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REVIEW

Biomaterial approaches for cardiovascular tissue engineering

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Abstract

Cardiovascular disease is the leading global cause of death. As a possible remedy, the field of cardiac tissue engineering has emerged as a regenerative medicine approach to develop bioartificial tissue constructs that can be implanted in order to provide support to the damaged heart tissue and restore function. Currently, there is a dire clinical need for suitable biomaterials that allow for cardiac graft integration, remodeling, and endogenous tissue regeneration. A range of biomaterial strategies can be used to address this need, by incorporating natural or synthetic materials to create tissue mimics such as vascular grafts, heart valves, and cardiac patches. Cardiovascular tissue engineering mainly relies on developing biodegradable polymeric scaffolds, often supplemented with biomolecules or natural proteins, to imitate the extracellular matrix architecture and biochemical composition of native tissues, while promoting tissue integration and regeneration. Considering the highly complex architecture of targeted cardiovascular tissues, there is a need for high-precision manufacturing techniques to generate cardiac grafts in a reproducible fashion. While methods such as 3D casting, electrospinning, and self-assembly have been traditionally used in the field, several new entrants, such as additive manufacturing (3D bioprinting) techniques, have shown great promise. This review is aimed at assessing the current state of the art of biomaterials and manufacturing techniques used in cardiovascular tissue engineering.

Keywords Biomaterials · Cardiac patch · Scaffold · Cardiovascular · Tissue engineering · 3D printing · Bioprinting · Biomanufacturing

1 Introduction

Cardiovascular disease (CVD) is a major contributor to total global mortality and loss of productivity and quality of life. In the USA, it is reported that over 92 million adults are affected by some type of CVD [1]. These numbers lead to enormous economic and healthcare burden of heart-related diseases, accounting for about 30% of Medicare expenditures and approximately $149 billion annually [2]. Full functional recovery is restricted primarily by the lack of therapeutic and autologous graft treatment options for diseases such as myocardial infarction (MI) and coronary artery disease. This clinical need has triggered a growing amount of research on design and development of new biomaterials that can be leveraged towards cardiovascular tissue replacement therapies and restorative clinical interventions [3, 4].

As a multidisciplinary paradigm, cardiovascular tissue engineering (CTVE) enables manufacturing novel graft materials that can precisely recapitulate the native heart tissue. The heart is a complex organ-system comprising multilayered tissues, each containing a variety of cell types and extracellular matrices (ECMs). Thus, the process of selecting a suitable graft material is often dependent on the specific function of diseased/damaged tissue and its complexity within the cardiac environment. This has necessitated the development of a broad range of both synthetic polymers and natural protein-based biomaterials that have been used to repair the heart (Table 1). Biomaterials are defined by natural and synthetic materials that are used in biological systems. Each biomaterial

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Table 1 List of selected biomaterials used in cardiovascular tissue engineering along with their key characteristics and benefits

Biomaterial	Benefits/characteristics	Drawbacks	References
Alginate	▪ Typically extracted from brown algae ▪ Immunogenic responses are currently being evaluated, little to no immune response ▪ RGD peptides can be chemically coupled to alginate	▪ Lacking long-term stability in vivo ▪ May induce homeostasis	[5–9]
Chitosan	▪ Biodegradable, antibacterial activity ▪ Natural polysaccharide ▪ Partially deacetylated derivative of chitin ▪ Second most abundant biomaterial in nature ▪ Similar structures to glycosaminoglycans found in the ECM	▪ Uncontrolled dissolution may occur	[10–15]
Gelatin	Denatured collagen via hydrolysis ▪ Bioactive protein enhances cell-scaffold interactions ▪ Often used with synthetic polymers with slower degradation kinetics ▪ Widely used to develop scaffolds for cardiac grafts	▪ Poor mechanical resistance	[16–20]
Collagen	▪ Abundant ECM component, suitable for cell attachment and proliferation		[21–23]
Fibrinogen	▪ Naturally occurring plasma protein ▪ Contributes to wound healing and clot formation ▪ Biodegradable, promotes cell migration		[24–26]
Polytetrafluoroethylene (ePTFE), Teflon™	▪ Nonbiodegradable ▪ Standard for large-diameter (> 6 mm) vascular grafts, prosthetic heart valves, mitral valve sutures	▪ Thrombogenic properties	[27–29]
Polyethylene terephthalate (PET/Dacron®)	▪ Nonbiodegradable ▪ Standard biomaterial for large-diameter vascular grafts ▪ Thrombogenic properties	▪ Thrombogenic properties	[27, 30]
Polylactic acid (PLA)	▪ Biodegradable ▪ Coatings for drug-eluting stents ▪ Investigated as a biomaterial in approaches such as heart valves, vascular grafts, cardiac patches		[13, 31, 32]
Polyglycolic acid (PGA)	▪ First absorbable suture ▪ Often used as copolymer with PLA ▪ Widely used in heart valve applications		[33–37]
Poly(ε-caprolactone) (PCL)	▪ Semi crystalline linear hydrophobic polymer ▪ Slower degradation rate in comparison with PLA and PGA		[38–41]
Polyglycerol sebacate (PGS)	▪ Synthetic polyester, bioresorbable ▪ FDA approved		[17, 42–44]

has their own chemical and physical properties and thus elicits distinct responses to biological and mechanical stimuli, making appropriate scaffold selection a critical, yet challenging step in successful tissue regeneration. This paper reviews the different biomaterial approaches and manufacturing methods to produce scaffolds for cardiovascular tissue engineering applications.

2 Biomaterials used for cardiovascular tissue engineering

2.1 Naturally derived biomaterials

Naturally derived scaffolds have been used to advance cardiac regenerative medicine by creating biomimetic organ scaffolds at clinically relevant scales [8, 45, 46]. Such materials are popular scaffolding options to integrate cells for a functional organ analog. For cardiac tissue engineering, natural biomaterials include well-characterized biopolymers such as chitosan, collagen, gelatin, Matrigel, chitosan, alginate, and decellularized ECM (dECM) [47, 48]. In addition, emergent biomaterials such as silk and various conductive materials (graphene and carbon nanotubes) have been recently evaluated [49]. Depending on specific application, these scaffolds can be crosslinked using different methods including ionic-based, enzymatic, and UV/vis light-initiated curing techniques [8, 50, 51].

Alginate is an attractive hydrogel for cardiac bioengineering, since it can generate highly porous structures that allow for seeding relatively high densities of cells into the tissue construct. Such approaches can easily and reliably generate tissue scaffolds at physiologically relevant cell density [8]. Further, chitosan can be mixed with alginate to generate polyelectrolyte complexes (PECs) of highly porous lattices suitable for 3D cell culture, while maintaining the target cells' paracrine profile. PEC patches have been used in MI models, demonstrating improved vascularization, attenuated fibrosis, and effective integration with the host tissue [52].

Collagen and gelatin are some of the most commonly used natural biomaterials for cardiac tissue engineering, where their biocompatibility and resorption make them attractive candidates to create cardiac patches and in vitro tissue models [53–58]. For instance, acellular type I collagen gel scaffolds, seeded with cardiogenic follistatin-like 1 protein, demonstrated a remarkable effect as cardiac patch in regenerating damaged heart tissue in mouse and pig models of MI [54, 59]. In another study, neonatal rat cardiomyocytes (CMs) were incorporated into thick collagen patches, matured in vitro prior to implantation, and applied to rat model of MI. Treatment with cellular grafts prevented dilation in the infarcted area and induced systolic wall thickening, while showing minimal induced arrhythmia [60]. Fibrin is another naturally occurring biopolymer that has been used in tissue engineering of the heart [58, 61]. It is biocompatible, its degradation can be precisely controllable by the use of aprotinin, is easy to process (moldable), and can be chemically (covalently) modified to polymerize under specific conditions, while still maintaining high cell viability [62]. Other key advantages of fibrin as an ideal candidate for cardiac tissue engineering include injectability and the ability to produce completely autologous scaffolds [62, 63]. For example, rat neonatal CMs, endothelial cells (ECs), and fibroblasts, either alone or together, have been successfully incorporated in fibrin-based patches, enzymatically crosslinked with thrombin, and aligned during culture through mechanical constriction [64, 65]. Cardiac cells were highly viable under these conditions, remodeled the fibrin hydrogel, and responded (contracted) to electrical pacing. Further, ECs and fibroblasts were shown to self-assemble into vascular networks within the fibrin tissue constructs [64, 65].

Silk fibroin scaffolds are a class of natural biomaterials that can be chemically modified to express a range of small molecules and attachment factors that can be readily tailored to mimic the cardiac niche microenvironment. For example, porous electrospun semialigned scaffolds were used to culture rat cardiac progenitor cells over a 21-day period, where cells expressed significantly higher levels of sarcomeric proteins such as titin and improved native ECM deposition onto and within the silk fibers [50].

Decellularized tissues and organs are a promising emerging source of biomaterials for diverse tissue engineering and regenerative medicine applications [66–68]. Decellularized tissues rely on isolation of the ECM from tissue with minimal loss, damage, or disruption, while maximizing native cell removal. This is usually achieved through physical, chemical, and enzymatic methods [69, 70], which can be applied to the cadaver hearts or any other target organ. This method can recover the intact 3D ECM of the target organ, which can be then reseeded with patient-derived cells to rebuild a functional tissue for implantation without the need for extensive immune-suppressive drugs or matched haplotypes between the patient and the donor [71, 72]. dECM scaffolds can be used to engineer clinically functional cardiovascular tissues to restore or repair the damaged organ. This is aided by the inherent ability of cells to self-assemble and organize into tissue mimics, if provided the right set of ques. Such scaffolds have been reseeded with both hESCs and hMECs in pilot studies [73], opening up new clinical possibilities, in the foreseeable future, for repopulating of whole organs. Such emergent materials have the potential to overcome the more significant challenges in organ transplantation, namely, the donor shortage and immunosuppression. The development of more suitable decellularization approaches may reduce host immune response and generate suitable natural biomaterials for use in cell seeding and cardiac tissue engineering applications.

Considering the significance of spatial arrangement of cells and ECM proteins for the proper function of a tissue/organ construct, natural biomaterials and fabrication methods that enable generation of complex biomimetic tissue architectures are in high demand. To this end, dECM-based tissue bioprinting has attracted increasing attention in recent years [74, 75]. While dECM bioinks provide a unique combination of biophysical and biochemical cues, resembling those of native tissue microenvironment, 3D bioprinting offers additional highly precise spatial control on the tissue architecture (cell, biomaterials, and small molecules), hence enabling fabrication of biomimetic functional tissue models [75]. Overall, dECM tissues have a few drawbacks that need to be addressed before they are translated in the clinical field of CVTE. Standardization of decellularization techniques and proper quality assessment needs to be thoroughly investigated.

2.2 Synthetic scaffolds

While most scaffolding materials used for cardiovascular tissue engineering are naturally derived, synthetic biomaterials are used primarily for their superior mechanical stability, tunability, diversity, and optimal degradation rates [76–78]. Further, unlike natural biopolymers, synthetic polymers can be used in a wide range of manufacturing techniques such as 3D printing, electrospinning, and solvent casting, allowing for facile manipulation while maintaining or improving the desired material properties and scaffold structure [79]. Polylactic acid (PLA) and polyglycolic acid (PGA) are bioresorbable polymers that have often been investigated for cardiovascular scaffold materials. PGA has widely been used by researchers as a biodegradable synthetic material in tissue engineering and surgical applications [32, 34, 35]. In fact, the first absorbable suture was composed from PGA and degrades through hydrolytic processes up to 4 weeks post implantation [27].

Current synthetic grafts in the market are usually composed of a nonbiodegradable material polytetrafluoroethylene (PTFE) or Dacron® [27]. These grafts have mainly been successful in the use of large-diameter (> 6 mm) graft options [27]. Synthetic vascular grafts in small diameter blood vessels have low graft patency due to early thrombosis [80]. Other synthetic materials have been looked at for a suitable vascular graft biomaterial such as poly(ε-caprolactone) (PCL) [40]. Pektok et al. showed that PCL vascular grafts promoted rapid endothelialization and ECM production in comparison with PTFE grafts [41]. In addition to use in synthetic vascular grafts, PCL has also been used in heart valve tissue engineering along with polymers such as PLA and PGA due to their adequate degradation rates and FDA acceptance [81, 82]. Polyglycerol sebacate (PGS) has also been investigated in tissue engineering heart valves and displayed excellent biocompatibility and degradation rates in 4 to 6 weeks [83]. Developed by Langer et al., PGS demonstrates elastomeric properties while being suitable for a host of biologic and ECM-like material [43, 84]. It has also been found that PGS demonstrates excellent stiffness and cell adhesion in comparison with PGA scaffolds, while promoting collagen fiber alignment in native heart valves [83]. PGS scaffolds supported endothelization under flow conditions within 14 days of EC culture, making this synthetic polymer suitable for vascularization techniques [85].

Bioresorbable, synthetic-based polymer scaffolds provide excellent mechanical strength and integrity, and processability, while natural materials typically better facilitate tissue remodeling and cellular interactions. Thus, multifunctional scaffolds that integrate both synthetic and natural components are often sought after to gain both the mechanical integrity and biological activity [40, 86]. These hybrid scaffolding systems would likely be the baseline for future clinically applicable cardiovascular biomaterials.

2.3 Composite (hybrid) scaffolds

Composite (hybrid) scaffolds aim to combine natural and synthetic biomaterial components to synergistically augment desired cellular and tissue responses [87]. Specifically, for cardiovascular tissues, these hybrid materials can give engineers access to a spectrum of biochemical, mechanical, and electrical properties necessary for functionality and biocompatibility [87]. Exploiting these tunable characteristics holds promise for finding optimized biomaterial performance, particularly for engineering cardiovascular scaffolds. The three major characteristics of composite biomaterials (biochemical, mechanical, and electrical properties) can be modified independently or in concert to achieve a wide range of desired functionalities, making such scaffolds useful in the clinic and for regenerative medicine.

The biochemistry of hybrid scaffolds often aims to modulate biodegradability, biocompatibility, angiogenesis, and cell adhesion, proliferation, and differentiation [88]. Synthetic materials for these applications include poly(lactic-co-glycolic acid) (PLGA), PCL, PGS, and their derivatives, combined with natural materials such as collagen, gelatin, elastin, alginate, fibrinogen, and associated peptide biomolecules [7, 42, 89–91]. Such hybrid combinations have shown increases in cardiac gene expression and metabolic activity versus each material alone [91]. In cardiac patches, in particular, maintaining scaffold placement and cell adhesion to the host are major challenges that hybrid biomaterials can address effectively [92].

The mechanical properties of hybrid scaffolds, on the other hand, can modulate material strength and responsiveness (e.g., stiffness, compliance, and (an)isotropy), mass transport (e.g., porosity and permeability), and tissue orientation (cell alignment and physical positioning) [87]. These are in addition to maintaining the mechanical integrity of scaffold in the dynamic, contracting environment of the heart. 3D arrangement of the aforementioned hybrid materials differs from macro- or microporous [7, 91] to electrospun scaffolds [7, 42, 90, 93] to injectable hydrogels [94]—yielding customized tissue patterns and alignment. More recently, adding crosslinkable elements (e.g., methacrylate groups) to natural materials has allowed controllable stiffness via chemical reaction or photoinitiation. For instance, gelatin methacrylate (gelMA) [95, 96], hydroxyethyl methacrylate (HEMA) [97], and poly(ethylene glycol) methacrylate (PEGMA) [98] have been used in cardiovascular applications. Mechanically stabilizing these hydrogels can better deliver the upwards of billions of cells needed for cardiovascular tissues.

Finally, the electrical properties of hybrid scaffolds modulate ion efflux by adding conductive elements, typically nanoscale constructs. For example, gold nanowire-infused alginate has been shown to improve electrical propagation in porous matrices that interfere with cell-cell connections [99]. Created cardiac patches showed enhanced synchronized contractile function. Incorporation of gold nanorods in gelMA hydrogels also yielded increased mechanical stability and electric conductivity [100]. Conductive polymers (e.g., polyaniline and polypyrrole) added to PCL [101], PLGA [102], and PGS [103] have shown similar results. Further, carbon-based nanomaterials have shown to exhibit biocompatibility and excitable cell proliferation [104].

Overall, tissue engineering advances in hybrid biomaterials combine desirable qualities from both natural and synthetic materials. Functionalization of such materials with specific biochemical, mechanical, and electrical components can better mimic the structure and function of target tissues and organs, such as cardiovascular tissues. Specifically, it has been previously shown that the contractile functionality of cardiac tissues can be improved by applying electrical stimulation to hybrid materials [105, 106].

3 Biomaterial fabrication techniques used in cardiovascular applications

3.1 Additive manufacturing (3D printing and bioprinting)

3D printing, an additive manufacturing technique gaining in popularity, encompasses a variety of processes that use computer-aided models to enable personalized 3D scaffolds through layer-by-layer depositions of material [20]. In the cardiovascular field, these are often patient-specific heart models that can be used for surgery planning, teaching, and anatomical studies. 3D printing using biopolymers, cells, or other biomaterials is referred to as bioprinting [20, 107]. 3D bioprinting is often used because it enables high accuracy and precision deposition of multiple biomaterials within the same construct, allowing for recreation of complex and heterogeneous structural features and mechanical properties. There are multiple bioprinting strategies, with some popular ones being extrusion-based, inkjet, and stereolithography techniques (Table 2) [20, 107].

Due to its ability to create complex 3D scaffolding and tissue constructs, 3D bioprinting is commonly used in CTVE, for both in vivo regenerative therapies and in vitro 3D cultures for pharmacological applications [108–110]. Bioprinted scaffolds can be seeded with a variety of cardiac cells, including CMs, leading to formation of biomimetic tissue microenvironments that allow for optimal cardiac cell survival and function [111]. Alternatively, artificial tissues can be bioprinted with cells encapsulated in the bioink. The main advantage of 3D cell printing is the possibility of assembling cells (and macromolecules) in a spatially controlled manner within the scaffolds. Cellular bioinks are more commonly used for engineering tissues and devices for implantation in the body, such as cardiac patch, heart valves, and coronary artery grafts [112]. However, cardiovascular tissues have yet to be bioprinted with full cardiac function, comparable with that of native tissues, and therefore have yet to translate into clinical practice [107]. More research investment is needed in the field to fulfill the promise of creating bioprinted tissues and organs that may be used to replace dead or diseased tissues. Additionally, while in vivo and two-dimensional (2D) models often lack accuracy in predicting human response to various pharmaceuticals, bioprinted models offer an alternative platform for more reproducible, accurate, and high-throughput drug screening and disease modeling [111].

3.2 3D patterning techniques

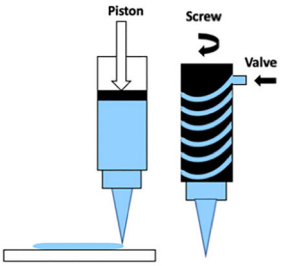
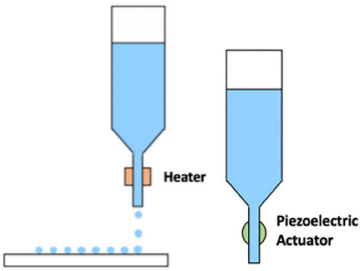
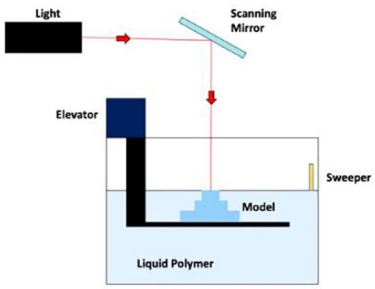
Micropatterning and microstamping are tissue engineering techniques suitable for generation of complex tissue arrays. Microstamping techniques use surface functionalization to attach proteins for guiding cell attachment and migration along predefined patterns [113–117]. This ability is particularly important as regulation of cellular interactions in 3D constructs is necessary for proper function of complex, multicellular tissues and dysregulation is often associated with diseases, specifically in cardiac and connective tissues [115, 118]. Micropatterning and microstamping are well suited for large-scale engineered tissue studies, since they are able to generate reproducible and consistent patterns that can be leveraged for cell-cell interactions [113, 119, 120]. These methods are vastly parallel and can generate patterns with resolutions from submicron to multiple centimeters, with high fidelity [117, 120, 121].

Micropatterning has been successfully used to generate functional cardiovascular models, where arrangement, ECM characteristics, and localization of small molecules are critical for cellular organization and functional recapitulation of the engineered tissues [51, 122–125]. The ability to incorporate different cell types within the same assembly has also been shown to improve maturation and development of the tissue arrays [125]. Recent advances in the field have enabled a range of patterning techniques that make it possible to produce biocompatible surfaces, without the often-toxic chemicals that are common in traditional lithography process flows [126, 127]. Multiple modes of patterning, such as reactive ion etching, light-based crosslinkers, enzymatic, or charge-based adhesion, have been used to generate hard and soft stamped surfaces without significant cell toxicity, allowing for advances into the translational and drug discovery areas [51, 115, 117].

Mask-based photolithography is a technique that uses light and a patterned mask to transfer a design onto a target material [116]. In vitro formation of capillary networks has been achieved using patterning techniques. For instance, ECs were cultured onto patterned poly (ethylene glycol) hydrogel substrates, created by photolithography, and demonstrated enhanced vascular network formation [117]. After implantation of the generated constructs in the mice, the engineered capillary network allowed for native blood cells to infiltrate, indicating successful integration and perfusion potential.

In cardiac muscle tissue engineering, patterned scaffold structures that can direct cellular alignment are in great demand, as they provide a biomimetic microenvironment to support the biomechanical functions of incorporated cells [118, 128]. For example, micromolding and microablation methods have been used together with mask-based lithography to fabricate elastomeric scaffolds with defined anisotropic surface patterns. These patterned substrates directed formation of highly aligned, engineered muscle tissues [128]. In another study, micropatterning was used to align rat ventricular CMs to follow the realistic murine ventricular microstructure, recreated from high-resolution diffusion tensor magnetic resonance imaging [118].

Table 2 Comparison of different 3D printing techniques

Printing Categories		Pros	Cons
Extrusion-Based Bioprinting		Faster printing times with more control over speed settings [110]. Capability to dispense high cell densities [21].	Only materials with high viscosity can be printed, more pressure needed, leading to lower cell survival [21].
Inkjet-Based Bioprinting		High resolution and thinner layers can be created. Compatible with many biomaterials and cell types [21, 110].	Low viscosity leads to lack of structural integrity and strength [110]. Longer print times [21].
Stereolithographic Bioprinting		Simplistic and has high printing speeds. No excess stress to cells from extrusion [21]. High resolution.	Possible cell damage form UV light. Limited materials that can be used. Difficult to print multi-material constructs.

A novel cell micropatterning approach to generate cardiac tissues was recently developed using bioacoustic wave patterning to create repeatable 3D cellular assemblies [129]. This process uses the Faraday wave principle to arrange cells into dense aggregates in a predefined pattern [58, 130]. Following wave activation, the cells, suspended in liquid prepolymerized hydrogel, are repelled from areas of higher force potential to areas with lower force potential. This results in stacking the cells into symmetric 3D structures. To sustain these patterns within the scaffold after patterning, the hydrogel is crosslinked using light-based or chemical crosslinking methods [129]. Compared with other tissue engineering techniques, wave patterning is relatively quick and has an inherent ability to generate reproducible and repeating patterns over large surface areas [131]. This makes wave assembled cardiac tissue constructs an attractive candidate for large-scale, high-throughput drug screening and tissue manufacturing. For example, Faraday wave patterning was recently used to assemble human-induced pluripotent stem cell-derived CMs into 3D tissue constructs at packing density similar to that of native myocardium (10^8 cells/mL).

3.3 Textile manufacturing

More recently, textile techniques have been investigated as robust manufacturing techniques for CVTE applications. Textiles are synergistic combination of additive manufacturing in conjunction with patterning techniques. 3D net fabrics can be manufactured utilizing textile processing techniques such as weaving, knitting, braiding, and stitching [132]. Among the techniques listed, weaving has the most processing flexibility. These structures have efficient strength due to anisotropic properties and interwoven connectivity [133]. Textile implants can be manufactured to mimic human tissue and its physical function such as their use in heart valve tissue engineering. For example, Baaijens' group developed a PCL weft-knitted patch that utilized ECM natural proteins such as fibrinogen and thrombin for gelation. The patch underwent cyclic testing (over 1 million cycles) without rupture [134]. This early work from 2006 presented novel works in this field, but there were some limitations. The most significant was the uncontrollable leaking of the gelatin network from the woven patch. The development of accurate

modeling, mechanical properties, and efficient processing of biomaterials will allow for fine tuning of complex architectures in CTVE.

3.4 Electrospinning

Another fabrication technique that is often utilized in conjunction with additive manufacturing techniques is electrospinning. In CTVE, one of the primary goals is to create graft materials with long-term potency that have the capacity to integrate with the living tissue, while exhibiting properties similar to those of the native organ. To this end, electrospinning is widely used to produce nanometer- and micrometer-scale fibers with high consistency and volume [135]. In this method, a polymer solution is loaded into a syringe pump, and a high voltage is applied to a conductive needle to extrude either fibers or microbeads. A typical system is then grounded at the collecting metal mandrel where the electrospun fibers are collected [136].

Many parameters in electrospinning determine the morphology and formation of the fibers. Altering these factors can allow for fiber alignment and diameters ranging from 100 nm to 5 μm [137]. The syringe pump is used to drive the polymer solution out of the syringe needle at a controlled dispensation rate [137]. The electrospinning technique has the capability of producing bioresorbable grafts that allow for in situ remodeling of the structure [138]. Since electrospun fibers can mimic the native ECM in terms of morphology and scale, this technique has been used to produce various tissue scaffolds, particularly in the fields of vascular, bone, nerve, and tendon and ligament tissue engineering [137, 139].

Current cardiovascular tissue engineering approaches often utilize biodegradable scaffolds, seeded with cells, to generate an ECM that can promote graft integration. Synthetic grafts have been also tested. For instance, Dacron vascular grafts were seeded with ECs to promote endothelialization and vascularization [140]. ECs have also been shown to lower the occurrence of thrombotic occlusions in electrospun vasculature [140, 141]. ECs and smooth muscle cells (SMCs) have been also used together to drive the formation of blood vessels. These cell lines were seeded onto electrospun multilayer PCL-PLA scaffolds and showed enhanced SMC adhesion, proliferation, and penetration within the construct [142]. Alternatively, cells can be recruited onto the scaffold material after implantation in the body where they are able to proliferate and produce ECM. In order to satisfy these requirements, properties of biomaterials must be properly analyzed before using as a graft material for cardiovascular engineering. One study showed that scaffold composition and alignment affected CM functionality on an electrospun myocardial graft [143]. CMs expressed myocardial-like sarcomeric structures on anisotropic-aligned fibers while showing an overall performance on PGS-blended electrospun scaffolds in comparison with gelatin scaffolds [17]. The facile tailoring of electrospun fibers in the nano- and microscale range makes this fabrication technique advantageous in the field of cardiovascular tissue engineering.

3.5 Self-assembled biomaterial structures

Self-assembly is a critical function of higher-order organisms and is the underpinning principle of organ development and regeneration [144]. In brief, self-assembly takes place by spontaneous organization of individual units into rational structures with little external input [145, 146]. Biomaterial self-assembly processes rely on biorecognition (i.e., biological recognition of specific chemical compounds) which allows for complex material design and enables generation of rational structures from nanometer to macroscales [147, 148]. At the macroscale biorecognition, hydrogels are the class of biomaterials that is of increasing interest as a potential tissue engineering platform. Self-assembled hydrogels can provide a high-throughput, yet consistent and reproducible pipeline to generate large volumes of biomaterials with desired properties [149].

A recent example of self-assembled hydrogels is genetically engineered polymers, where the building blocks are encoded on genes to be produced by bacteria [149]. Such biofactories have the benefit of scale and reliability to generate smart polymer variants with features including pH and temperature sensitivity, controlled cell adhesion, modulated elasticity, and well-defined solid structure, all based on the sequence of building blocks [149, 150]. Hybrid self-assembled hydrogels are another class of emergent biomaterials that is of interest. These materials usually contain at least two distinct classes of components, such as a polymer backbone and biologically active molecules, bound in a stable state [151, 152]. Pairing synthetic (or natural) polymer backbones with peptides or enzymes introduces a higher level of functionality to the biomaterial, allowing to perform defined tasks such as drug activation and release [153]. Self-assembled constructs have been bioengineered as cardiac patch to treat MI (Fig. 1) [54, 55, 154, 155]. Such engineered tissues have shown significant engraftment associated with cardiac cell proliferation, neovascularization, and intercellular junctions [156–158]. These cardiac mimics exhibit enhanced functionality with reduced left ventricular remodeling post-MI, less fibrosis, and preserved wall thickness [156, 157, 159].

3.6 Cell sheet tissue manufacturing

Cell sheet tissue manufacturing is a scaffold-free self-assembly method to bioengineer (2D) monolayers of cells for creating 3D living constructs. This approach is advantageous

because it eliminates physical barriers interrupting cell-cell connections and circumvents specific fibrotic and immune responses evoked by foreign materials. Cell clearance in vivo is avoided, unlike injectable hydrogels, and 3D spatial resolution is highly controllable to the approximate size of a cell [160]. Yet, long fabrication times, slow vascular ingrowth, and cell sourcing currently limit the scalability of this biomanufacturing technique [160].

Methods to create cell sheets typically employ surface coatings with temperature sensitive materials like poly(N-isopropylacrylamide). At body temperature, adherent cells grow and, when cooled, cell monolayers uniformly peel off in one piece [158, 160–162]. In contrast to cell dissociation methods using proteases, the temperature-controlled detachment approach maintains the basis of cellular and ECM-deposited linkages. Cell sheets have been expanded from cell types such as ECs [157], SMCs [157], primary and induced pluripotent stem cell-derived CMs [158, 163, 164], and cardiac progenitor cells [156, 165]. In vivo animal models have shown significant regenerative potential of cell sheets in rat, canine, and porcine models [162]. In addition, 3D arrangements from cell sheets can help retain stem cell pluripotency, in vitro, when preparing for differentiation into cardiovascular tissues [162].

Cardiovascular applications of cell sheet constructs—especially as cardiac patch for repairing myocardial defects—have demonstrated significant graft integration via vascular anastomoses, CM proliferation, and cell junctions [157, 158, 163, 165, 166]. Functional assays in the treated hearts indicated decreased left ventricular remodeling, fibrosis, and wall thinning and conserved ejection fraction [156, 157, 159, 165]. Further, harmonized pacing and reduced arrhythmias have been validated in electromechanical analyses [158, 163].

More accurate in vitro mechanical testing techniques are emerging to better condition and assess cell sheet-based construct prior to implantation [161]. Pushing beyond the diffusion barrier of three-sheet thickness, research groups have achieved up to twelve layers of cells by integrating perfusable vascular beds in bioreactor cultures (Fig. 2) [160, 167]. Looking ahead, advancements in stimulating vasculature, culturing cells on the order of billions, stem cell nutrition, and "omics" technology assays will lead to the next generation of cardiovascular biomaterials [167].

3.7 Nanoscale technologies for cardiovascular tissue engineering

Nanoscale technologies have recently demonstrated promising potential to improve efficacy of the tissue engineering approaches in cardiovascular medicine [122]. Due to their unique physical, chemical, electrical, and mechanical properties, nanotechnologies (and nanobiomaterials) could improve the safety and therapeutic efficacy of the tissue engineered constructs [168]. More specifically, nanotechnologies can provide additional imaging modalities, controlled release of drugs and biomolecules, and lowers risks of rejection of the implants by the immune system [169]. More details on the use of advanced nanotechnologies for the early detection and treatment of coronary atherosclerosis, regeneration/repair of ischemic myocardium, and delivery of molecules and/or (stem) cells into the injured myocardium are provided in our recent review article [122].

Maturation of stem cell-derived CMs is one of the critical aspects of developing therapeutic cellular biomaterials. To enhance maturation in the early differentiated CMs, polydimethylsiloxane substrates with nanoscale 3D topography of the mature CMs were developed and used as cell culture substrates [170]. Culturing of either stem cells or immature CMs on the nanopatterned substrates, resembling the structure of mature CMs, resulted in accelerated differentiation and maturation processes. Such nanoscale substrates could substantially enhance the maturation phenotype of the CMs compared with the cells cultured on conventional tissue culture substrates.

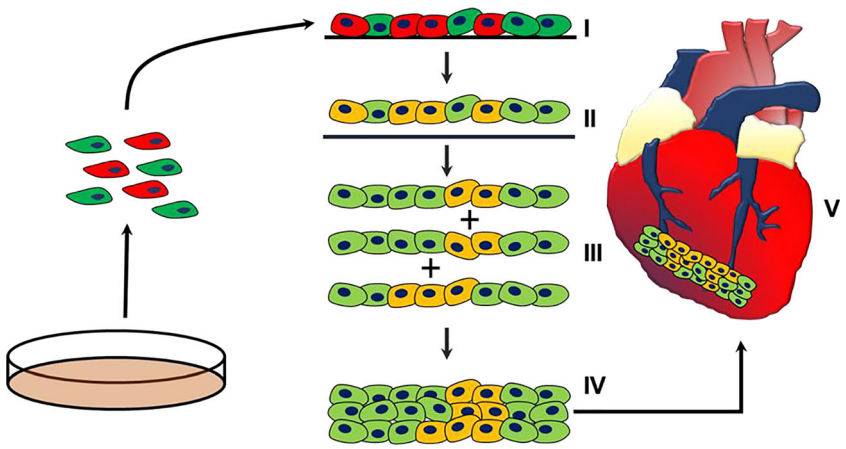


Fig. 1 Self-assembly process for generation of engineered cardiac patches with defined ECM biomaterial. Target cell populations are grown in standard culture, then harvested and seeded onto a biomaterial (I). Cells self-assemble according to provided ques (II), and hybrid building blocks are then recovered (III) to self-assemble in a specific sequence (IV). The produced self-guided tissue construct is subsequently applied to an infarcted heart tissue (V) as a regenerative therapy application

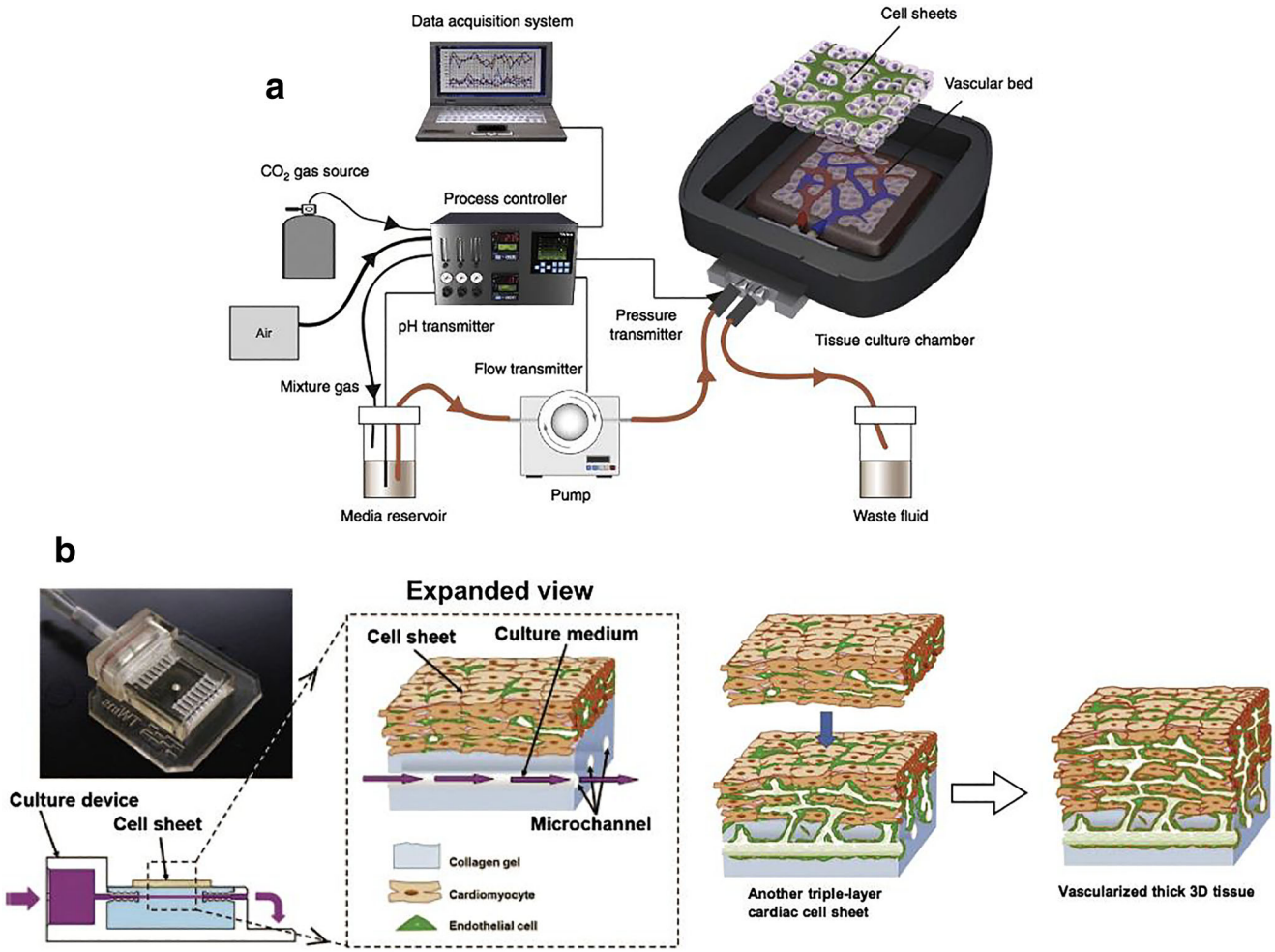


Fig. 2 Prevascularization of cardiac tissue via bioreactor-mediated perfusion of cell sheets [167]

3.8 Shape memory structures

Shape memory constructs are composed of smart materials that are capable of returning from a deformed, temporary state to a permanent, targeted state, when a certain external stimulus is applied [171, 172]. These stimuli include temperature, magnetic fields, and light [173]. Shape memory structures are conventionally metal alloys or polymers. To date, shape memory polymers (SMPs) have taken over the alloy counterparts for use in biomedical research and medicine, as they are inherently biocompatible and cost efficient [173, 174]. SMPs include polymers that are thermoplastics and thermosets. The programming that is applied often consists of deformations by cold drawing at a temperature less than its transition temperature (T_{trans}) or heating up a polymer sample greater than its T_{trans}. After this part of the programming procedure, the polymer is deformed and the desired temporary shape is fixed or recovered [174].

Shape memory technology can lead to structures that vary in sizes, shapes, and pharmacological properties [175]. 3D printing techniques have been used to create SMPs with different ratios of constituent materials, with distinctive properties to create desired functions [173]. Randall et al. outlined the benefits of 3D bioprinting these changing scaffolds for cell culture purposes [175]. The primary use of SMPs in medicine today is in making devices for less invasive surgical procedures [175–177]. In addition, shape memory structures have many novel applications in cardiology, such as arterial catheters for the removal of plaque, and ventricular cardiac leads. SMPs are fascinating candidate materials for use in cardiac stent and catheter systems, as they provide high degree of control on structure and geometry and deploy at body temperature [177]. However, this technology comes with a number of limitations. For example, not all geometric patterns can be made into an SMP while avoiding self-collisions [173]. Some SMPs are not biocompatible over long periods of time, making them imperfect for clinical applications [178, 179]. Finally, functionalization and manufacture of SMPs can be limited in order to preserve their macroproperties, again constricting their usability in the clinic. Considering these limitations, shape memory materials still appear to be an actively

growing subfield in the biomaterials engineering field and will likely find clinical applications in the near future.

3.9 Conventional casting methods

A variety of hydrogel biomaterials (e.g., collagen, fibrin, and gelatin) have been used in conventional 3D casting (molding) methods to create 3D scaffold constructs for cardiovascular tissue engineering applications [54, 55, 57–59, 130, 180]. For example, an embryonic-like cardiac patch was developed by casting type I collagen gel scaffolds in molds of desired shape (24-well culture plate for the mouse study and 6-well plates for the pig study) and compressing the resulting hydrogel [54–56, 59]. The effect of epicardial patch application on cardiac function was evaluated in mouse and pig models of MI. Unconfined plastic compression of highly hydrated collagen gels resulted in formation of dense sheets of collagen with precisely tuned stiffness and protein density [180–183]. Treatment of MI heart with engineered collagen patch, laden with cardiogenic molecules, showed a remarkable recovery in myocardial structure and function in both animal models [54].

Solvent casting has been also used to engineer tissue scaffolds. In this approach, the scaffold construct is made of biocompatible, biodegradable materials with water-soluble particulates in a proper mold. The solvent is evaporated while the particulates are leached away using water to form the pores of the scaffolds [184]. This scaffold-based approach can be applied to creating biosynthetic heart values by using common biomaterials such as PLA and PGA. Following the synthesis, various cells can be seeded into the scaffolds to proliferate, differentiate, and remodel the matrix, hence developing a neotissue [81]. Incorporation of interconnected pores within cast scaffolds is critical in maintaining viable, functional cells, as they facilitate nutrient and waste exchange.

One of the main drawbacks of solvent casting technique is the potentially toxic effects of the residual solvent within the fabricated scaffolds. This can be resolved by fully lyophilizing (vacuum drying) the cast constructs to remove any remaining toxic agents [185]. Other solution is to combine this method with particulate leaching techniques for the scaffold fabrication. In a comparative study by Johnson et al., two solvent casting particulate leaching methods were employed to create cylindrical porous scaffolds, using poly(vinyl pyrrolidone) (PVP) and poly(vinyl alcohol) (PVA) as dispersing agents [186]. Results showed that scaffolds with significantly different pore size and interconnectivity were obtained by changing the porogen, likely due to distinct adsorption kinetics of the two reagents. Further, the two types of scaffolds showed notably different responses when cultured with human coronary artery SMCs, in terms of cell attachment, viability, and spreading.

Freeze drying is another cast-based fabrication technique to generate porous scaffolds based upon the principle of sublimation [187]. In this method, a polymer is first dissolved in a solvent, forming a solution at defined concentration, and cast into a mold. Subsequently, the solution is frozen, and the solvent is removed by lyophilization under vacuum, resulting in formation of highly porous scaffold structure. A variety of biopolymers have been used in this method including silk, PGA, PLLA, PLGA, and their blends [188]. Some of the advantages of this technique include relatively simple fabrication processes, not requiring high temperatures or separate leaching step. Main drawbacks are the inability of incorporating cells in the initial polymer solution (aggressive fabrication steps), smaller pore sizes, and relatively longer processing times.

4 Summary and future perspectives

The development of biomaterials and optimal fabrication techniques will drive the field of cardiovascular tissue engineering by providing the opportunity for creating patient or damage-specific regenerative therapy options. The design of biomaterial scaffolds that are able to host functionalized groups necessary for cell attachment, proliferation, differentiation, and function is a promising bioengineering tool that is being increasing used in both basic research and translational applications. Combining these scaffolding materials with autologous cell sources will offer tissue engineering methods that are more recapitulative of the native tissue microenvironment, as well as regenerative therapies that are safer and potentially more effective in treating patients.

A wide range of biomaterials, of both natural and synthetic types, have been used for cardiovascular tissue engineering, using a variety of manufacturing techniques. For this purpose, fine-tuning material properties such as stiffness, nonimmunogenicity, degradation rate, biocompatibility and bioactivity, electrical conductivity, and biochemical composition is a key in developing next-generation cardiovascular tissue constructs that are capable of offering long-term graft functionality in the near future. The main types of scaffolding biomaterials that are currently being investigated for cardiac tissue engineering include hydrogels, decellularized scaffolds, and self-assembled cell sheets.

The future of cardiovascular biomaterials engineering promises many perspective applications in clinical applications. Emergence and rapid growth of bioink materials for use in a variety of 3D printing and bioprinting processes can provide an unprecedented opportunity to engineer highly complex, patient-specific scaffold systems for in vitro disease modeling and drug screening, as well as in vivo applications to regenerate damaged heart tissue. Decellularized ECM scaffolds, alone or in conjunction with 3D bioprinting (as bioink), have also shown great promise in the field, by allowing to develop patient-derived biomaterials that will significantly

increase engraftment rate and efficiency of cardiac implants. While the future of the cardiac biomaterials field is bright, there remain several drawbacks and problems that require further research. For clinical translation, vascularization is an important factor that most in vitro approaches fall short in. To achieve optimal survival and function of engineered tissues in vivo, adequate vascularization must be incorporated into the scaffold structure prior to implantation. This involves complex cocultures of vascular and cardiac cells in conjunction with angiogenic growth factors implemented in the 3D cardiovascular engineered tissue. The optimal scaffold characteristics, paracrine factors, and/or small molecules to best support cardiac tissue regeneration and long-term function are yet to be fully defined. Suboptimal capacity of current biomaterial-biofabrication techniques in encapsulating physiologically relevant cell densities, approaching that of native myocardium, while maintaining the cardiac function, is another challenge that requires more robust tools to modulate scaffold remodeling, intercellular connections, and cellular contractile function.

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