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Views & Comments

Research and Progress of Implantable Cardiovascular Materials and Devices

Yunbing Wang

National Engineering Research Center for Biomaterials, Sichuan University, Chengdu 610064, China

Cardiovascular diseases (CVDs) are the global leading cause of mortality, being responsible for over 17.7 million deaths annually [1]. In China, the number of patients with cardiovascular diseases has reached 330 million and accounts for more than 43% of deaths caused by diseases—a much higher proportion than that of cancer, respiratory diseases, or other diseases [2]. Among such diseases, coronary heart disease (CHD) and structural heart disease (SHD) are common CVDs with the highest risk. In recent years, implantable materials and devices—especially minimally invasive interventional ones—have become the most effective tools for the treatment of cardiovascular diseases. Examples of such tools include vascular stents, drug-eluting balloons, heart valves, cardiac occluders, artificial grafts, injectable hydrogels against heart failure, and left ventricular assist devices (LVADs) [3,4].

Cardiovascular stents and drug-eluting balloons

Drug-eluting stents (DESs) are currently widely used for the treatment of CHD, as they successfully reduce the in-stent restenosis (ISR) ratio associated with bare metal stents. However, long-term clinical results have revealed the existence of late or very late thrombosis and the risks of negative complications from DESs. The local release of antiproliferative drugs inhibits the excessive proliferation of smooth muscle cells, while simultaneously causing delayed healing of endothelial cells; this ultimately leads to a thin neointima with an incomplete and dysfunctional enthothelial layer. Innovations in materials for both stent backbones and surface coatings have continuously promoted the evolution of DES. For surface coating, researchers have focused on optimizing drug coatings with a desired drug-release profile or developing functional coatings that can mimic endothelial cell function [5,6]. Regarding stent backbones, the permanent existence of a non-degradable stent can cause a continuous inflammatory response; moreover, it makes it difficult for blood vessels to recover their physiological pulsation. Biodegradable vascular stents (BVSs) prepared from biodegradable polymers or metals are expected to hold potential for the healing of native blood vessels and are likely to be the future of DES. Current studies on BVSs are concentrating on optimizing stent struts to obtain sufficient radial strength with less thickness and smaller crossing profiles. More importantly, it should not be overlooked that the standard adopted for a regular DES, in which the necessary lumen loss is as small as possible, might not be applicable to the design of BVSs. When a BVS is implanted, if the thickness of the neointima is too thin, there is a risk of a small amount of fragments of the BVS falling off into the blood vessel when the stent is degraded and fragmented, which may cause adverse events such as thrombosis. Thus, when developing a BVS, a great deal of attention should be paid to the issue of how to heal blood vessels in a way that allows a relatively thicker neointima, in order to protect the stent struts during degradation.

Aside from stents, drug-eluting balloons (DEBs) are an option for CHD treatment that addresses the limitations presented by DESs. The use of DEBs eliminates the need for stents, allowing serious side effects to be avoided. Despite their benefits, DEBs normally show poor drug delivery efficiency due to the short balloon inflation time (30–60 s), which limits passive drug diffusion from the balloon surface to the luminal lesion. Therefore, there is high demand for an optimized drug loading or delivery carrier and technique that can enhance the therapeutic efficiency of DEBs.

Artificial heart valves

Valvular heart disease is a common cardiovascular disease, for which artificial heart valve replacement has been the optimal solution. In recent years, the development trend of heart valve replacement surgery has shifted from surgical thoracotomy to minimally invasive interventional surgery with transcatheter bioprosthetic heart valves. Commercial bioprosthetic heart valves are usually made from glutaraldehyde-treated xenogenetic tissues, such as porcine or bovine pericardium. However, such valves still have several deficiencies, including the high toxicity of aldehyde residues, calcification, the risk of thrombosis, immune rejection reaction, and the difficult adhesion of endothelial cells, resulting in a short service life of only about ten years. Furthermore, the conventional storage of bioprosthetic heart valves in glutaraldehyde solution further limits their service performance. Current research is focusing on fundamentally promoting the comprehensive performance of artificial heart valve materials through advanced methods,

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including: ① modified glutaraldehyde crosslinking through the introduction of anti-calcification and anti-thrombosis moieties; ② novel non-glutaraldehyde cross-linked xenogenetic tissues with better biocompatibility; ③ dry-tissue storage of heart valve materials; and ④ synthetic polymer valve materials and new materials with low immunogenicity [7,8]. Artificial valves are mainly used for aortic valves at present, and are expected to gradually extend to pulmonary, mitral, tricuspid, and venous valves. In particular, when developing venous valves, a robust anti-thrombosis design is urgently needed to overcome the high risk of thrombosis. In addition, tissue-engineered valves, including those prepared with acellular extracellular matrix materials and biodegradable synthetic materials, are expected to achieve valve function reconstruction to valve regeneration, which is an important research direction in the future.

Heart failure therapy

Heart failure (HF) affects approximately 26 million people globally, with a five-year case fatality rate after hospitalization of 42.3%. HF has thus emerged as a leading cause of mortality worldwide. Traditional clinical therapies for HF include medications (e.g., angiotensin-converting enzyme inhibitors and diuretics) and surgical treatments (e.g., cardiac resynchronization therapy and LVADs). These therapies are not designed to reverse myocardial necrosis and cardiac dysfunction, but rather to mitigate symptoms. Heart transplantation is still the only effective treatment to restore cardiac function. However, the extremely scarce number of donors and the complex surgical procedures involved limit its application. Therefore, it is urgent to develop novel therapeutic approaches for treating HF.

Recently, biomaterials aimed at the regeneration of myocardial tissue and the restoration of cardiac function have attracted increasing attention due to their good therapeutic performance. Cardiac patches and injectable hydrogels are the two major applications of biomaterials in HF treatment. Cardiac patches are polymeric scaffolds or hydrogels that are attached onto the surface of the heart via spontaneous adhesion or suture fixation after thoracotomy. In comparison with cardiac patches, the transcatheter injection of a hydrogel has the advantages of a simpler surgical operation, smaller trauma, and better effects on the restoration of cardiac function. Thus far, injectable hydrogels based on alginate or the extracellular matrix have entered clinical trials. The injected hydrogel thickens the ventricular wall and thereby restrains wall stress, which is inversely proportional to wall thickness according to Laplace's law. As a platform, the injectable hydrogel may also encapsulate cells or contain biomolecules to promote cardiomyocyte regeneration, regulate inflammation, enhance angiogenesis, or inhibit fibrosis in the diseased myocardium. However, most of these hydrogels are single-functional, so they cannot fully meet the requirements for treating the complex clinical syndrome of HF. The challenge of developing a multi-functional injectable hydrogel that can meet all the requirements for myocardium repair and cardiac function restoration still remains. Total artificial hearts (TAH), including mechanical TAH, cellularized or acellularized three-dimensional (3D)-printed polymeric hearts with a natural architecture, and decellularized whole hearts, are also undergoing pilot research for HF treatment at present. The development of TAH would alleviate the severe shortage of donor hearts and meet the needs of more patients for heart transplantation.

Cardiac occluders

Congenital heart disease refers to abnormal development of the heart and large blood vessels, which occurs in newborns and children. Among the various types of congenital heart disease, a hole in the chamber wall or vessel is a common species of structural congenital heart defect that affects nearly 1% of births, with a global annual increase in case number of 1.4 million. Examples include patent ductus arteriosus, atrial septal defect, ventricular septal defect (VSD), and patent foramen ovale. A structural heart defect can be sealed by transcatheterly delivering an occlude through a catheter into the patient's body, without the need for thoracic surgery. Current commercially available occlusion devices are composed of a non-degradable mesh of nitinol alloy and a polymeric membrane. After implantation, the metal remains in the heart for life and usually causes long-term complications, such as insufficiency of the endothelium, thrombosis, valve wear, perforation, or even fatal late atrioventricular block. A biodegradable occlusion device would be the best method to solve this problem, as it could act as a temporary scaffold to guide the regeneration of heart tissue, and then fade away while the original hole is sealed by new tissue, eventually restoring the heart perfectly.

Artificial vascular grafts

Artificial vascular grafts are useful alternatives for blood vessels in coronary artery bypass grafting surgery and arteriovenous fistula, and hold a significant position in the field of cardiovascular medical materials. Hemocompatibility and mechanical compatibility are both requirements and challenges for the successful post-implantation functioning of artificial vascular grafts. Large-diameter artificial vascular grafts (> 6 mm) made of polyethylene terephthalate and expanded polytetrafluoroethylene have been widely used. However, it is difficult for small-diameter vascular grafts, which may have a reduced blood-flow velocity that results in thrombosis and intimal hyperplasia at the anastomotic site, to fully meet the ideal clinical requirements. Despite challenges in product development, scientists are making great contributions to research on artificial small vascular grafts using various technologies. From conventional materials to smart materials, xenogeneic decellularized materials to tissue engineered scaffolds, and textiles and electrospinning to 3D printing and electronics, a wide variety of options on material designing have emerged. To date, all artificial vascular grafts are implanted through surgery, which may become the key limit to their wide application in the clinic. Thus, the development of smart techniques to implant artificial vascular grafts using minimally invasive intervention is a direction worth exploring in the future.

Conclusions

The development of various new cardiovascular materials and minimally invasive cardiovascular interventional techniques has provided powerful solutions for the treatment of various cardiovascular diseases. In order to access better treatment options in the future, further investigation of the following principles is needed: ① cardiovascular materials with improved tissue-regeneration function; ② intelligent medical devices with smaller size and facility; and ③ smart or precise techniques to address more solutions for patients. Once these innovations are achieved, more advanced and powerful treatment for cardiovascular diseases will become available.

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