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Review

Nanofibrous bioengineered heart valve—Application in paediatric medicine

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ABSTRACT

Heart valves are currently under thorough investigation in tissue engineering (TE) research. Mechanical and biological heart valve prostheses which are recently used have several shortcomings. While allogenic and xenogenic biological prostheses are related to graft rejection, degeneration and thrombosis, resulting in a high rate of reoperation. Mechanical prostheses on the other hand are based on metallic, carbon, and polymeric components, and require continuous treatment with anticoagulant, which result in adverse reactions, e.g. endocarditis and thromboembolic complications. Therefore, there has been efforts to synthesize bioartificial heart valve using bioengineering. The resulting product must be durable with appropriate mechanical properties, biocompatible, and have the ability to grow. Diseased heart valves replacement by surgery is now common, this enhances quality of life and survival for many patients. The center of attraction of recent methods in regenerative medicine are based on the restoration of pathologically altered tissue architectures by cells transplantation in combination with supportive scaffolds, and growth factors. We propose that nanofiber scaffold for paediatric Tissue Engineered Heart Valve (TEHV) will meet most of these requirements, particularly those related to somatic growth, in addition, as the nanofiber scaffold is eroded and new valve is formed, the valve develops in the child until adulthood.

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1. Introduction

One of the major worldwide health challenges is cardiovascular diseases. An ample amount of these diseases represents heart valve failures [1–3]. Heart valves include the aortic, pulmonary, mitral and tricuspid valves. Surgical restoration of unhealthy heart valves by tissue and mechanical valve substitutes is now common, this enhances patients' quality of life and survival. However, the repairs of congenital deformities crave for a very small sized valve which are not available. In paediatric heart valve bioengineering applications, replaced heart valve growth is crucial to abscond the demand for reoperations as the patient grows [4–6].

There are several devices available for heart valves replacement, however, all available devices have significant shortcomings that leads to continue risk for mortality and morbidity. Presently, bioengineered heart valve prostheses can be categorized into two groups; biological and mechanical prostheses [7–9]. Mechanical prostheses are synthesized from pyrolytic carbon combined with polymeric and metallic components [10,11]. Although, valve replacement with these devices mainly ameliorate a heart patient condition as compared with untreated valvular heart disease, but, each type of valve replacement device has precise problems [12,13]. Mechanical valves replacement leads to graft rejection, and thus require a continuous use of anticoagulation drugs, which decreases (but does not annul) the risk of valve thrombosis and embolization of thrombotic material [14,15]. These types of valves are also much more prone to infection, and once established, infection is highly difficult to cure without replacing the prosthesis [16,17]. Thus, constructing bioartificial valves using TE methods is another way of improving the quality of the heart valve prostheses [18].

Tissue repair by TE remain one of the most likely techniques for the regeneration of tissues. TE has emerged as a great approach for the regeneration/repair of damaged tissue, with the possibility of circumventing all the limitations of allogenic and autologous tissue repair [19]. TE approaches involves the use of cells, scaffold and growth factors either alone, or in combination to repair, control, or improve tissue function. TE approaches proceed with the isolation of cells that are in good condition from a patient, followed by their proliferation *in vitro*. These proliferated cells are further seeded onto a three dimensional (3D) biodegradable scaffold which gives a structural support, and also accommodate bioactive molecules like growth factors. The scaffold steadily deteriorate with time to be restored by newly grown tissues emanating from the seeded cells [19].

A number of novel methods have been established for the synthesis of biomaterial-based 3D scaffolds. Currently, nanofiber-based scaffolding systems are being examined as scaffolds for TE. Synthesizing a scaffolds that will mimic the shape of damage tissue at the nanoscale level is one of the main challenges in TE. Presently, the three methods available for the fabrication of nanofibers include: phase separation, electrospinning, and self-assembly. Amongst these methods, electrospinning remains the most vastly studied method and has also been shown to give the most promising results in respect to TE applications. The abundance of wide range of synthetic and natural biomaterials has widened the scope of nanofibrous scaffolds development, particularly using the electrospinning method.

Nanofibers development has largely enhanced the scope of scaffolds for fabrication that can potentially meet this challenge [20]. Nanofibers are great material for biomedical applications for many reasons. Compared with other materials, the surface of nanofibers, promote cells adhesion, although, drugs and proteins are much larger. The 3D synthetic biodegradable scaffolds synthesized using nanofibers serve as a great framework for cell proliferation, differentiation, and adhesion. Hence, nanofibers, regardless of their fabrication method, have been used as a scaffolds for musculoskeletal TE (including skeletal muscle, cartilage, bone, and ligament), heart valve TE, skin TE, neural TE, vascular TE, and as a carriers for the controlled release of drugs, DNA, and proteins [20].

Pediatric patients account for a few portion of the heart valve replacements carried out, but a pediatric pulmonary valve replacement with the ability to grow is yet an unmet clinical need. Reimer et al. [21] reported for the first time a tubular heart valve fabricated from two decellularized, engineered tissue tubes connected with absorbable sutures, which met this need, in principle. Tissue engineered tubes were synthesized by allowing ovine dermal fibroblast cells to reconstitute a sacrificial fibrin gel with an aligned, cell-produced collagenous matrix, which was later decellularized. Previously, these engineered tubes became greatly recellularized following implantation into the sheep femoral artery. Thus, a tubular valve synthesized from these tubes may be responsive to recellularization and, ideally, somatic growth. They observed that valve efficiency was controlled under different trans-root pressure gradients and no damage in tissue observed after 2 million cycles of fatigue testing. To this end, this review outline the recent available ways for the fabrication of nanofibers scaffold and discusses their application in paediatric heart valves engineering [22].

2. The shape of the heart valve

The wall of the heart comprise of three layers: the external layer (epicardium), the middle layer (myocardium) and the inner layer (endocardium). The epicardium is the light, transparent outer layer of the wall and is comprised of delicate connective tissue. The myocardium, comprised of heart muscle tissue, makes up the main cardiac wall and is in charge of the heart pumping action. The endocardium is a thin layer of endothelium overlying a light layer of connective tissue. It supply a smooth lining for the heart chambers and encase the valves. The endocardium continues the endothelial lining of the large blood vessels attached to the heart. The heart valve (Fig. 1) comprises of three layers [23–25]: ventricularis, closest to the inflow surface and highly rich in radially aligned elastin fibers. Fibrosa, closest to the outflow layer, containing radially aligned, and macroscopically crimped, densely packed collagen. Spongiosa, located in the central part and rich in glycosaminoglycans (GAGs), and loosely packed collagen.

There are several cell types found in heart valves, these include valve interstitial cells (VIC), endothelial cells (EC), smooth muscle cells (SMC), fibroblasts, and nerve cells [27–29]. The four heart valves include (Fig. 2): The tricuspid valve (found between the right atrium and ventricle), the pulmonary valve (The pulmonary valve is located between the right ventricle (RV) and the

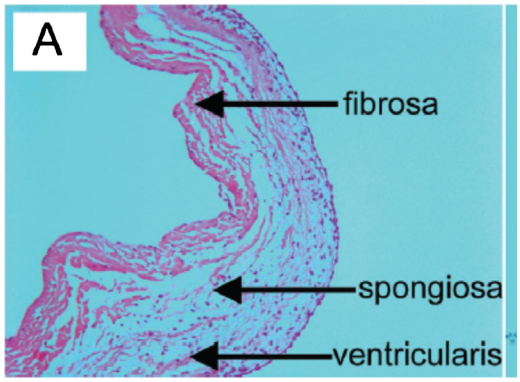

Fig. 1. The Three layers of heart valve (Tissue-Engineered Heart Valves) [26].

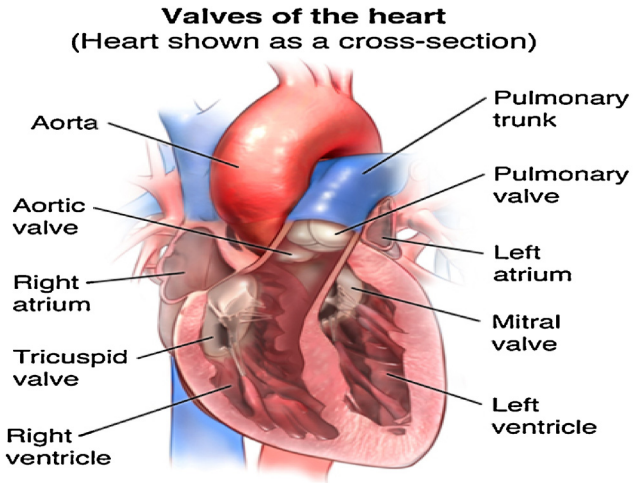

Fig. 2. The Architecture of the Heart showing Valves.

pulmonary artery), the mitral valve (found between the left atrium and the left ventricle (LV)), and the aortic valve (the aortic valve is located between the LV and the aorta).

Malfunction of the heart valve can occur in several ways, these include: Regurgitation (or leakage of the valve), Stenosis (or narrowing of the valve), and Atresia.

Heart valve development rely on the flow of blood. Heckel et al. [30] identified two mechano-sensitive channels and the mechano-transduction pathway that leads to the morphogenesis of early heart valve. Cellular response corresponded with the oscillatory constituents of the flow, showing that mechano-transduction is based on sensing of oscillatory stimuli.

3. Natural and synthetic polymers for scaffolds

Polymers have been routinely used as biomaterials for the synthesis of TE scaffolds and medical devices. The unique characteristics of polymeric scaffold such as high surface area-to-volume ratio, biodegradation, high porosity with very small pore size, and mechanical property led to researchers' great attention towards these materials [33,34]. They possess distinct merit of versatility of chemistry, biocompatibility, and biological characteristics which are crucial in TE application, and organ substitution. Over the years, researchers have studied ways of growing bone, cartilage, skin, liver, bladder, pancreas, corneas, nerves, heart valves and arteries, and several other soft tissues [35–37].

The main types of polymers used as biomaterials include, synthetic biodegradable and non-biodegradable polymers, and naturally occurring polymers. Synthetic polymers are very crucial in biomedical field since their characteristics (degradability, porosity, and mechanical properties) can be tailored for specific applications. Synthetic polymers, accounts for most of the biodegradable polymers, and they can be fabricated under controlled conditions. PGA, PLA (Fig. 4), and PLGA (Table 2) copolymers are among the most frequently used synthetic polymers in TE. PHA is a member of microbial polyesters and is being progressively investigated for applications in TE [38–43]. Natural polymers on the other hand can be grouped into proteins (collagen, fibrinogen, keratin, gelatin, elastin, silk, actin, myosin, and albumin [33]), polysaccharides (glycosaminoglycans, cellulose, amylose, chitin and dextran), or polynucleotides [44–47]. Different types of scaffolds, include; porous scaffold, acellular scaffolds, fibrous scaffold, microsphere scaffold, hydrogel scaffold, and polymer-bioceramic composite scaffold.

Developing a scaffolds that mimic the structure of tissue at the nanoscale level is one of the most crucial barrier in TE. Polymeric scaffolds shows a great potential with mechanical properties, and degradation rate, the qualities which are important for a range of TE applications [48–50].

In a study by Zhang et al. [51], the advancement of scaffolds that reiterate the anisotropic biological functions and mechanical behavior of the ECM in leaflets would be transformative for heart valve TE. In this study, the anisotropic mechanical characteristics were established in poly(ethylene glycol) (PEG) hydrogels *via* crosslinking PEG diacrylate (PEGDA) within PEGDA based hydrogels by a photolithographic patterning method. Biomimetic PEG-peptide hydrogels were fabricated by tethering the RGDS cell-adhesive peptide and blending the collagenase-degradable peptide PQ (GGGPQG↓IWGQGK) into the polymer network. The precise quantity of PEG-PQ and RGDS within the synthesizing hydrogels affect the elongation, de novo ECM deposition and hydrogel degradation behavior of the incorporated valvular interstitial cells (VICs). In addition, the shape and activation of VICs grown, a top PEG hydrogels could be controlled through the concentration or micro-patterning profile of PEG-RGDS. These products are promising for the synthesis of PEG-based hydrogels using biologically and anatomically inspired scaffold design properties for heart valve TE [51].

Nakayama et al. [31] have maintained that, in-body tissue architecture, a new and practical regeneration medicine technology can be used to fabricate an entirely autologous heart valve, in

Table 2
Advantages and shortcomings on electrospun-based nanofibrous synthetic scaffold.

Nanofibrous Polymers	Advantages	Shortcomings
Type I collagen and nano hydroxyapatite [71]	Nanoscale characteristics of nanofibrous collagen and nano-HA able to mimic bone extra cellular matrix and has the potential application as scaffold for hard tissue regeneration in a low or non-load bearing organs	Surface modifications of electrospun nanofibrous structure to aid cells- integrin binding
PCL/gelatin [72–74]	PCL/gelatin nanofibrous scaffold shows a suitable bio-composite materials for nerve tissue restoration and regeneration	Electrospun fibrous construct for nerve tissue regeneration
Poly (DL-lactide-co-glycolde) gelatin (PLGA/Gel) [75–77]	PLGA/Gel nanofibers possibly bring one of an endogenous cardiomyocyte proliferation and will reducing the cardiac dysfunction, and also improving cardiac remodelling, and biomechanical support for injured myocardium	Build up TE that matches the biological, chemical, mechanical characteristics and extracellular matrix morphology of native tissue use for cardiac patch
Poly(L-lactic acid)-co-poly(3-capro-lactose), gelatin and hydroxyapatite(HA)[78,79]	Using electrospinning technique in electrospinning process may create more appropriate bio-composite nanofibrous scaffolds for bone TE	Bone replacement therapy using a nano-structured materials
Poly(L-lactic acid)-co-poly(e-caprolactone) (PLACL)/gelatin [80,81]	Electrospun nanofibers have the opportunity to be implemented as skin regeneration	Extracellular matrix (ECM) like configuration for skin tissues applications.

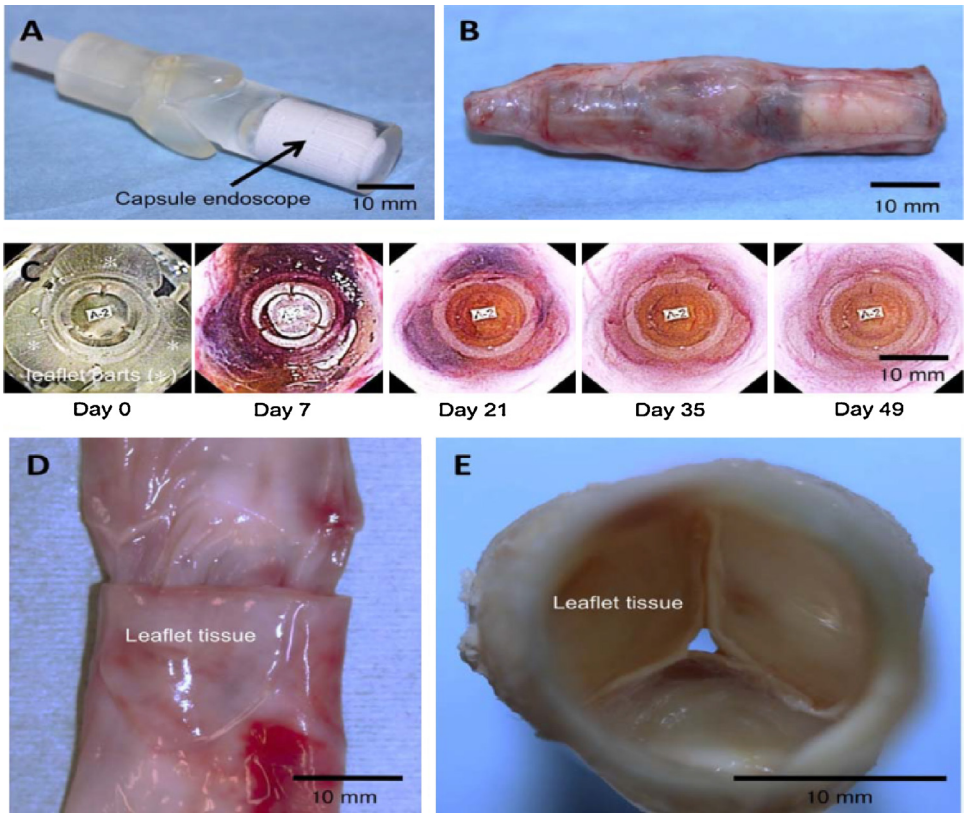

Fig. 3. Shows the preparation mold, loaded with a capsule endoscope, (A) before encapsulation and (B) after encapsulation. (C) the leaflet synthesis process at the aperture of the mold detected using a capsule endoscope non-invasively. Figure (D) the biovalve luminal surface and (E) the closed form having three protrusions like the sinus of valsalva. This figure was adapted from Nakayama et al. [31].

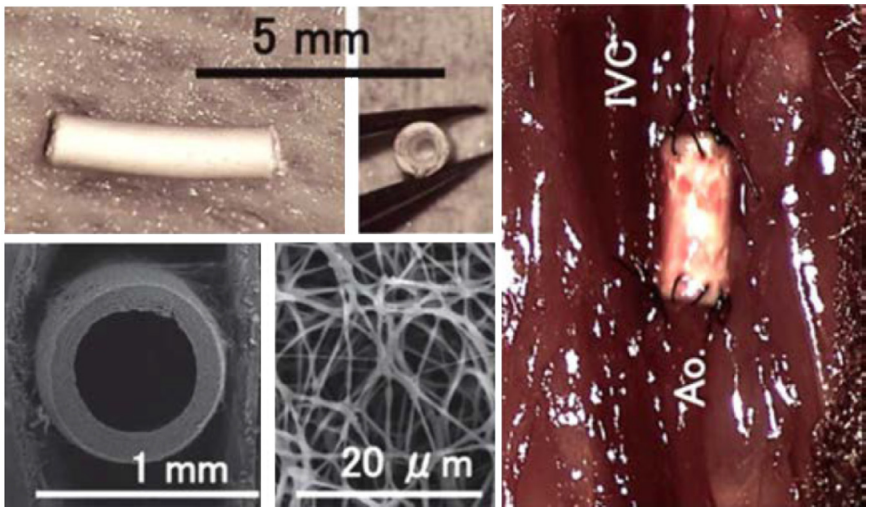

Fig. 4. (A) The structure of tissue engineered vascular graft (TEVG). TEVG implanted was made of biodegradable electrospun polylactic acid (PLA) nanofibers of 3 mm and inner luminal diameter of 500–600 μm. Scanning electron microscopy shows graft macro- and micro arrangement. (B) TEVG after surgical implantation [32]. Ao = aorta; IVC = inferior vena cava.

respect to the shape of a mold (Fig. 3). They used a 3D printer to produce the molds within several processing hours. Biovalves were synthesized from entirely autologous connective tissue, containing fibroblasts and collagen, within 2 months after the subcutaneous embedding of the molds (success rate, 27/30). *In vitro* analysis, with a pulsatile circulation circuit, gives a great valvular performance with a durability of approximately 10 days. One month following implantation, they observed smooth white leaflets with minimal thrombus formation. Functional, autologous, 3D-shaped heart valves with clinical application potential were produced following in-body embedding of specially designed molds that were created within several hours by 3D printer.

3.1. Porosity and pore size of scaffolds

Scaffolds must be highly porous in structure with full interconnected geometry for enabling a large surface area that will promote uniform cell distribution, cell growth, and improve

the neovascularization of the construct [52]. Average pore size, pore volume, pore size distribution, pore interconnectivity, pore throat size, pore shape, and pore wall roughness are crucial parameters to be taken into account while fabricating a scaffold. Pore size is also a very crucial parameter because, if the pores synthesized are too small, pore occlusion by the cells will result, which will prevent cellular penetration, neovascularization, and extracellular matrix production of the inner areas of the scaffold. Pore interconnectivity is also important to ascertain that all cells are within 200 μm from blood supply in order to provide mass transfer of nutrients and oxygen [53].

3.2. Scaffolds for TEHV

The main design criteria for heart valve replacement were originally expressed in 1962 by pioneering heart surgeon Dwight Harken [54], and a notion that TEHV must be non-obstructive, and its closure must be complete, and prompt; in addition, it must be made up of a non-thrombogenic living tissue that lasts throughout the lifetime of the patient; it must give an ongoing remodelling process that aid a homeostatic functional state and repair of any cumulative injury; and it must accommodate the somatic growth of the recipient. The design of polymeric scaffolds with specific biological and mechanical properties remain one of the main aspect of TE scaffold design.

TE scaffolds function as temporary ECMs, seeded with cell until repair or regeneration has been accomplished. Subsequently, the cell/scaffold construct can be implanted into a defect site for tissue regeneration or repair. Although the desired properties of a scaffold vary slightly with the type of tissue to be regenerated, there are general factors that are desirable. First, the scaffold should be biocompatible, by this, it must harmonize with the host tissue without causing a major graft rejection [18].

The scaffold should also be porous with a high surface-volume ratio to allow cell attachment and in-growth, as well as nutrients exchange during *in vivo* or *in vitro* culture.

Finally, a TE scaffold should be biodegradable, so that a second surgery will not be required to remove the implant. The rate of degradation should be controllable and align with the rate of neo-tissue formation [26,55].

3.2.1. Nanofibers

Nanofiber technology is an area attracting the attention of many research branches. Nanofibers provide connections between the macro-and nano world because their diameters are in the order of nanometres, while their lengths can run into hundreds of metres or more. Nanofibers must have a fiber diameter of less than 100 nm [52,56].

3.2.2. Methods for nanofiber synthesis

Three techniques are common for the fabrication of nanofibers; electrospinning, phase separation, and self-assembly. Of the above fabrication techniques, electrospinning remain the most extensively studied and used technique [57,58]. This technique seems to possess the most promising results for TE applications [59].

3.2.2.1. Electrospinning. Electrospinning represents an enticing method for the synthesis of polymeric biomaterials into nanofibers. This technique also present the opportunity for control over composition and thickness of the nanofibers with nanofibers meshes porosity using a comparatively easy experimental setup (Table 2). Although electrospraying [60] or electrospinning concept has been recognized for more than a century, polymeric nanofibers fabricated by electrospinning have become a topic of great interest only in the past decade. The high surface area and high porosity of electrospun nanofibers allow favorable cell attachment, and hence make them a potential precursor for tissue regeneration [61] (Figs. 5 and 6).

3.2.2.2. Phase separation. Ma and Zhang, develop a new method known as thermally induced liquid–liquid phase separation [63] for the fabrication of nanofibrous foam materials in the quest to mimic the 3D collagen structure present in natural ECM. The nanofibrous foams synthesized are very similar in size (50–500 nm) [64] to the native collagen present in the ECM of tissue [65]. This technique involves five basic steps listed in Table 1.

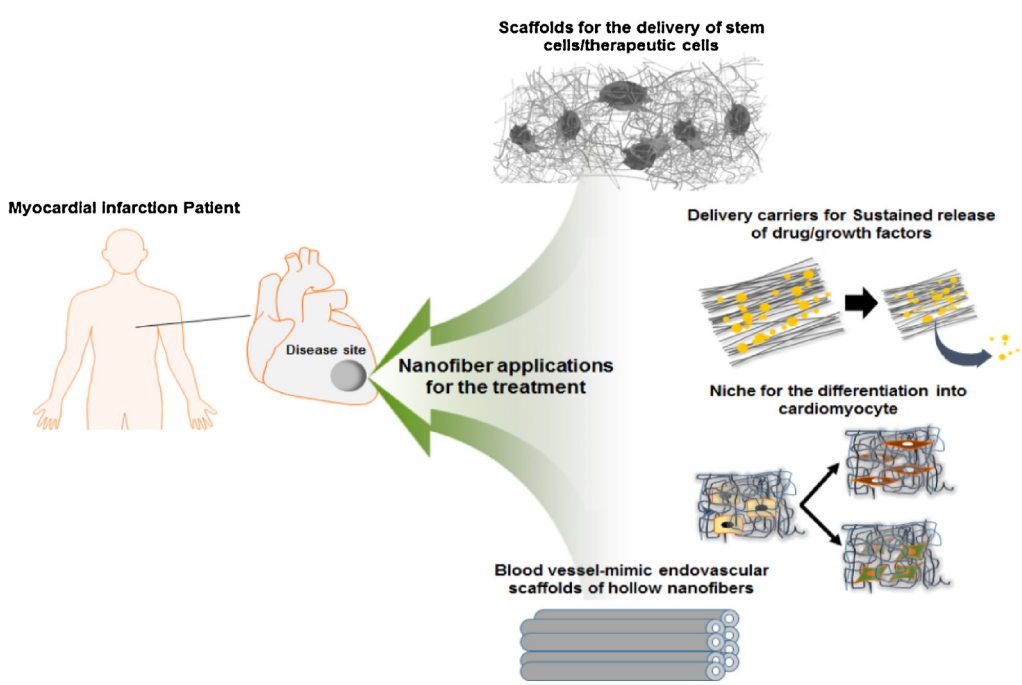

Fig. 5. Schematic representation of method of multi-functional nanofiber-based scaffolds for pediatric myocardial regeneration [62].

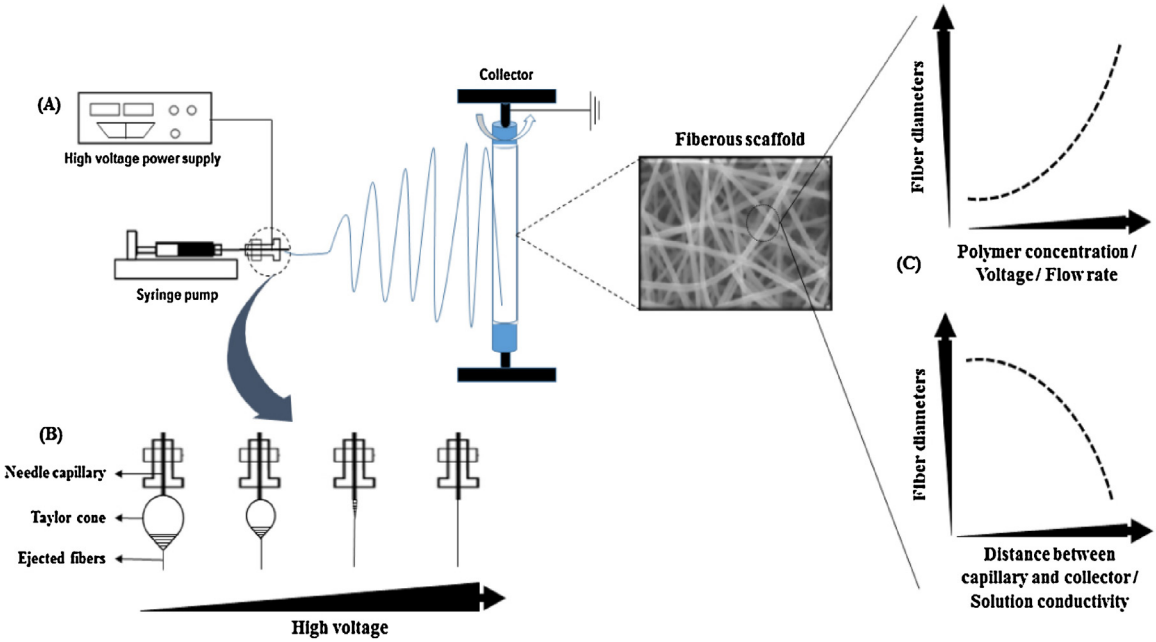

Fig. 6. Representation of the electrospinning set-up composed of major four parts diameter (A), the change of Taylor cone (B) fiber diameter according to a broad range of voltage. The diameter of fiber fabricated by electrospinning is changed depending on the polymer concentration, flow rate, voltage, distance between capillary and collector, and solution conductivity (C) [62].

Table 1
Phase Separation Technique.

	Phase Separation Technique Steps
1	Polymer dissolution
2	Phase separation process (liquid–liquid)
3	Polymer gelation (controls the porosity of nanoscale scaffolds at low temperature)
4	Solvent extraction from the gel with water
5	Freezing and freeze-drying under vacuum

3.2.2.3. Self-assembly. Eukaryotic cells can respond to their local environment *via* cell receptors that recognize their complementary extracellular tissue markers such as fibronectin and collagen. Thus, mimicking the extracellular matrix (ECM) with biomaterials would be a reasonable method for engineering several tissue types. In other to mimic the human ECM, Berndt et al. [66] synthesized a peptide amphiphile (PA)-based self-assembling system with the aim of designing a simple self-assembly system that permit the formation of thermally stable protein-like molecular architectures [67–70].

3.3. Dynamic cultivation systems for heart valve tissue engineering

For successful engineering of the heart valve, it is important to trigger the physiological mechanical loading of the tissues *in vivo* by dynamic cultivation *in vitro*. Presently, two types of dynamic systems are used for *in vitro* tests: Simple systems, intended for unidirectional bending or stretching of samples that are not pre-formed in the shape of the valve sophisticated systems, with more physiological dynamic loading of the valve-shaped samples or bioengineered valves together with the entire aortic root [82].

4. Nanofibers applications in biomedicine

Nanofibers have been used for artificial organs, drug and gene delivery, medical facemasks, and artificial blood vessels. For instance, hollow carbon fiber nano-tubes, that are smaller than blood cells, possess the potential of carrying drugs into blood cells. Webs and nanofibers are capable of delivering medicines straight to the internal tissues. This nanofiber can also find application in sutures and bandages, which will eventually dissolve in the body. Nanofibers application in biomedicine are outline in Table 3. Many

Table 3
Application of nanofibers in biomedicine.

Field	Nanofibers application in biomedicine
Wound Healing	Novel dressing materials made of spun biopolymers containing various active constituents useful for wound healing, fiber segment sizes ranges from 10 nm to several microns.
Scaffolds	Sufficient surface and several surface chemical characteristics aiding cell adhesion, growth, differentiation and migration can be achieved using biocompatible nanofibers.
Drug Delivery	Biodegradable or non-biodegradable nanomaterials can be used to moderate drug release either through diffusion or diffusion coupled with degradation.
Tissue Engineering	Replacement of damaged tissues including the bones, skin, cartilage, blood vessels, lymph nodes, muscles, and other tissues.

in vitro studies of nanofiber wound healing bandages, scaffolds and drug carriers have depicted that nanofiber materials perform better than their micro or macro counterparts, even though, they are made from thesame materials. The characteristics of nanofiber layers, such as porosity, can largely be adapted [45,61,70,83].

4.1. Applications of nanofibers in tissue engineering

Several methods has been reported lately for the fabrication of scaffolds used in TE. However, in the past decade, nanofiber systems have been established and explored as potential scaffolds for TE [61]. By the virtue of their porosity and high surface area, they have the potential of providing an enhanced cell adhesion and by the virtue of the similarity of their 3D structure to natural ECM, they provide an excellent micro/nano milieu for cells expansion and perform their regular functions. TE research field create an avenue to synthesize bioactive scaffold for supporting the function of defective tissue or organ, *via* the development of bio-composite scaffolds construct. The construct that match the biological, chemical, mechanical properties and ECM morphology of native tissue could be great for supporting heart recovery after the failure.

Wang et al. [84] reviewed several typical biomimetic nanofibrous structures that have great potential for TE scaffolds, and described their synthesis, merit, and applications in TE. They concluded with perspectives on challenges and future directions for design, fabrication, and utilization of scaffolds based on electrospun nanofibers [84].

4.1.1. In heart valve engineering

The study conducted by Reimer et al. [21] depicted a breakthrough and hope for tubular pediatric heart valve fabrication from two decellularized, engineered tissue tubes connected with absorbable sutures.

Syazana et al. [85] reported current development and future prospective on using electrospun-based scaffold for TE application. To this end, there are some advances on the use of nanofibrous scaffold for cardiac TE [86]. Nanofibers, when strongly pursued as a scaffolds for TE applications of paediatric heart valve will give a full insight to the treatment of congenital heart valve deformities [87,88].

Cellular alignment and mechanical anisotropy is crucial in tissues and organs such as axonal bundles, muscle, and cardiac valves [28,89,90]. Badrossamay et al. [91] measured the mechanical characteristics of SANF scaffolds through uniaxial mechanical testing with samples which was maintained at 37 °C in a PBS bath. Elastic stress-strain behavior of SANF PCL and PCL/Collagen-75/25 showed mechanical anisotropy between the fiber (FD) and cross-fiber (X-FD) directions. The Young's modulus and maximum strain of the PCL/Collagen scaffold is on the same order of magnitude as cardiac muscle and heart valve leaflets [39], suggesting their suitability for cardiovascular TE applications.

The use of nanofibers in tissue regeneration is expected to give an efficient, compact organ, and fast recovery due to the protein nanofibers large surface area, used for healing wound, epithelialization of implants, biocompatible prostheses construction, face masks, cosmetics, bone substitutes, artificial blood vessels, drug delivery, and heart valves applications [92–95]. TE is a promising option for synthesizing new heart valve substitutes, able to overcome the serious shortcomings encountered with mechanical substitutes or tissue valves [96].

Dube et al. [97] studied the possibility of using a living tissue sheet synthesized by the self-assembly technique, to replace the bovine pericardium recently used for the reconstruction of a stented human heart valve. They cultured human fibroblasts in the presence of sodium ascorbate to produce tissue sheets, these sheets were superimposed to create a thick nanofibrous construct. The heart valve engineered was stimulated in a pulsatile flow bioreactor, and multiple duty cycles was sustained. This prototype of engineered heart valve harboring cells in their own ECM and sewn on a wire frame has the potential to be durable, thereby assisting physiological stress [97]. Tissue spheroids biofabricated from stem cells of human fat tissue have been used to engineer leaflet-like construct on compliant electrospun scaffold using a tissue fusion approach or self-assembly. Incubation of this TEHV leaflet construct with a growth factor; TGFb as well as periostin transfection significantly elevate the stiffness of TEHV leaflet, the result of their study clearly showed that heart valve can be biofabricated by selfassembly of closely placed tissue spheroids or tissue fusion, and that genetically and chemically induced accelerated tissue maturation and collagen deposition can stimulate mechanical characteristics of tissue engineered leaflet. Additional optimization of accelerated tissue maturation technologies could ultimately lead to the development of living autologous human TEHV construct with natural-like biomechanical features suitable for pediatric cardiac patients [98].

Wu et al. [99] integrated woven fabric with heart valve cell laden bioactive hydrogel to fabricate composite scaffolds for heart valve engineering. Their results suggest that the continuously fabricated nanofiber have great processability and cellular responsive behaviors, which would potentially be suitable for heart valve TE and regenerative medicine applications.

5. Conclusions

TE is one of the most interesting interdisciplinary and multidisciplinary research areas, growing rapidly over time. It is set to revolutionize the treatment of patients. A Scaffolds should meet certain fabrication parameters to be useful in this area, regardless of whether they originate from synthetic or natural sources [34,100–102]. The scaffold should be structurally suitable and its surface must be compatible with the host environment [103]. The interest in the theories and principles of the fabrication process with polymers would be useful to create a new design for implants and also to comprehend the behaviour of the scaffold used in the biomedical applications. Nanotechnology can give us the strategies that can assist in creating the features on a scaffold in a dimensional range that may be appropriate for biomolecules, cells and treatment of paediatric heart valve. Nanofiber-based scaffolds is beneficial for tissue engineering heart valves [104,105].

Conflict of interest

None.

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