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Chapter 12

Polymeric Scaffolds for Bioartificial Cardiovascular Prostheses

Marcel Ricklefs, Sotiris Korossis, Axel Haverich and Tobias Schilling

Additional information is available at the end of the chapter

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Abstract

The reconstruction or replacement of diseased heart valves, the revascularisation of coronary arteries by coronary artery bypass grafting, the replacement of the central or peripheral blood vessels, and the reconstruction of the irreversibly damaged heart muscle represent the most common fields of application of cardiovascular surgery. In such cases, the diseased tissue is replaced by either a synthetic (metallic or polymeric) or a biological (xenograft, homograft, or autograft) prosthesis, or tissue engineered constructs. The aim of this book chapter is to give an overview over the most frequently used synthetic and biologic polymers as scaffold material in cardiovascular surgery.

Keywords: tissue engineering, polymer, scaffold, heart valve, cardiothoracic surgery

1. Introduction

Cardiovascular disease is the leading cause of death worldwide. In 2015 alone, 17.7 million people died due to cardiovascular disease, accounting for 31% of all deaths worldwide [1]. Beyond limiting the risk factors that could potentially lead to cardiovascular disease and the administration of a pharmaceutical regime, surgical treatment represents a life-saving option for severe forms of cardiovascular disease. The reconstruction or replacement of diseased heart valves, the revascularisation of coronary arteries by coronary artery bypass grafting, the replacement of the central or peripheral blood vessels, and the reconstruction of the irreversibly damaged heart muscle represent the most common fields of application of cardiovascular surgery. In such cases, the diseased tissue is replaced by either a synthetic (metallic or polymeric) or a biological (xenograft, homograft, or autograft) prosthesis, or tissue engineered constructs.

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1.1. Limitations of currently available implants

The limitations of currently available cardiovascular prostheses necessitate further research and development of improved materials for diseased tissue replacement. For example, the implantation of synthetic prostheses, such as mechanical heart valves, requires lifelong anticoagulation treatment. On the other hand, glutaraldehyde-treated biological prostheses (xenografts) tend to calcify [2–5], whereas homograft prostheses have been reported to initiate an immunogenic reaction in the recipient, which leads to rejection responses. Also, most implants that are in direct contact with the bloodstream show thrombogenicity [6]. Especially small calibre vessels are prone to stenosis due to thrombus formation, intimal hyperplasia, or neointima formation. Synthetic implants are very susceptible to infections, which like any graft failure is at the very most an indication for high-risk and expensive revision surgery [7]. Moreover, cardiovascular implants need to meet biomechanical requirements for appropriate long-term *in vivo* function. The development of aneurysms is not a rare case with prostheses in the high-pressure arterial system. Also, the characteristics of the prosthesis should support its integration with the surrounding tissues. Accordingly, grafts with high porosity can lead to good tissue integration, but high porosity could also potentially cause bleeding complications due to the insufficient sealing. Covering the prosthesis with anti-thrombogenic substances such as albumin, collagen, or gelatine predisposes to the same complication [8]. Owing to the ageing of the population and the subsequent need for cardiovascular implants, optimised materials and prostheses are necessary in the future to avoid high-risk, stressful and expensive revision surgery, which induces a threatening economic pressure on healthcare systems.

1.2. Requirements for ideal cardiovascular prostheses

Based on previous experience and large-scale clinical studies with implants and the long-term postoperative medical aftercare, there are some characteristics of an ideal cardiovascular prosthesis. The prosthesis should demonstrate high long-term durability and should have the capacity for regeneration and growth. Grafts that have the potential to regenerate would be especially beneficiary for the paediatric population since they would be capable of growing in the host, avoiding reoperations. Prosthetic vessels and valves should also present physiological hemodynamics, allow for unrestricted blood flow without any volume losses, turbulences, or stasis, and present no thrombogenicity [9] or interference with the blood constituents [10]. Since anticoagulation or platelet inhibition therapy might lead to bleeding complications, these therapeutic regimes should be avoided [11]. Furthermore, there should be no interference with other cardiac structures [12, 13]. In case of *in vitro*–seeded prostheses, the utilised cells need to be non-immunogenic (autologous or HLA-silenced homologous) and functional. Homologous donor cells in homografts can cause immunogenic reactions and subsequent graft degeneration, scar tissue formation, loss of flexibility, and, ultimately, graft rejection [14]. Moreover, any degradation products of the implanted prosthesis should be non-toxic and metabolise physiologically [15, 16]. Preferably, the ideal prosthesis should also possess a physiological structure, resembling the tissue it replaces [17, 18]. The prosthesis should be available for all patients in need, easily storable, transportable, and implantable.

1.3. Tissue engineering of regenerative grafts

Tissue engineering allows for the development of viable implants, with a regenerative and growth potential after implantation in the patient. The fundamental approach of tissue engineering comprises five steps [19, 20] (**Figure 1**):

A. Cell sourcing, cultivation, and expansion *in vitro.*

B. Development of a scaffold of either synthetic or biological origin (e.g. collagen or decellularised tissue), which could either be implanted for subsequent endogenous cell repopulation (*in vivo* tissue engineering) or seeded with appropriate cells *in vitro* prior to implantation (*in vitro* tissue engineering).

C. Cell seeding of the scaffold *in vitro*, followed by physical conditioning and maturation (regeneration and neo-tissue formation) in a functional simulation system (bioreactor).

D. Implantation of the scaffold or the tissue-engineered construct.

E. *In vivo* remodelling of the graft (guided tissue engineering).

Scaffolds should contain as many physiological characteristics of the natural extracellular matrix (ECM) as possible, including histoarchitecture and composition. Numerous complex interactions between the ECM and cells are necessary for inducing appropriate cellular function, including adhesion, migration, proliferation, and differentiation, as well as ECM degradation and synthesis [21–25]. The closer the scaffold's substrate for cell seeding is to its natural equivalent, the more the seeded cells develop their physiologic phenotype [26] to produce a viable, metabolically active prosthesis. Mainly interstitial cells and endothelial cells are used in cardiovascular tissue engineering. Seeding with endothelial cells (ECs) fulfils two main functions especially for cardiovascular tissue–engineered constructs; the scaffold is a foreign body and, therefore, a target not only for thrombocytes but also for immune cells. An EC layer shields the scaffold material and reduces both thrombogenicity and immunogenicity, the latter being the reason for the prostheses' degradation.

Mimicking natural ECM synthesis and degradation processes, the scaffold of the tissue-engineered construct would be degraded and regenerated by the seeded connective tissue cells. To maintain structural and mechanic integrity, the degradation rate of the scaffold should match the formation of new tissue [27]. Because of these remodelling, the tissue-engineered prosthesis would not be indistinguishable from the native organ after a while.

Decellularised xenogeneic or allogeneic tissue ECMs or polymers are commonly utilised substrates for engineering of cardiovascular scaffolds. The main drawbacks of xenogeneic or allogeneic tissue ECMs are the potential risk of disease transmission, variability in production, and limited availability (allogeneic) [28]. On the other hand, polymers made of biological or synthetic substances can be produced in unlimited amounts under sterile conditions. The aim of this chapter is to give an overview of polymer-based synthetic or biologic cardiovascular prosthesis.

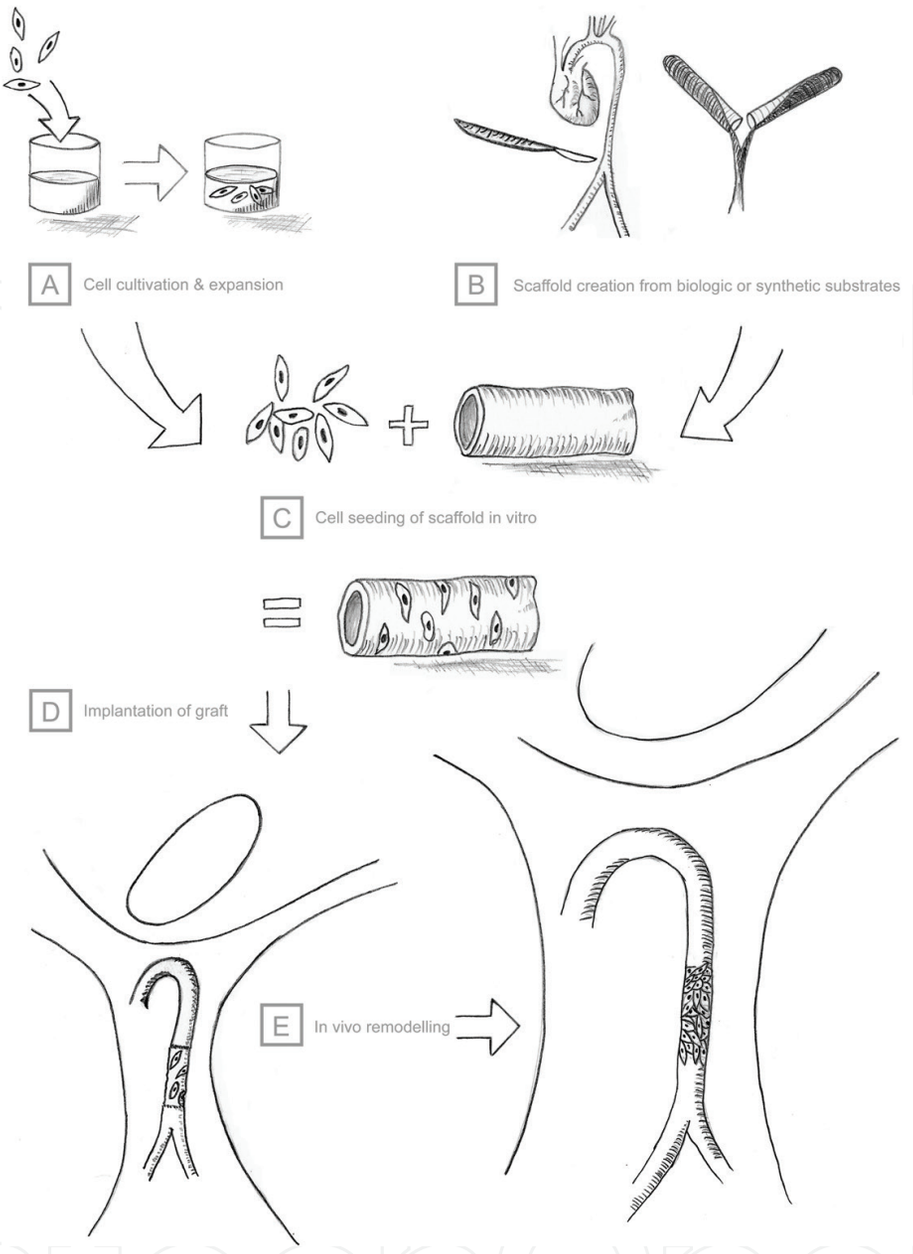


Figure 1. Drawing of the principles of tissue engineering. A: Cell sourcing, cultivation, and expansion *in vitro*. B: Development of a synthetic or biological scaffold. C: Cell seeding of the scaffold *in vitro*. D: Implantation of the scaffold. E: *In vivo* remdelling of the graft.

2. Indications for the use of polymer-based cardiovascular implants

2.1. Aetiology, pathophysiology, and surgical therapy of heart valve disease

There is a huge diversity of aetiologies of heart valve defects requiring surgical intervention. **Table 1** gives an overview of heart valve diseases requiring surgical intervention. Tricuspid or pulmonary valve dysfunction has a lower incidence than pathologies of the aortic or mitral valve [29, 30] since the left heart bears higher blood pressures and the valves are, therefore, subjected to a higher grade of mechanical stress. In general, heart valve dysfunction involves regurgitation,

Congenital	Immunological	Infectious	Degenerative	Traumatic	Others
• Prolapse • Aortic aneurysm • Bicuspid valves • Primary cardiomyopathy • Stenosis • Atresia • Regurgitation • Marfan syndrome • Ehlers-Danlos syndrome	• Rheumatic fever • Scarlet fever • SLE • Scleroderma	• Endocarditis • Endomyocarditis	• Prolapse of mitral valve • Calcification	• Aortic dissection • Aortectasis • Blunt thoracic trauma	• Ischemia • Mechanic (HOCM) • Idiopathic

Table 1. Overview of heart valve diseases with the potential need for surgery (mitral- and aortic valve).

stenosis, or a combination of both. Left untreated, valvular dysfunction, which initiates either a concentric (stenosis) or an eccentric (regurgitation) hypertrophy, results in congestive heart failure—a considerable economic burden and the most common reason for hospitalization of the elderly [31]. Since the early days of valve replacement, the procedure is being carried out by applying either mechanical (**Figure 2A**) or biological (**Figure 2B**) prostheses, the latter being xenogeneic (made from treated animal valves or animal-derived pericardium) or allogeneic.

There are different access paths and principles to implant heart valve prostheses. Since the 1960's, the standard surgical approach, via full sternotomy, is the therapy of choice for most patients. In surgery of the elderly and severely co-morbid patients, it is beneficial to reduce the time of the intervention to a minimum, which can be achieved by implanting sutureless heart valve prostheses (**Figure 2C**). In contrast to the standard surgical approach, these valves do not require the time-consuming suturing of the valve into the annulus, as those grafts keep their position by an expandable metal stent. The third approach is the percutaneous, catheter-based application of a heart valve transcatheter aortic valve implantation (TAVI). This intervention is performed in the operating room, cardiac catheter laboratory, or hybrid operating room (**Figure 2D**). Innovative materials for polymer-based valve prostheses, the aforementioned different procedures, and the resulting options and restrictions should always be considered.

2.2. Aetiology, pathophysiology, and surgical therapy of vascular disease

Arteriosclerosis is an arterial disease, in which the lumen of the vessel is occluded by calcification [32]. In case of a complete obstruction, the area perfused by the affected artery undergoes critical hypoperfusion. A complete acute obstruction of the vessels leads to myocardial infarction, apoplexy, or insufficient blood circulation in the extremities. An overview of the aetiology of aortic disease with the need for interventions is presented in **Table 2**. The ischemic cardiovascular disease carries the highest mortality rate worldwide [1]. The gold standard for the treatment of severe cases of occlusive vascular disease is surgical revascularisation. In these cases, the affected vessels are replaced, or the obstruction is bridged by a vascular graft (i.e. "bypass-surgery"). Synthetic polymer grafts made from alloplastic materials, such as Dacron,

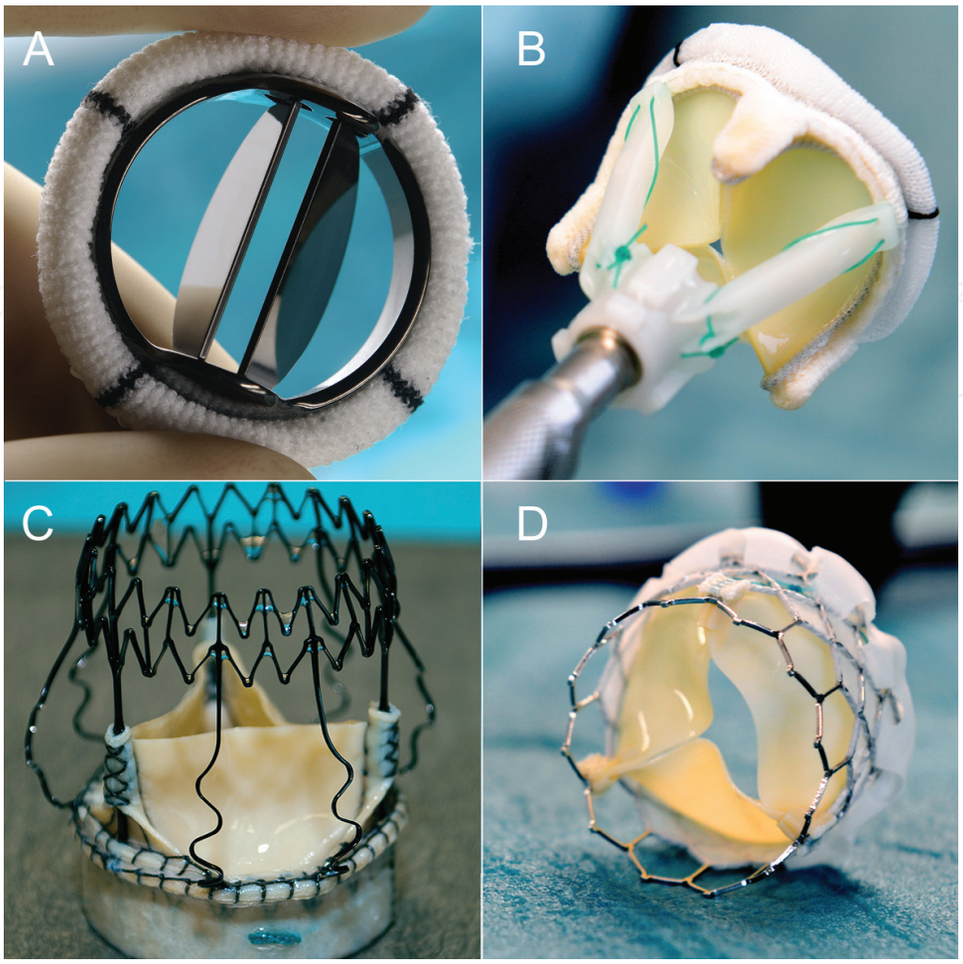


Figure 2. Currently used valve prostheses: (A) mechanical valve, (B) biological, xenogenic valve, (C) sutureless, biological valve, and (D) valve for TAVI procedure.

are routinely used clinically for the replacement of large vessels, such as the aorta (**Figure 3**). However, synthetic polymer grafts for small vessels still show problems regarding patency and development of an intimal hyperplasia or thromboembolic events [6]. Furthermore, a life-threatening adverse effect of long-distance replacement of large vessels is therapy-refractory hypertension with subsequent end-organ damage, since the currently available aortic grafts lack the function of Windkessel. Owing to this, the identification of suitable, anti-proliferative, regenerative, and mechanically functional materials, manufacturing processes, and coatings still are the primary objectives of current research in the field of vascular prostheses.

2.3. Aetiology, pathophysiology, and surgical therapy of myocardial disease

Ischemic heart conditions, such as chronic coronary artery disease, myocardial infarction or infection, or immunologic diseases such as sarcoidosis or amyloidosis, lead to a loss of viable heart muscle cells (cardiomyocytes). In contrast to other cells, adult human cardiomyocytes cannot proliferate. Therefore, the necrotic myocardium is replaced by functionless scar tissue. This weakens the heart muscle pump and eventually causes heart failure. The heart is not able to generate an adequate blood flow. Congestive heart failure is characterised by a high mortality and recurrent, long hospitalisations [33]. In 2013, congestive heart failure was the reason for every

Deformation	Occlusive diseases	Aneurysm	Trauma	Others
• Aneurysm	• Arteriosclerosis	• Arteriosclerosis	• Blunt thoracic trauma	• Aortic insufficiency
• Aortic coarctation	• Stenosis	• Familial thoracic aortic aneurysm	• Penetrating wounds	• Shunts (dialysis)
• Aortic arch abnormalities	• Thrombosis (acute vs. chronic)	• Marfan syndrome	• Iatrogenic trauma	
• Aberration	• Embolism	• Trauma	• erosion (tracheostomy)	
• Stenosis		• AV fistula		
		• Inflammatory (e.g. SLE)		
		• Infection (e.g. rheumatic fever)		
		• Iatrogenic (e.g. puncture)		
		• Pregnancy		

Table 2. Overview of large vessel diseases with the potential need for surgery.

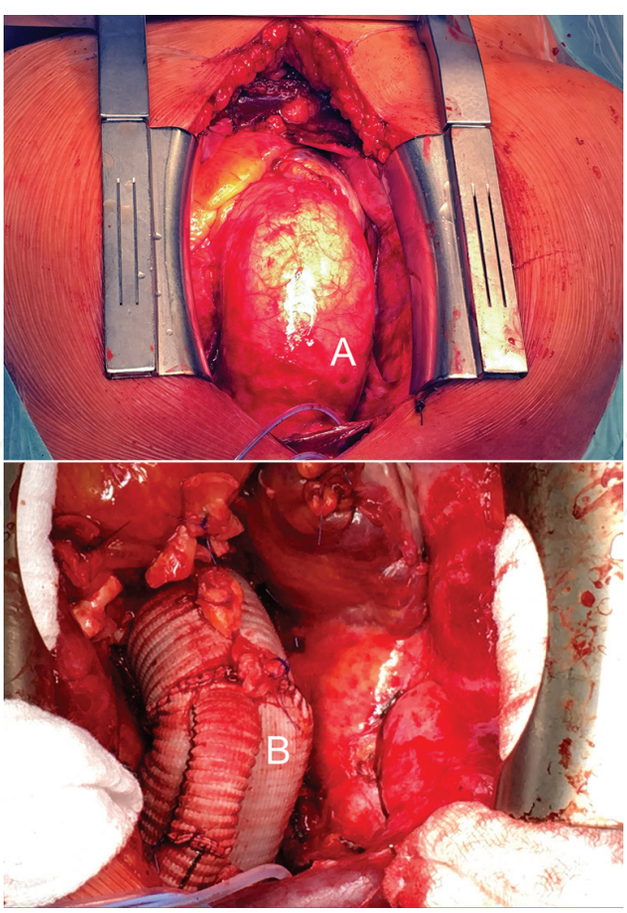


Figure 3. Operative situs of aortic surgery: (A) severe aneurysm of the ascending aorta and (B) aortic prostheses made of Dacron following surgical replacement of the dilated segment.

third death in Germany [34], producing a cost of 3.2 billion Euro [35]. The mortality of congestive heart failure has been reported to reach rates up to 36% per year. In addition to pharmacological therapy, there are surgical options for the treatment of end-stage heart failure, including heart transplantation, implantation of ventricular assist devices, or myocardial reconstruction (Dor procedure) [36]. In a ventriculoplasty, non-functional, dilated tissue is resected and the physiologic geometry and size of the heart chamber are reconstructed utilising a repair patch. For this purpose, a large variety of patch materials and biologic substrates have been assessed.

3. Polymers as a substrate in engineering innovative cardiovascular prostheses

Although the first work on polymeric heart valves goes back to the late 1950s [37–39], polymeric heart valves are not implanted in patients on a regular basis, since they have not yet shown satisfactory results. Depending on the type of polymer, the main issues with polymeric heart valves were low durability due to the tendency to become stiff with subsequently regurgitation or even complete shredding of the leaflets [40], poor long-term survival and a high mortality rate due to perioperative complications [41, 42], and thrombotic and calcific degeneration of the valve leaflets, leading to severe complications (thromboembolic events with end-organ damage, regurgitation, and heart failure) [43]. Thus, extensive research has been done on different polymers. Although there are many ways to classify polymeric scaffolds, the materials used to develop heart valve scaffolds can be classified as natural or synthetic. Examples of synthetic polymers include polycaprolactone (PCL), polytetrafluoroethylene (PTFE), polyethylene glycol (PEG), and polyurethanes (PU) [44–46], whereas examples of natural materials include, amongst others, hyaluronic acid, fibrin and collagen [47–51], and the combination of them [52].

The major drawbacks of natural polymers are their poor mechanical properties and fast degradation rate. Several studies have reported on mixing natural polymers with biologic and synthetic materials to combine the high biocompatibility of the natural polymers with the increased mechanical properties of the co-material with encouraging results [53–55]. For example, Stamm et al. used enzymatically decellularised porcine aortic valves and impregnated them with biodegradable polyhydroxybutyrate, since decellularisation leads to the exposure of the ECM collagen and by that to a high thrombogenicity. In that study, impregnating the valves with polyhydroxybutyrate had two positive effects: (a) the collagen matrix was covered and, therefore, was no longer thrombogenic and (b) the biomechanical properties of the valve were improved since decellularisation using enzymatic digestion weakened the mechanical properties of the valve. In large animal testing, the aforementioned valves functioned well for up to three months and partially developed the morphological characteristics of the native aortic valve [56].

The work of Stamm et al. is a good example for the feasibility of implanting polymeric scaffolds *in vivo*. However, the implantation of these valves is still not an option in the clinical setting. On the one hand, the lack of long-term results by means of safety and effectiveness, in

comparison to regularly implanted valves, does not allow for clinical use; only long-term *in vivo* studies can reveal, for example, the toxicity and side effects of degradation products. On the other hand, a major hurdle for the clinical use is calcific degeneration. Although tissue-engineered polymer-based heart valves show a lower tendency to calcify *in vivo* compared to standard bioprostheses, there is again a lack of long-term clinical studies, since the standardly used sheep model is less thrombogenic than the human coagulation system. Experience with the utilisation and application of the most frequently used synthetic and natural polymers as graft material will be introduced below. An overview of the pros and cons of these polymers is given in **Table 3**.

3.1. Polycaprolactone-based polymers (PCL)

Thermoplastics based on polycaprolactone have been largely used in biomedical applications, as they show excellent biocompatibility and a controlled biodegradation. Examples of these types of polymers are polylactide (PLA) or polyglycolide (PGA), which are used in a mixture with other natural or synthetic materials, or alone. Both PLA and PGA are classified as biocompatible and non-toxic and are FDA-approved for human implantation [57, 58]. Degradation of these polymers *in vivo* is facilitated through a hydrolytic splitting of the ester bonds that leads to the formation of the natural metabolite lactic acid and glycolic acid. The risk for acidosis through local accumulation of these degradation products is low [59]. Owing to the presence of the additional methyl group, PLA is more hydrophobic than PGA and has

Polymer	Pros	Cons	References
Synthetic polymers			
Polycaprolactone	Excellent biocompatibility, controlled biodegradation	High stiffness, limited ability for cell adhesion	[57, 58, 61, 62]
Polyhydroxyalkanoate	High flexibility, occurs naturally, thermoplasticity	High production costs	[66–69]
Polyurethane	Resistant to degradation, high durability	Limited biocompatibility	[75, 76]
Polyglycerol sebacate	Low stiffness, high elastic properties	Low porosity, poor cell adhesion	[82–84]
Polyethylene glycol	Good mechanical properties, potential for functionalization	Poor cell adhesion	[98]
Biological polymers			
Collagen	High biocompatibility, low immunogenicity	Very high thrombogenicity, poor mechanical properties	[106–108]
Fibrin	High biocompatibility, low immunogenicity, easily derived	Poor mechanical characteristics	[48, 112]
Hyaluronic acid	High biocompatibility, low immunogenicity	Poor mechanical characteristics	[104, 118]

Table 3. Overview of pros and cons of most frequently used synthetic and natural polymers.

a lower degradation rate; while PGA is generally completely degraded in 2–3 months, the degradation of PLA in its preferred metabolic D-configuration takes an average 2 years [57]. A possibility for the regulation of the degradation rate is the copolymerization of PLA with PGA [60]. However, PCL scaffolds have a high stiffness and have a limited ability for cell adhesion and proliferation [61, 62]. Hence, the production of hybrid compound scaffolds is only indicated for myocardial grafts, vascular prostheses, and bioartificial heart valves.

Shinoka et al. used a scaffold made of a PLA mesh between two layers of randomly orientated PGA fibres and seeded it *in vitro* with ovine fibroblasts, smooth muscle cells (SMCs), and ECs. The autologous implantation as a replacement of the posterior leaflet of the pulmonary valve showed an adequate functionality, although the flexibility was reduced in comparison to the native leaflet. Furthermore, the cellular architecture and synthesis of collagen were indicative of a delicate expression of ECM [63]. Sodian et al. reported on the production of a tricuspid heart valve made of a PGA structure that unfortunately demonstrated insufficient structural integrity under physiological flow and pressure conditions [64]. To improve both the plasticity and mechanical properties, Hoerstrup et al. coated the fibre structure above with poly-4-hydroxybutyrate, which resulted in a thermoplastically editable composite [65].

3.2. Polyhydroxyalkanoate (PHA)

Linear polyesters of hydroxy fatty acids are generally pooled as polyhydroxyalkanoates. PHAs show a high biocompatibility and occur naturally as reserve substances in a variety of bacteria [66, 67]. The widespread use as scaffold materials in valvular tissue engineering, in combination with other materials, or as a standalone substrate is due to their higher flexibility in comparison to PLA and PGA, as well as their thermoplasticity, which allows for moulding with different thermal procedures [68, 69]. The degradation rates, besides the specific molecular weight, are dependent on their crystallinity [70]. Thus, poly-4-hydroxybutyric acid degrades rather fast *in vivo* [71], whereas polyhydroxyoctanoate is still detectable after 24 weeks [72]. The mechanism of degradation is based on a hydrolytic splitting of ester bonds and distinguishes through a delayed loss of mass, as the loose chain fragments only start to diffuse at a certain length [16]. Furthermore, it is expected that these degradation products are non-toxic and show a lower acidity compared to PLA [67, 73]. Sodian et al. seeded ovine vascular cells onto a tricuspid heart valve scaffold made of porous polyhydroxyoctanoate and implanted it in autologous pulmonary position. After 17 weeks, the collagen content was above the reference value of native tissue, whereas after explantation, the valves showed a characteristic non-linear stress-strain behaviour. Although there was no confluent endothelium on the grafts' surface, there was no sign of material-induced thrombogenicity [74].

3.3. Polyurethane (PU)

Polyurethanes are polymers of organic units joined by carbamate links and similar to PCL-based polymers; they are widely used in biomedical applications. PUs show a good long-term durability since they are resistant to degradation. However, modifications of the original structure of PUs have been conducted to allow for a controlled biodegradation, mechanical stability, and improved cell colonisation in PU-based heart valve prostheses, vascular grafts, and myocardial patches [75, 76]. PUs often were used in combination with other materials or

as an unblended polymer. Scaffolds made of PU are a promising option for tissue engineering of myocardial replacement tissue, especially after seeding with mesenchymal cells [77] and in combination with other polymers for improving cell adhesion, porosity, and mechanic stability [78]. Fromstein et al. seeded PU scaffolds with embryonic stem cells in a bioreactor and investigated the effect of the macro-architecture on the adhesion, viability, and morphology on the seeded cells [79]. The authors found cells with the typical morphology of cultured cardiomyocytes on electrospun fibrous scaffolds, whereas there were no cardiomyocyte-like cells on scaffolds made through thermally induced phase separation (TIPS).

In vascular prostheses, McCarthy et al. investigated PGA, PLA, PCL, and PU as supportive materials of the elastica interna of a decellularised murine aorta [55]. The developed grafts were comparable to the native saphenous vein regarding burst pressure and wall diameter. In a direct comparison of their hybrid grafts, polyurethane grafts showed better burst pressure and tensile properties than the other polymeric scaffolds. Furthermore, Nieponice et al. reported that in vitro seeding of the PU grafts with muscular stem cells improved stability and functionality [80]. The authors implanted seeded and non-seeded grafts in the aortic position of a rat model and found a substantial lower graft failure in the cell-seeded group. In developing vascular prostheses, not only the superior mechanical properties of the polyurethane grafts should be pursued, but also the potential neointima formation and graft stenosis should be considered in the production of these grafts, which could be addressed with drug release mechanisms [81].

3.4. Polyglycerol sebacate (PGS)

Firstly produced in 2002 by a polycondensation reaction of glycerol sebacic acid, PGS has been widely studied in the context of biomedical applications. Owing to the low stiffness and high elastic properties, PGS has been reported to be a promising scaffold material for tissue engineering [82–84]. Depending on the production parameters and structural conditions, the elastic modulus of PGS can vary between 0.025 and 12 MPa, which corresponds to the modulus of human myocardial tissue [85]. The mechanical properties can be altered by adjusting the duration of the cross-linking and the concentration of the educts, which have been FDA-approved regarding their biocompatibility [84]. To improve the mechanical properties, Xu et al. combined PGS with PLA, and they reported a stiffness that was comparable to the native myocardial tissue [86].

One major challenge in the production of PGS-based scaffolds is the fabrication of a porous structure [87]. To face this challenge, Masoumi et al. used laser ablation to produce a diamond-shaped porous microstructure [88]. Sant et al. produced a fibrous scaffold using electrospinning; however, they needed to adapt the viscosity of the fluid by adding polycaprolactone. Following the seeding of these scaffolds with human valvular intermediate cells (VICs), the authors found a high cell viability, as well as the expression of a dense collagen network [27]. Jeffries et al. compared electrospun fibrous PGS matrices to porous PGS foam and found a fivefold higher torque strength and better suture retention of the former [89]. The porosity of the PGS scaffolds is crucial for *in vitro* and *in vivo* cell seeding [90], as well as for mechanical stability. This is of particular importance in the development of cardiac patches and myocardial prostheses since these grafts need to have a reliable mechanical integrity, which normally is

achieved by increasing the wall thickness of synthetic grafts. However, the increase of the wall thickness limits oxygen supply by diffusion to the seeded cells, posing the need for vascularisation. Therefore, PGS grafts are produced with a high porosity to mimic native vascularisation [90, 91]. Furthermore, cell adhesion can be improved by simulating epitope sequences of laminin and fibronectin through connecting specific amino acid sequences with the PGS scaffolds [92].

In an *in vitro* haemocompatibility study with human blood, PGS showed a lower adhesion of thrombocytes and release of inflammation markers, compared to polytetrafluoroethylene, which is indicative of improved haemocompatibility [93]. Guler et al. investigated the ECM of decellularised sheep aorta connected to PGS *in situ* and showed that there was no additional impairment on the smooth muscle cells of a human aorta [94]. In this fashion, Guler et al. augmented the regenerative potential of allogeneic prostheses with the superior mechanical properties of PGS elastomers. To investigate *in vivo* degeneration, Pomerantseva et al. implanted disc-shaped PGS samples subcutaneously in rats, which only generated a minor tissue reaction. They reported a superficial degradation process by enzyme-mediated hydrolytic splitting of ester bonds [83]. The PGS samples were maintained *in vivo* for several weeks and were characterised by a linear loss of mass [83, 95]. The degradation products were glycerine and a metabolic intermediate of the ω-oxidation (sebacic acid) [84]. Moreover, Stuckey et al. implanted myocardial PGS patches in rodent hearts. They found a significant faster degeneration than in previous *in vitro* experiments [96]. Khosravi et al. have found aneurysms after infrarenal implantation of aortic grafts made from electrospun PGS [54]. The authors suggested that the reason of the aneurysms was the suspected degradation of the PGS without a sufficient remodelling process simultaneously. However, there was no aortic dissection, since the grafts were covered with a thin PCL layer. In contrast to these findings, Wu et al. reported on an early remodelling process after implantation of a heparin-covered PGA graft in the abdominal aortic position [97].

3.5. Polyethylene glycol (PEG)

PEG is a hydrophilic polyether bond of the divalent alcohol ethylene glycol, which is neither toxic nor immunogenic and FDA-approved for implantation in humans. Also, it has been used on a regular basis in the field of tissue engineering [98] due to its potential for functionalisation of the terminal hydroxyl groups by means of an adaption for cell adhesion and degradation, as well as its mechanical properties [98]. For example, a hydrolytically degradable copolymer results from an integration of PLA or PGA into the polyether structure [99]. Benton et al. cross-linked the PEG chains with peptide sequences, which contained a proteolytic sensitivity towards matrix metalloproteinases, therefore, allowing for a cell-controlled degradation. Also, a specific amino acid sequence (arginine-glycine-asparagine) was integrated into the hydrogel matrix. The encapsulated porcine VICs showed an increasing elongated morphology, as well as an improved occurrence of integrin binding as a sign for increased cell adhesion [100]. Moreover, porcine VICs cultivated in a copolymer of methacrylised hyaluronic acid and PEG molecules produced both collagen and elastin [101]. Hockaday et al. combined photopolymerisation of PEG with 3D printing and reproduced an anatomically precise aortic valve [102]. Zhang et al., however, produced an anisotropic scaffold structure by using an

aperture that allowed for local varying light irradiation and, subsequently, a varying grade of cross-linking [103].

3.6. Collagen

Collagen is the most prevalent structure protein of the human body and is also a substantial component of the valvular extracellular matrix [104, 105]. Subsequently, collagen is highly biocompatible and shows only low immunogenicity [106]. Moreover, the specific peptide sequences promote cell adhesion, which could drive the cellular population of collagenous matrices [107]. However, the conventional isolation from animal tissue bears the risk of zoonosis [108]. Furthermore, collagen has a high thrombogenic potential [109]. Therefore, its use in the engineering of tissues with contact to the blood flow requires coating or masking of the surface. This is often realised by endothelialisation [104].

Further limitations of collagen-derived hydrogels as a scaffold material are its poor mechanical properties in comparison to native valve tissue as well as the rapid and hardly predictable degradation process in vivo [104, 106]. The degradation happens enzymatically through collagenases [110]. The degradation rate varies depending on the implantation site [109]. Cross-linking of peptide chains may improve the stability and influence the degradation rate [98]. For this, both chemical agents (glutaraldehyde and formaldehyde) and physical procedures (UV radiation and heat treatment), as well as insertion of polymers, are applied [110].

To improve the compressive strength, Flanagan et al. integrated chondroitin sulphate into a collagen matrix and subsequently seeded it with porcine VIC and valvular endothelial cells (VEC). During the total cultivation time of 28 days, the cells were mitotic active and kept their initial phenotype. Histochemical examination showed both collagen synthesis and, most likely because of chondroitin sulphate, the production of elastin. Nevertheless, they observed a significant contraction of the matrix through cellular interaction [111], which was in line with the findings of Benton et al. who also reported on halving the initial matrix dimension due to contraction in *in vitro* studies [100].

3.7. Fibrin

Fibrin represents the fundamental substrate for ubiquitous tissue repair mechanisms and, therefore, is a natural scaffold material, whose precursors are relatively easy and can be derived from the patients' blood plasma. Thus, allogenic and autologous scaffolds can be generated by fibrin, which contains only a low risk of a graft-versus-host disease. The degradation products also stimulate the production of extracellular matrix angiogenesis [112]. Hence, fibrin displays favourable properties for tissue engineering of cardiovascular scaffolds. On the other hand, cardiovascular implants are in direct contact with the bloodstream and its inherent lytic enzymes such as plasmin, which may rapidly degrade fibrin [48].

In a study done by Ye et al. fibrinolysis was not evident at a concentration of fibrin at a level of 20 μg/ml in a surrounding culture medium, whereas the fibrin hydrogel degraded in two days without adding the plasmin antagonist aprotinin. The modified-release degradation also led to an increased collagen expression in human myofibroblasts [113]. However, the cellular

production of collagen fibres led to a contraction of the fibrin matrix. Jockenhövel et al. inhibited the contraction through fixation of the fibrin scaffold margin with a poly-l-lysine-solution [48]. They also introduced an injection moulding process to produce and to seed cardiac valve–shaped scaffolds. The polymerisation of fibrin took place in a mould and was triggered by a gradual injection of a fibrin solution into a thrombin-containing cell suspension. The produced fibrin gel showed a homogenous distribution of cells [48]. Robinson et al. set up a mould, in which the fibrin matrix compacted in a determined direction. In this way, an anisotropic collagen expression similar to a native heart valve's configuration was initiated [114].

However, the mechanical stability of fibrin-based scaffolds is not sufficient to withstand the hemodynamic loads of the high-pressure zones of a human circulation. Flanagan et al. performed a pulsatile preconditioning of fibrin-based heart valve prostheses to face this problem and achieved an improved synthesis of extracellular matrix with a subsequently higher stability of the fibrin structure [115].

After that, they populated a cardiac valve scaffold with fibroblasts, smooth muscle cells, and endothelial cells of an ovine carotid artery for 28 days. They implanted this preconditioned, autologous scaffold into pulmonary valve position. Three months following implantation, the scaffolds showed a biological tissue-like consistency as well as a functional endothelium, whereas no fibrin could be detected in the grafts anymore. However, the remodelling led to a contraction of the leaflets with a subsequent valve insufficiency [50].

Keeping up the structural integrity of fibrin-based scaffolds was of lesser importance in a study by Chi et al. They seeded a fibrin–hyaluronic acid matrix with bone marrow mesenchymal stem cells and used the patches in a rat infarction model [116]. However, the patch was not used as a prosthesis, but as a vehicle to deposit stem cells in the infarction area.

For the production of fibrin-based vessel prostheses, Aper et al. condensed blood-derived fibrin by centrifugation [117]. The resulting cross-linking of the fibrin fibres led to a higher mechanical stability of the vessel segments up to a pressure of 230 mmHg. Six months after the replacement of carotid arteries of sheep, the authors reported on an almost complete physiologic remodelling of the grafts.

3.8. Hyaluronic acid

Hyaluronic acid is an unsulphated glycosaminoglycan, whose repetitive disaccharide units consist of d-glucuronic acid and n-acetylglucosamine. Hyaluronic acid occurs in mammals mainly as an extracellular part of the connective tissue, has a water-binding as well as a texture-priming function [118], and is to be found in large extent in heart valve tissue (up to 50% of the glycosaminoglycan content) [104]. Hyaluronic acid is also an essential component of the embryonic development of the heart [119]. Furthermore, the immunogenic potential of commercially available hyaluronic acid (mainly made from bacterial fermentation) is low due to the cross-species structural homology [120]. Finally, the presence of hyaluronic acid promotes the expression of extracellular matrix proteins: VIC cultivated on a hyaluronic acid coated surface produced significantly higher amounts of ECM proteins than VIC on uncoated polystyrene [49].

However, the weak mechanical properties of hyaluronic acid and the high *in vivo* degradation rate advise against its utilisation in tissue engineering of cardiovascular scaffolds [118]. The process of degradation is based on the enzyme hyaluronidase, and its half-life period lasts from several hours up to a few days as a function of the local enzyme concentration.

To manufacture a hydrogel employable as a scaffold for cardiovascular prostheses, cross-linking of hyaluronic acid is possible. For this purpose, methacrylation is an often used tool [121]. The resulting methyl acrylate hyaluronic acid is photo–cross-linkable, whereby the mild conditions of a photopolymerisation allow for the encapsulation of cells into the manufactured hydrogel [119]. Hyaluronan benzyl ester can be processed in manifold ways to serve as an appropriate substrate for tissue engineering [122]. By seeding neonatal rat cardiomyocytes on knitted hyaluronan benzyl ester, Boublik et al. produced hybrid myocardial prostheses with sufficient mechanical properties for an in vivo implantation in a rat model [123].

4. Conclusions

Currently, no optimal polymer for manufacturing an ideal cardiovascular prosthesis has been identified yet. There are rather specific requirements, such as functionality, biocompatibility, and regenerative potential to be taken into account while selecting a substrate for a particular application, implantation site, and host species. Beyond promising synthetic and biologic elastomers, their combination with natural, cell-free matrices can be employed to develop cardiovascular scaffolds as well. However, the huge variety of the currently available materials, coatings, and manufacturing processes, the differences of investigation techniques in vitro and in vivo, as well as the inconsistent selection of evaluation criteria and test parameters impede the comparability of the currently conducted investigations. Consistent analytical standards would facilitate a clear, valid, and comparable perspective on polymer research and thereby would increasingly lead to a faster translation of this important field of research into clinical reality.

The current overview of developments in the investigation of cardiovascular implants warrants the hope for innovative grafts, which are manufactured according to the principles of tissue engineering and which can be used clinically to make sustainable and regenerative therapies available for all patients in the future.

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