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Biomaterial applications in cardiovascular tissue repair and regeneration

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Abstract

Cardiovascular disease physically damages the heart, resulting in loss of cardiac function. Medications can help alleviate symptoms, but it is more beneficial to treat the root cause by repairing injured tissues, which gives patients better outcomes. Besides heart transplants, cardiac surgeons use a variety of methods for repairing different areas of the heart such as the ventricular septal wall and valves. A multitude of biomaterials are used in the repair and replacement of impaired heart tissues. These biomaterials fall into two main categories: synthetic and natural. Synthetic materials used in cardiovascular applications include polymers and metals. Natural materials are derived from biological sources such as human donor or harvested animal tissues. A new class of composite materials has emerged to take advantage of the benefits of the strengths and minimize the weaknesses of both synthetic and natural materials. This article reviews the current and prospective applications of biomaterials in cardiovascular therapies.

Keywords

biomaterials; cardiac repair; decellularized tissues; extracellular matrix; metals; polymers; regeneration; stem cells; tissue reconstruction

Cardiovascular disease remains the leading cause of death in the USA, resulting in nearly US\$300 billion in healthcare costs annually [1]. The irreversible organ damage from the disease creates an urgent need for novel methods of repair for the heart. Treatments for cardiac disease include approaches ranging from medications to surgical interventions. Most surgical options involve circumventing the damaged tissues, as in bypass grafts, or replacing them, as in heart transplants. However, sources for human donor tissues are in chronic shortage. Creating alternative therapies would significantly expand patient care options. Efficient means for repairing, reconstructing or regenerating damaged tissues would greatly diminish the need for scarce donor organs. Biomaterials have shown increasing potential as a tool for such procedures. This article reviews the different types of biomaterials used in

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cardiovascular therapies and the cardiac conditions these materials are designed to treat. Novel cardiovascular treatments involving engineered tissue and composite materials are also discussed.

A biomaterial is broadly defined as a material that interacts with biological systems for medical purposes. Biomaterials fall into two main categories: synthetic and natural (Figure 1). Synthetic materials include the classically defined materials of metals, polymers and ceramics. Natural biomaterials are derived from native tissues from autogenic (same individual), allogenic (same-species donor) or xenogenic (animal) sources. Nonhuman tissues are harvested from animal sources such as cows or pigs. In medical applications, preference in the choice of biomaterial has traditionally been for inert materials, in order to minimize reaction with the biological tissues it is in contact with. Examples are titanium metal implants used in hip replacements that do not react chemically with the local area, or biologically inert gold dental fillings. However, newer research has revealed many advantages of interactive biomaterials for expanding treatments to include drug delivery for therapeutics or stem cell transplants for tissue repair and regeneration.

The term 'biocompatibility' is somewhat ambiguous, as the field continues to redefine the nomenclature based on the latest research findings. Biocompatibility generally refers to a biomaterial with properties favorable for implantation while eliciting minimal adverse reactions. Whether the need is for cardiovascular reconstruction purposes or tissue replacement, a biomaterial for implantation must have durability, strength and flexibility to withstand approximately 2 billion cardiac cycles expected to occur in an average lifetime. Equally important are the materials' biologic properties, the most desirable of which being anti-thrombogenicity, noncalcification, hemostasis, nonimmunogenicity and endothelialization capability.

Synthetic biomaterials

Synthetic biomaterials used in cardiovascular applications primarily encompass polymers, metals or a combination of both (Figure 2). Ceramics are used to a much lesser extent in cardiac-related treatments. The main benefits of synthetic materials are their strength and durability, although their biocompatibility issues can create complications. Toxicity is of utmost concern with synthetic materials, especially in the case of biodegradable materials, which can release potentially harmful byproducts of degradation into the body. Chemically inert materials have served as a practical foundation for implantable substances, allowing for stand-alone use or drug delivery through coatings. The most commonly used synthetic materials for cardiac-related applications are described in this article and are summarized in Table 1.

Expanded polytetrafluoroethylene

The use of expanded polytetrafluoroethylene (ePTFE) in cardiovascular applications has become routine owing to this material's performance and ease of use. Commercially, this material is better known as Gore-tex®, and is manufactured by Gore Medical into cardiovascular products for general cardiac reconstruction, vascular grafts and pediatric shunts [201]. ePTFE is composed of a fluorocarbon polymer, formed into sheets by extrusion. A three-layer polymer is created, with a middle microporous, elastic layer surrounded by two layers of polymer fibrils [2]. The resultant structure provides for a high strength-to-weight ratio and resistance to dilatation. The chemical composition promotes low thrombogenicity, lower rates of restenosis and hemostasis, less calcification and biochemically inert properties [3-6]. In addition, ePTFE has been shown to have high resistance to allergic reaction and inflammation [7]. These material properties have made ePTFE an excellent option for creating shunts [8-10], reconstruction [11] and valve repair

[12], and have even been used for covering implantable devices to minimize inflammation [5]. However, since ePTFE is a synthetic material, it can elicit a negative immune response and thrombosis.

Polyethylene terephthalate

Polyethylene terephthalate (PET), or Dacron[®], is a thermoplastic polymer manufactured by Maquet Cardiovascular, with a chemical inertness contributing to its biocompatibility. This material can be manufactured in many forms, but is typically used in cardiovascular purposes as vascular grafts in the woven or knitted configuration. Woven PET has smaller pores compared with the knitted form, which therefore reduces blood leakage. In cardiovascular applications, PET is used for constructing vascular grafts. PET grafts are available with a protein coating, usually collagen or albumin, in order to reduce blood loss and to act as an antibiotic to prevent graft infection [13]. The surfaces of PET grafts are often crimped to stimulate tissue incorporation. Advantageously, PET grafts have been found to promote endothelialization by recruiting endothelial cells to the graft's luminal surface, with no calcification or tissue overgrowth. Collagen and glycosaminoglycan deposits have also been found in implanted grafts, and circumferential mechanical properties show little degradation over time [14]. Similar to ePTFE, PET also has the disadvantage of being a synthetic material and can cause a foreign body reaction with increased chance of thrombus formation.

Prelining PET vascular grafts with endothelial cells has been explored as a means for improving patency rates. In animals, this approach has resulted in improved graft performance [15]; however, human clinical trials showed low patency rates compared with autologous grafts [16]. Currently, PET grafts are used more often than ePTFE ones, although new evidence shows that ePTFE offers some advantages such as lower thrombogenicity [17]. Application of either biomaterial is dependent on the parameters required for the specific cardiovascular tissue to be repaired or replaced.

Polyurethane

Polyurethanes (PUs) belong to a class of compounds called reaction polymers, and are formed by the reaction of an isocyanate group with a hydroxyl group to form a foam. Alternatively, PU can be manufactured into a harder thermoplastic form used in medical applications. Thermoplastic PU has high shear strength, elasticity and transparency. The microbial resistance is ideal for preventing infection, and the material's pliability contributes to improved handling characteristics. The probability for thrombosis of PU is similar to other materials such as PTFE [18]. This material was used frequently in the past in valve replacements [19], until metal and bioprosthetic replacement valves emerged. Currently, PU is mostly used in cardiac pacing leads as an insulator [20]. Although PU is durable, it lacks flexibility. To solve this problem, pacing leads are manufactured with the option of a PU–silicone copolymer to take advantage of silicone's flexibility [202]. Pacing leads coated with silicone alone are also available in the market. Silicone-coated leads have been shown to maintain electrical properties important to pacing better than PU-insulated leads [21]. Each material (PU or silicone) has its own advantages, and leads insulated in either material or a copolymer of both are selected based on the specific requirements of the patient.

On the research side, PU is being investigated as a substrate in cardiac stem cell therapy, with *in vitro* studies being carried out on the influence of patterned PU substrates on stem-cell-derived cardiomyocyte phenotype [22,23]. One disadvantage to PU cardiovascular implants is the material's tendency to oxidize and degrade *in vivo*, creating problems after implantation. Modifications to the material have been effective, as it has been shown that chemically coating the surface with an antioxidant aids in reducing oxidation [24].

Metals

Chemically nonreactive metals have been used for many medical purposes for several decades because of their strength and biocompatibility. Commonly used biocompatible metals include titanium, stainless steel, gold and silver. In the cardiovascular arena, metals are used in stents for opening the lumen of obstructed vessels. Titanium and stainless steel have been classically used in stent design, with newer stents utilizing cobalt–chromium or platinum–chromium alloys for their greater strength [25,26]. Nitinol stents made from a nickel and titanium alloy dominated the market in the past because of their shape memory properties, but nickel allergies have since eliminated their use [27]. Metals are also extensively used in the replacement of heart valves. Mechanical replacement heart valves are constructed from metals such as stainless steel or titanium [28]. Mechanical valves can last the lifetime of a patient, although anticoagulant medications are required for the remainder of their lives because of the higher chance for blood clot formation [29]. Patients who cannot take anticoagulants must choose other valve options, such as natural tissue valves discussed in more detail below.

Natural biomaterials

Whereas synthetic materials have performed better in repair and replacement of damaged cardiovascular tissues, they pale in comparison with the functional capabilities of natural tissues. Each of the tissues in the body is uniquely optimized to its specific organ system, and offers an innate biocompatibility. Autologous tissue, or tissue harvested from and used for the same patient, is the current gold standard for its superior functionality and nonimmunogenicity. Supply of tissues needed and health status of the patient are major hindrances to obtain autologous tissue. The next best choice is allogenic tissues or donor tissues from organisms of the same species; in humans, these tissues are called homografts. Unfortunately, human donor tissues needed for treating cardiovascular disease are in very limited supply, and heart transplant lists remain long. Xenogenic tissues from animals have helped to fill this need, particularly with tissue repairs or valve replacements [30].

Immune response is of particular concern with allogenic and xenogenic tissues. With allogenic human donor tissues, immunosuppressive drugs must be taken by the patient, and even then the tissue or organ may still be rejected [31]. To eliminate immune rejection with xenogenic tissues, they are decellularized before use in patients [32]. Mostly, extracellular matrix (ECM) materials such as collagens and proteins remain after decellularization, leaving a scaffold for damaged tissue to repair in and around the area. In cardiovascular applications, bovine (cow), porcine (pig) and equine (horse) tissue sources have become quite popular for their compatibility to human-sized organs. In this article, common examples of natural materials that are most often used in cardiovascular treatments are described and are summarized in Table 1.

Small intestine submucosa

A material gaining recent popularity in cardiovascular applications is derived from the submucosa of the small intestine. This material is retrieved from porcine sources. Though the small intestine submucosa (SIS) can be processed in many ways, it is generally prepared by first opening the harvested small intestine longitudinally and then mechanically removing the submucosa layer while keeping the basement membrane intact. Cells are removed with an acid, and the resultant ECM sheets are sterilized for patient use [33]. The SIS-ECM is comprised of collagens I, III, IV, V and VII, fibronectin, elastin, glycosaminoglycans, glycoproteins and growth factors such as VEGF, FGF-2 and TGF- β [34].

Used successfully for decades as a wound dressing, other clinical applications have been explored for SIS. In cardiac treatments, so far SIS has been used for pericardial

reconstruction and carotid repair [35,36]. Advantages to this material include its biodegradability, hemostatic capability, nonencapsulation and noncalcification [33]. Disadvantages include a relative shortage in supply and potential immunogenicity issues from the decellularized xenogenic tissue. Interestingly, in an orthopedic application, SIS was shown to promote cell migration into itself once implanted and to encourage subsequent local tissue remodeling and regeneration [37]. These results are promising for regenerating cardiac tissue.

Several animal studies have been conducted to investigate other possible cardiac-related applications of SIS. An emulsion form of SIS has been tested for effectiveness in treating myocardial infarction (MI). Infarcted animal hearts were injected with the SIS emulsion. Angiogenesis was significantly increased compared with control infarcted hearts injected with saline. Echocardiography showed improved fractional shortening, ejection fraction and stroke volume [38]. The potential of SIS to serve as a scaffold for cardiac tissue engineering has also been examined. In one study, neonatal rat cardiac cells were mixed with a gel form of SIS and deposited onto polymer substrates. The resulting tissue constructs showed significantly higher contraction rates and greater troponin T expression compared with Matrigel™ (BD Biosciences) controls [39]. A combined SIS and stem cell therapy for treating chronic MI was also investigated. Bone marrow mesenchymal stem cells (MSCs) were seeded onto patches of SIS and grafts were implanted onto the epicardial surface of infarcted myocardium in rabbits. Patches of SIS alone were also implanted for comparison. Left ventricular contractile function and dimension, capillary density of the infarcted area and myocardial pathological changes were significantly improved in both SIS groups with and without cells.

Results with cells were slightly better [40]. These animal studies show that SIS has potential to be used for treating MI and also for cell delivery with the purpose of regenerating the damaged areas of the heart. Finally, in a clinical study on patients undergoing primary isolated coronary artery bypass grafting, a statistically significant decrease in the rate of postoperative atrial fibrillation was seen in patients who also underwent pericardial reconstruction using SIS compared with those without any reconstruction [35].

Pericardium

The pericardium is a fibroserous sac surrounding the mammalian heart. It has long been used in cardiac repair for reconstruction, valve repair and pericardial closure [41,42]. Xenogenic pericardium is commonly derived from bovine, porcine and, less frequently, equine sources. Tissues from these sources are available in large patches, allowing custom configuration to a variety of cardiovascular applications. It is largely comprised of collagen fibers and has elastic properties allowing conformity to complex anatomy. Pericardial tissue has exceptional handling characteristics and uniform suture retention. In addition, it is nonthrombogenic and naturally resists infection [43].

To reduce the probability of an adverse immune response, the pericardium is decellularized using one of many possible processing procedures, resulting in predominantly ECM components. Tissue morphology and collagen structures are dependent on the decellularization process chosen [44]. Following removal of cellular content, the tissue is typically crosslinked using glutaraldehyde for preservation and to increase strength of the biomaterial. However, calcification of pericardial grafts postimplantation is attributed to glutaraldehyde processing [45,46]. Hence, several studies have investigated new methods for processing the pericardium to maintain ECM content and structure, and to strengthen the biological tissue without causing calcification *in vivo*. Approaches have included treating the glutaraldehyde-processed pericardium with glutamic acid [45], modifying the decellularization procedure [44], and nanocoating pericardial grafts with titanium to prevent

immune reactions and thus calcification [47]. Some anticalcification technologies are being used in commercially available pericardial grafts [203], although most techniques still require more testing in order to become routine practices.

There are slight differences between pericardium from the different sources. Pericardium from bovine sources has higher collagen content than that derived from porcine origins [48,49]. Valves fabricated from bovine pericardium have shown less obstruction than valves made from porcine pericardial tissue, although both valves show similar hemodynamic results [50]. Bovine and porcine tissues did not exhibit a significant difference in the degree of calcification under varying glutaraldehyde treatments [46].

Bioprosthetic valves

Severely damaged heart valves require replacement. Generally, metal mechanical valves or bioprosthetic (i.e., biological) valves obtained from human donor or animal sources are used. Blood has a tendency to adhere to the metal in mechanical valves, resulting in blood clots. Therefore, patients with mechanical valves must take anticoagulant medications for the rest of their lives [51]. Natural tissue valves do not require the use of anticoagulants, which is an advantage over mechanical valves. The most common animal sources for biological valves are bovine or porcine tissues [52]. On average, bovine valves typically last 15–20 years whereas porcine valves last 8–15 years [202]. Differences between commercial valves are mostly due to the variation in manufacturers' specifications, including variable parameters such as hemodynamics, implantation method, suturability and valve dimensions [203]. When bioprosthetic valves fail, it is usually due to calcification and tearing [53].

Although mechanical valves made of titanium or carbon are stronger and last longer than biological valves (typically up to 25 years), patients implanted with mechanical valves must continually take an anticoagulant medication (e.g., Coumadin[®]; Bristol-Myers Squibb). Age is a major factor in longevity of a replacement valve. Children and younger patients use up replacement valves faster than older patients because of activity and metabolism [54]. Patients younger than 65–70 years of age typically receive mechanical valves, while patients older than that receive bioprosthetic valves. Middle-aged patients may select either type of valve, although there is evidence that bioprosthetic valves are a better choice for this age group because these valves are likely to last the remainder of the patients' lives without the use of anticoagulant medications [55].

Injectable biomaterials

In recent years, injectable biomaterials have seen significant increase in application towards treating MI [56–58]. Injectable materials mostly encompass: hydrogels composed of alginate, fibrin, chitosan, collagen or matrigel; and self-assembling peptides generally in the form of nanofibers. Injectables originally generated interest owing to their biocompatibility, ability to provide beneficial chemical environments and, above all, for their potential to be delivered noninvasively. Efficacy of these materials has been explored extensively in animal infarct models and has shown success in improving cardiac function, reducing infarct size, increasing wall thickness in the infarcted area and increasing neovascularization. Alginate hydrogel is a polysaccharide derived from seaweed. It is used as a temporary ECM substitute and has affinity-binding moieties, enabling binding of proteins and their controlled release for drug delivery and transfer of growth factors [59]. Alginate gel has been shown to reverse left ventricular remodeling following MI [60]. Fibrin is formed from the interaction of the blood proteins fibrinogen and thrombin during the process of clotting in a wound following injury. Fibrin glue is used surgically as a sealant, to control bleeding, speed wound healing, to fill holes after surgery, and in drug and cell delivery [61,62]. Chitosan is a polysaccharide extracted from the exoskeleton of crustaceans and is primarily

used to promote rapid blood clotting. In addition, chitosan hydrogel has been used as a delivery vehicle for proteins [63,64] and cells, which in the latter case resulted in enhanced stem cell engraftment, survival and homing in an ischemic heart [64]. As a major ECM component, collagen plays an important role in the remodeling process that occurs in infarcted tissue. Collagen gel has been a popular material to test for its ability to repair infarcted heart wall because its ECM origins have potential to recruit endogenous cells for regeneration. For this reason, collagen gel was one of the first materials to be used for cell encapsulation and delivery into the heart [56,65]. Many studies have used collagen gels to deliver MSCs to infarcted regions and have shown improvement in cardiac function by increased vascular density [66]. Matrigel is a protein mixture derived from mouse sarcoma cells, and contains many important ECM proteins such as laminin and collagen, and growth factors that promote proliferation and differentiation [56,67]. Matrigel is widely used as an attachment substrate for embryonic and induced pluripotent stem cells in culture, with logical follow-up application to support stem cell survival in *in vivo* animal studies. Matrigel is able to retain stem cells after injection into infarcted tissue and subsequently improve cardiac function. However, as this gel is derived from mouse tumors, it is not applicable to human use. Self-assembling peptides are nanostructures formed from spontaneous aggregation of peptides, usually into nanofibers. These peptide chains are able to provide 3D microenvironments capable of recruiting cells, promoting vascularization and delivering growth factors. When injected into an infarcted heart, infarct size was reduced, vascular density was increased and cardiac function was recovered [68]. Self-assembling peptides have also been coinjected with MSCs, resulting in sustained growth, survival and differentiation of the stem cells, and reduced infarct size and significant improvement in cardiac functional measures (e.g., systolic function indices, left ventricle ejection fraction and left ventricle fractional shortening) [69].

Engineered tissues

Many attempts have been made to engineer various cardiac tissues, particularly of the heart valve. Although mechanical and bioprosthetic valves have been valuable for restoring heart function and quality of life for patients, each valve has its drawbacks, mostly owing to dependency on anticoagulants and limited durability due to tissue deterioration. More importantly, neither valve type is able to grow and expand with the patient as they grow older. For these reasons, tissue-engineered heart valves have been explored extensively. Desirable parameters for tissue-engineered valves include nonthrombogenicity, biocompatibility, capability for growth and remodeling, easily implantable, hemodynamically compatible and life-long durability [70]. Tissue-engineered valves would be particularly applicable to pediatric cases. The current challenge is to produce a tissue-engineered valve with the mechanical strength to withstand the blood pressure and contractility forces of the heart that is capable of seamlessly integrating with the native cells and tissues [71]. The classic approach for engineering valves is to use decellularized allo- or xeno-grafts on which different types of cells are seeded. Some examples of various combinations are homografts seeded with cardiac-derived mesenchymal stromal cells [72], porcine valve and pericardium seeded with bovine fibroblasts [73] and a fibrin gel combined with human dermal fibroblasts [74].

Despite the success in creating different types of tissue-engineered heart valves, clinical use has yet to be achieved due to lack of *in vivo* verification of feasibility. There have been a few clinical studies with conflicting results. One study involved 93 patients undergoing right ventricular outflow tract reconstruction using the Matrix P/Matrix Plus® (AutoTissue GmbH) xenogenic decellularized tissue-engineered pulmonary valve conduit. Conduit failure occurred in 33 patients (35.5%) and conduit dysfunction occurred in 27 patients (29%). Reasons for failure were conduit stenosis, pseudoaneurysm, conduit dilatation,

stenosis of distal anastomosis involving pulmonary bifurcation and allograft dissection. Histological analysis showed inflammatory cells and poor endogenous cell seeding in all explanted specimens [75]. Conversely, in another study of 11 patients undergoing right ventricular outflow tract reconstruction, valves were replaced with pulmonary allografts seeded with autologous endothelial cells. At 10 years, multislice computed tomography showed no evidence of calcification, and echocardiography showed a mean pressure gradient of 5.4 ± 2.0 mmHg. Biopsies showed a confluent monolayer of endothelial cells covering the allograft's inner surface [76]. In addition, another study involving the Matrix P conduit showed mixed negative and positive results of valve failure and no calcification [77]. These conflicting results demonstrate the need for further testing.

Other myocardial tissues have been created *in vitro*, based on the general approach of seeding cells onto a scaffolding material. Commonly used cell types have been skeletal myoblasts, murine neonatal cardiomyocytes, MSCs mainly from bone marrow or adipose tissue, cardiac progenitor cells, cardiosphere-derived stem cells, endothelial progenitor cells, embryonic stem cells and induced pluripotent stem cells [78-80]. Scaffolding material has included hydrogels, polymeric fibers (randomly configured and aligned), decellularized ECM and peptides [80-83]. Monolayers of cells have also been stacked to form scaffold-free tissues [84]. These materials are favored for their chemical, structural, biocompatible, degradability and formable characteristics. Engineered tissues transplanted into various animal models help to restore or improve tissue function, and clinical trials have shown some success [84-86]. However, as in the case of tissue-engineered valves, engineered myocardium and vascular tissue still need further developments to make them more relevant to the clinic.

Composite & modified biomaterials

Both natural and synthetic biomaterials have their limitations and can produce unwanted effects, such as limited durability and a higher chance for thrombosis. Natural biomaterials are superior in functionality and biocompatibility, but lack robustness. Synthetic biomaterials have advantages of strength and durability, but are deficient in functional capabilities. Combining materials into composites has created better options that benefit from the strengths of different materials and minimizes the weaknesses. Composite materials are achieved through the methods of blending (physically combined without forming chemical bonds), coating (by submersion or spraying), copolymerizing (polymer structure modified to form multiple block monomers then polymerized) and multilayering (sandwiching of materials followed by mechanical fixation) [87,88]. Injectable hydrogels are commonly combined with each other and other elements, and have the benefit of tunable properties that can be controlled by modifying crosslinking [89-91]. Bioprosthetic valves have been reinforced with polymeric material to abate the natural tissue's innate lack of strength [92], providing an example of a composite taking advantage of the assets of each biomaterial.

Biomaterials can be combined with cells to provide support structure to enhance cellular growth and survival. Tissue regeneration using cellular material has been investigated as a healing mechanism for damaged and diseased heart tissue. Their proliferative capability and potential to differentiate into cardiovascular lineages make stem cells an ideal option [56]. Many different adult stem cells have been investigated in preclinical and clinical studies [56-64]. The major issue delaying stem cell therapy from widespread use is the fact that once injected *in vivo*, engraftment is low due to cell migration out of the wound site, and/or the cells simply die [69]. Delivering stem cells with biomaterials has become an increasingly popular method, and has developed into a field of its own. Numerous studies are testing biomaterials such as injectable hydrogels or patch material from natural and synthetic

sources, or growth factors as solutions for maintaining stem cells to the wound site to improve engraftment and to aid in their survival and proliferation post-transplantation [40,56,93-95]. Most of these studies are at the preclinical stage. In one study, human MSCs incorporated into a collagen patch-assisted engraftment decreased left ventricle systolic interior diameter, increased anterior wall thickness and increased fractional shortening by 30% [94]. In another study, human bone marrow CD133⁺-derived cells transplanted on a collagen patch onto an injured heart resulted in formation of new microvessels, thought to be induced by the patch [95]. A mixture of growth factors was able to prolong survival of transplanted cardiomyocytes derived from human embryonic stem cells, improving cell engraftment after infarct [93]. In a clinical trial, a collagen matrix seeded with bone marrow cells was applied to the heart in patients with left ventricular postischemic myocardial scars. At 10 months after treatment, left ventricular end-diastolic volume beneficially decreased and left ventricular filling deceleration time significantly improved with the collagen matrix. Scar area thickness was increased in the matrix group through the addition of viable tissue. Ejection fraction results were independent of treatment group, as left ventricular ejection factor improved with or without the collagen matrix [85]. Overall, the research findings show that there is much potential for stem cells to effectively treat cardiovascular ailments, as long as methods for administering such treatments are developed to optimize therapeutic outcomes. In the future, successful application of stem cells will most probably involve delivery with biomaterials.

Biomaterials can be modified to extend their usefulness for drug delivery and gene therapy. Polymers are engrafted, and gels easily mixed with growth factors, cytokines and pharmaceuticals to allow drug-releasing systems capable of controlled release [96,97]. Different drugs and growth factors can be delivered, such as anticoagulants and peptides that promote endogenous cell proliferation and angiogenesis [96,98]. Tissue-engineered grafts have incorporated various drugs and growth factors into their scaffolding structure to enhance differentiation of the cells seeded onto it. Growth factors such as EGF, TGF, VEGF and BMPs have been used to stimulate differentiation of seeded cells towards cardiovascular lineages [96,99,100].

Expert commentary & five-year view

Future efforts should focus on perfecting composite materials to take full advantage of the optimal combination of both synthetic and natural biomaterials to improve the overall performance of implantable materials. This approach will exploit the combined advantages of both material types. Composite biomaterials have the potential to solve the current dilemma of having to choose between either synthetics or natural tissues and foregoing the benefits of one or the other material. Given the diversity of cardiovascular conditions and resulting variable treatments needed, the wider use of composite biomaterials may be the best approach for improving disease management.

In addition, efforts for supporting stem cell retainment and survival using biomaterials should become more aggressive. There is much potential for translation of stem cell therapy to be realized using this approach. This could lead to regular application of tissue regeneration techniques, creating the ideal solution for cardiovascular tissue repair.

As the field develops, stem cells will increasingly enter the arena of cardiovascular therapy. Solutions to the challenges of stem cell survivability and proliferation post-transplantation are under intense exploration in the laboratory, and will probably involve the use of biomaterials. With the countless efforts towards this end, development on the material side will conceivably come to a conclusion and produce a narrowed down list of efficacious materials coupled with the appropriate stem cell. While tissue repair and replacement have

been acceptable means of treatment, tissue regeneration would be far more ideal for restoring full function of the diseased heart, and is the next frontier to aim for.

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Key issues

- Biomaterials used in cardiovascular therapies fall into two major categories: synthetic and natural materials.
- Synthetic materials used for cardiac repair mostly encompass polymeric materials, with a few applications of metals, and offer advantages of strength and durability.
- Natural materials are derived from autologous, allogenic or xenogenic sources, and have superior functional properties but lack robustness.
- Stem cells have potential to develop into a viable cardiovascular therapy by facilitating tissue regeneration, although problems involving cell survivability need to be overcome first and solutions thus far are heavily dependent on biomaterials.

Figure 1. Overview of biomaterials currently used in cardiovascular applications

Figure 2. Examples of various biomaterials used in cardiovascular products

Uses for synthetic biomaterials composed of polymers include (A) expanded polytetrafluoroethylene, or Gore-tex[®], for pericardial repair; (B) polyethylene terephthalate, or Dacron[®], for vascular grafts and (C) polyurethane in leads. Synthetic biomaterials of metals are used in (D) heart valves and (E) coronary stents. Natural biomaterials used for cardiovascular repair include (F) small intestine submucosa extracellular matrix, (G) bovine pericardium and (H) human pulmonary heart valves. (A) courtesy of W.L. Gore & Associates, Inc.; (B) courtesy of MAQUET Cardiovascular LLC; (C) & (E) courtesy of Medtronic, Inc.; (D) courtesy of St Jude Medical, Inc.; (F) courtesy of the authors (material from CorMatrix Cardiovascular, Inc.); and (H) courtesy of CryoLife, Inc.

Table 1

Applications of biomaterial products in treatment of cardiovascular conditions.

Biomaterial	Material composition	Source	Applications	Benefits	Ref.
<i>Synthetic materials</i>					
GORE-TEX®	ePTFE	Gore Medical	Shunts, reconstruction, vascular graft, atrial septal defects, valve repair and extracardiac Fontan procedure	Nonbiologic, low thrombogenicity, high strength, nonfraying, conformable, restorable, good patency, avoidance of excessive shunt flow, kink resistance, improved handling, better tissue approximation for use in neonates, palliate or correct interrupted aortic arch	[201]
Dacron®	PET	Maquet Cardiovascular	Vascular graft	Tissue ingrowth, high patency, hemostasis and biocompatibility	[204]
NA	Polyurethane	St Jude Medical, Medtronic	Pacing leads and valve repair	Strength, elasticity, transparency, resists infection and improved handling	[205,202]
Metals	Titanium, stainless steel, nitinol, cobalt–chromium and platinum–chromium	Medtronic, Edwards Lifesciences	Mechanical heart valve and stents	Strength, durability, low thrombogenicity and excellent hemodynamics	[202,203]
<i>Natural materials</i>					
SIS	ECM (collagen, elastin, glycoproteins, glycosaminoglycans, proteoglycans, growth factors and others)	Porcine (Cook Biotech, CorMatrix Cardiovascular)	Pericardial closure, cardiac tissue repair, carotid repair (off-label use: valve reconstruction)	Biodegradable, nonencapsulation, noncalcification, promotes tissue remodeling, scaffold for native cells to migrate and integrate into, and hemostatic	[206,207]
Allogenic pericardium	Donor pericardial sheets	Human (CryoLife)	Reconstruction, buttressing, leaflet repair and aortic root enlargement	Biocompatibility, good mechanical properties, durability (glutaraldehyde fixed) and pliable	[205,208]
Xenogenic pericardium	Crosslinked collagen patch	Bovine, porcine, equine (St Jude Medical, Neovasc, Edwards Lifesciences, Vascutek Terumo)	Atrial and ventricular septal defect repair, pericardial closure and valve replacement	Good host tissue response, reduced adhesion formation, nonthrombogenic, noncarcinogenic, less intraoperative suture line bleeding, good tensile strength, resists infection and biocompatible	[203,209,210]
Autogenic/allogenic valve	Self, donor valve	Human (CryoLife)	Ross procedure and valve replacement	Low immune response, biocompatibility and superior functionality	[208]
Xenogenic valves	Animal valve	Bovine, porcine (St. Jude Medical, Sorin Group)	Valve replacement	Anti-thrombogenic and biocompatible	[205,211]

ECM: Extracellular matrix; ePTFE: Expanded polytetrafluoroethylene; NA: Not applicable; PET: Polyethylene terephthalate; SIS: Small intestine submucosa.