and thermal stability. The chemical structure of PTFE is shown in Figure 2. It undergoes process such as extrusion and sintering to form e-PTFE which is more amorphous and porous than the original material. The node-fibril arrangement of e-PTFE is characterized by solid nodes connected by fine fibrils, with a typical graft's average internodal distance of 30 µm. Expanded PTFE is one of the most commonly used synthetic conduits in the clinical application of vascular grafting (14).

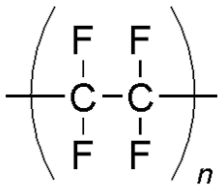


Figure 2. Chemical structure of e-PTFE.

Expanded PTFE is non-biodegradable and has an anti-thrombotic electronegative luminal surface. It has been used for lower-limb bypass grafts (7 - 9 mm) with outstanding performances (15). The electronegative surface of this material has minimized the reaction with blood components (16). Commercial e-PTFE-based prosthetic vascular grafts with an internal diameter greater than 6 mm are effective to be used for the application on large diameter (more than 6 mm) vessel such as arteriovenous access for hemodialysis or peripheral arterial bypass above the knee (17). Figure 3 shows the morphology image of e-PTFE membrane. Tzchori *et al*. (18) conducted a study on the patency of e-PTFE grafts. In that study, the control e-PTFE and the e-PTFE grafts seeded with endothelial cells were implanted on porcines by connecting its carotid arteries and jugular veins. The grafts seeded with autologous venous endothelial cells expressing fibulin-5 and vascular endothelial growth factor (VEGF). The results demonstrated that 6 months upon grafting, 80% of endothelial cells seeded graft were patent whereas only 29% of patency was observed on the control e-PTFE grafts.

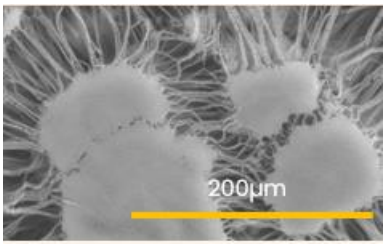

Figure 3. SEM image of e-PTFE membrane.

Polyethylene terephthalate (PET) also known a**s** Dacron® is a polyester fiber that is obtained by the condensation of ethylene glycol and terephthalic acid (19). Polyethylene terephthalates are manufactured industrially by transesterification process that involve the reaction of dimethyl terephthalate with ethylene glycol at 150°C to produce Dacron® and methanol. The volatile methanol constantly vaporized from the reaction mixture to complete the polymerization process (20). Figure 4 shows the molecular structure of Dacron®. This material has properties of high tensile strength and stretch resistance, good resistance to degradation by chemicals and to abrasion (21).

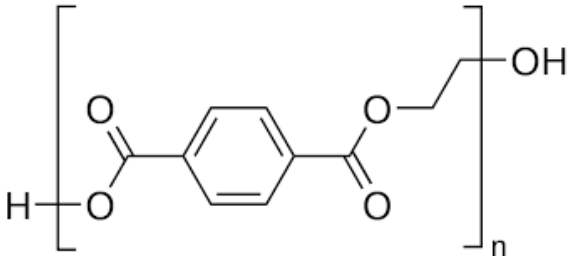

Figure 4. Chemical structure of PET.

Woven or knitted sheets of PET are commonly used in vascular surgery as vascular grafts because of its various factors such as strength, tensile ability, stability and low manufacturing cost. DeBakey created the first vascular PET prosthesis to repair a descending aortic aneurysm in 1950s. Since then, until 2005, the number of PET grafts implanted worldwide is estimated to be 1.2 million. Woven form of crimped PET (Figure 5) is the most commonly used type to substitute damaged blood vessels and to cover the heart valve swing ring and vascular stent (22). The woven form of PET grafts offers advantages for replacing large and medium diameter vessels in order to restore normal flow of blood and cardiac output due to its proven mechanical properties and micro-porous structure. However, owing to their susceptibility to bacterial infection and biofilm production, prosthetic valve endocarditis (PVE) or prosthetic vascular graft infection (PVGI) has become the leading cause in short-term patency of PET grafts. Thrombosis and inflammation are also some of the serious complications that lead to graft failure.

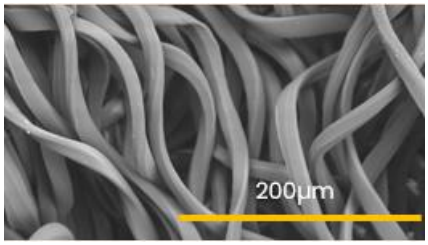

Figure 5. SEM image of PET membrane.

Differences in the mechanical properties between the prosthetic graft and the native aorta can have unwanted hemodynamic effects such as pressure and flow of the vasculature, causes excessive stresses at the suture lines which can lead to anastomotic aneurysms, intimal hyperplasia and eventually to graft failure (23). It is well-known that PET vascular replacements have relatively good mechanical characteristics in terms of their ability to withstand cyclic loads produced by pulsatile blood flow (24). However, compared to the native blood vessels, PET prosthetic materials are stiffer and less compliant. In the study conducted by Tremblay *et al*. (23), PET graft is approximately 25 times stiffer than the human ascending aortas. This reduced elasticity has minimized energy redistribution from systole to diastole when major portion of aortic tissues were replaced with PET grafts.

## 4. CONCLUSION

Tissue engineering involves the concept of cell sources, fabrication scaffold and biological factors, is among the standard practice in cardiovascular treatment and regeneration. There are few techniques have been used to fabricate scaffolds for cardiovascular implantation. Cardiovascular tissue engineering is a highlight method to replace the current treatment of vascular disease which involves the employment of vascular patches or membranes using commercialized e-PTFE and PET membranes. These commercialized patches or membranes have post-complication limitation that require the adoption of optional approach such as tissue engineering.

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**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

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