Collagen and Leather

REVIEW

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Engineering collagen-based biomaterials for cardiovascular medicine

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Abstract

Cardiovascular diseases have been the leading cause of global mortality and disability. In addition to traditional drug and surgical treatment, more and more studies investigate tissue engineering therapeutic strategies in cardiovascular medicine. Collagen interweaves in the form of trimeric chains to form the physiological network framework of the extracellular matrix of cardiac and vascular cells, possessing excellent biological properties (such as low immunogenicity and good biocompatibility) and adjustable mechanical properties, which renders it a vital tissue engineering biomaterial for the treatment of cardiovascular diseases. In recent years, promising advances have been made in the application of collagen materials in blood vessel prostheses, injectable cardiac hydrogels, cardiac patches, and hemostatic materials, although their clinical translation still faces some obstacles. Thus, we reviewed these findings and systematically summarizes the application progress as well as problems of clinical translation of collagen biomaterials in the cardiovascular field. The present review contributes to a comprehensive understanding of the application of collagen biomaterials in cardiovascular medicine.

Keywords Collagen, Tissue engineering, Cardiovascular disease, Cell therapy, Drug delivery system

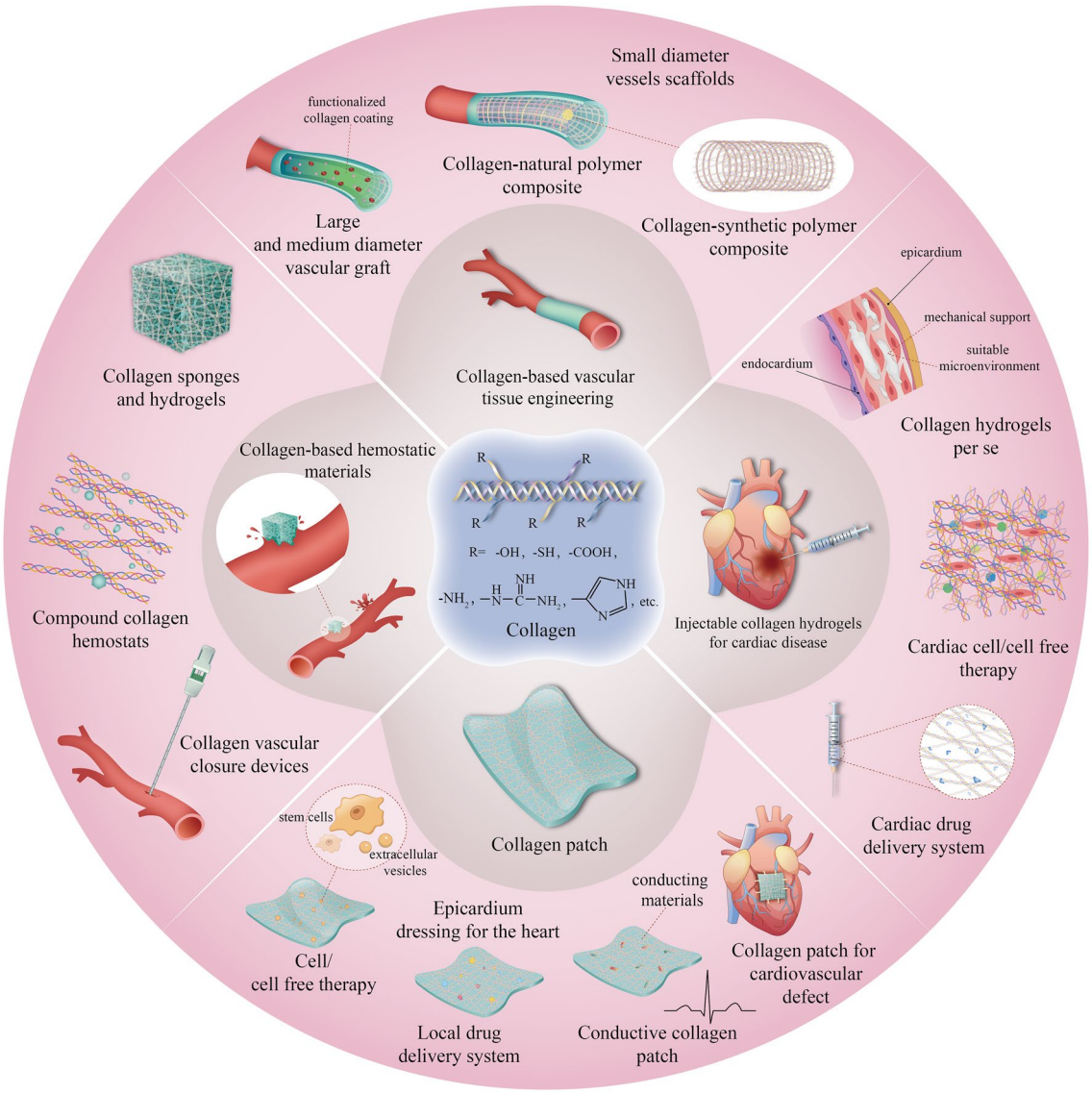
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Graphical abstract



1 Introduction

Collagen is the most abundant protein in mammals, accounting for about 1/3 of the total protein in the whole body, and acts as the major component of the extracellular matrix (ECM) [1]. The molecular structure of collagen is characterized by three α chains, which consists of a highly conserved amino acid sequence [2]. Different substructures and modifications result in various collagen subclasses (totally 29 types up to now) that assume distinct physiological functions [3]. Among the collagen family, fibrous collagen type I and III are the main collagen in the heart and blood vessels, cross-linking their trimeric helical structures with glycosaminoglycan and chondroitin sulfate to form a network as the skeleton of the ECM, which synergistically play a role in mechanical support, damage repair, and cell proliferation and differentiation (Fig. 1) [4–6]. Mutations and defects in collagen proteins can introduce severe cardiovascular disease. For example, mutations in human collagen type I/III genes (COLIAl or COLIA2) can lead to aortic dilatation, arterial dissection, and rupture [7, 8].

As mentioned above, collagen (especially collagen type I and III), as an endogenous conserved constituent rather than a foreign matter, possesses well biocompatibility,

weak immunogenicity, low toxicity, hydrophilia, and wide sources (various animal sources or recombinant expression). Although the extracted collagen itself has compromised mechanical strength, collagen has superior functional plasticity by modifications of the molecular structure through exogenous chemical, physical or biological cross-linking, endowing it with excellent biomaterial advantages including adjustable bio-absorption after implantation and regulable mechanical stiffness (Fig. 1) [3, 9]. Moreover, the potent thrombogenicity of collagen seems a double-edged sword, making it a promising hemostatic biomaterial, while requires additional anticoagulant design when utilized as a blood-contacting devices [10]. However, as a natural polymer, batch-to-batch inconsistencies and the potential risk of pathogenic contamination and disease transmission are inherent defects of collagen biomaterials (Fig. 1) [11, 12]. In the past, collagen-based biomaterials have been widely applied to medical cosmetology, wound dressings for burns and plastic surgery, dentistry, orthopedics, and 3D bioprinting [9, 13–15]. In recent years, with the development of tissue engineering technology, collagen-based products have been emergingly applied to the field of cardiovascular medicine, including three-dimensional cardiovascular culture models in vitro and cardiovascular disease treatment in vivo, and achieved promising results [16, 17]. Hence, our review will focus on the advances of collagen-based biomaterials in cardiovascular medicine from the aspects of collagen-based vascular prosthesis, collagen hydrogel, collagen-based cardiac patch, and hemostatic materials.

2 Collagen-based tissue engineering in vascular medicine

With the prevalence of unhealthy lifestyles and population aging, cardiovascular diseases (CVDs) have become the leading cause of global mortality and a major

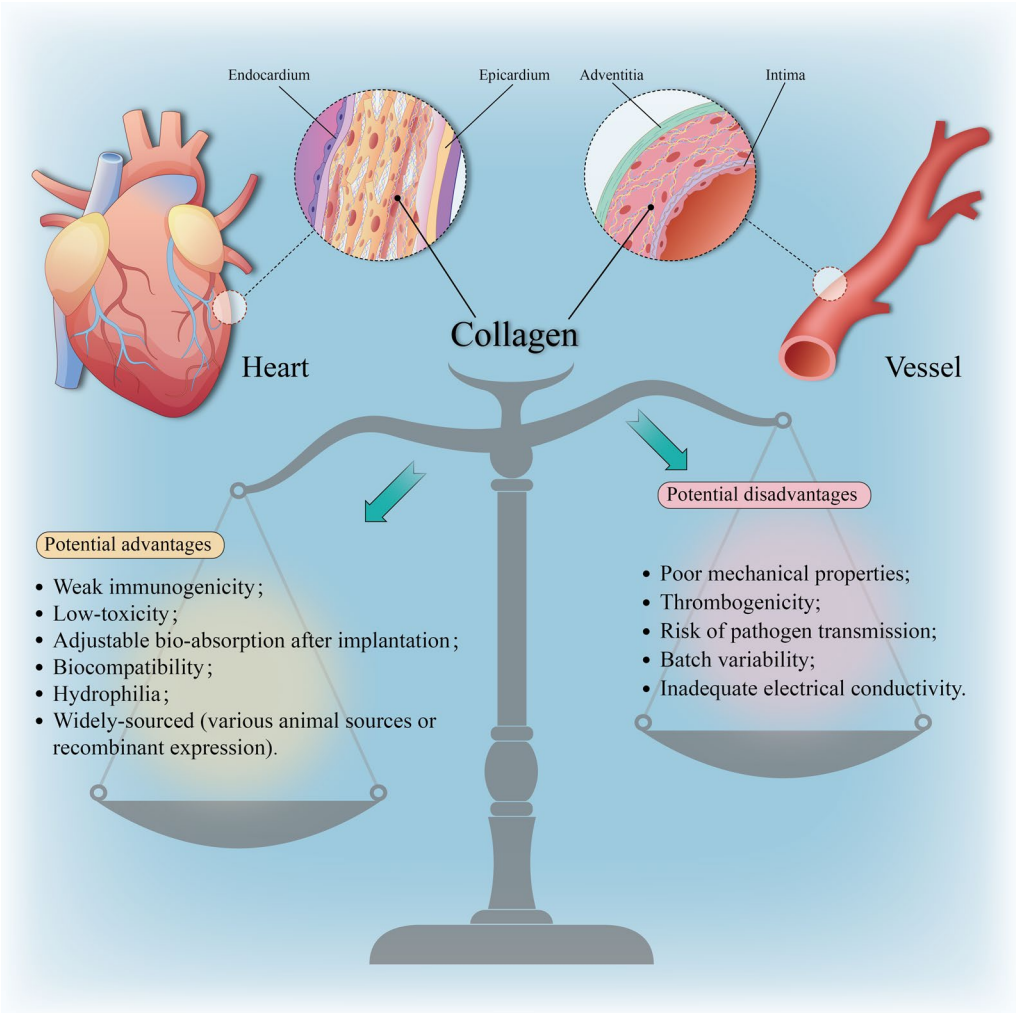


Fig. 1 Cardiovascular distribution of collagen and its advantages and disadvantages as a tissue engineering material. Collagen is the major component of the extracellular matrix of the heart and blood vessels and is a promising biomaterial for cardiovascular tissue engineering

contributor to disability, affecting 523 million people worldwide [18]. Atherosclerosis is the main pathological basis of cardiovascular diseases, characterized by gradually increasing cholesterol plaque deposition and vascular blockage, resulting in coronary heart disease, ischemic stroke, and peripheral artery disease [19, 20]. Vascular bypass or replacement surgery is an effective solution for occlusive cardiovascular diseases, especially for complex stenotic lesions [21]. Autologous vessels such as the great saphenous vein and the internal mammary artery are usually the first choice for clinical vascular replacement. However, the use of these autografts is not always feasible, mostly due to poor vascular condition (such as great saphenous vein varicosis, atherosclerosis or stenosis) or intolerance for autograft harvesting procedures [22]. In this scenario, synthetic vascular prostheses have become a vital alternative source of vascular transplantation [23]. The ideal vascular graft should have sufficient biological and mechanical characteristics to integrate into the systemic vasculature, such as biocompatibility (low cytotoxicity, cell adhesion), non-thrombogenicity, suitable biodegradation rate, blood impermeable, sufficient tensile strength as well as viscoelasticity to withstand the pulsatile blood flow and surgical suture procedure [23–25].

Collagen is the main ECM component of the vascular wall, responsible for load carrying and pressure resistance [26]. Compared with synthetic polymers, collagen has superior biological performance, including biocompatibility, cell adhesion and biological recognition sites, biodegradability, weak immunogenicity, availability, and hydrophilicity, which makes them mainstream biomaterials for vascular tissue engineering (Fig. 2) [12]. In addition to collagen, elastin is another ECM constituent of the vascular wall, and possesses excellent viscoelasticity, which can complement the deficiency of collagen, making it a partner for collagen to construct small diameter vessels [27]. Chitosan and silk fibroin are also natural polymers that have great biocompatibility, but they are not ECM components, which means its ability of cell adhesion and recognition may be inferior to that of ECM proteins [28, 29]. In fact, few biomaterials can alone constitute engineered blood vessels. Although collagen has excellent biological properties, pristine collagen has poor mechanical properties, which usually requires pretreatment or combination with other natural/synthetic materials when applied in vascular engineering.

2.1 Collagen coatings for large and medium diameter vascular graft

Large and medium diameter (inner diameter > 6 mm) vascular grafts are often woven with synthetic materials such as PET, and the vessel wall is often porous filamentous to ensure the tissue ingrowth and biological integration of the graft. To prevent blood leakage caused by the porosity of implanted graft, preclotting treatment is mandatory for such blood vessel prosthesis before implantation, which employs controlled blood coagulation to fill the graft interstice with fibrin [30]. Although the preclotting method can make the artificial blood vessel impermeable, the process is cumbersome, and hampers the roughness of the flow surface and the flexibility of the vessel prosthesis, possibly increasing the risk of long-term graft failure. The collagen coating of porous Dacron vascular grafts is an alternative to the pre-coagulation method, which does not need special treatment before implantation [31]. The collagen coating will be completely absorbed, without significantly affecting the mechanical properties of the graft [32]. Results of prospective clinical trials showed that the long-term patency rate of collagen coated vessels was well-performed, with secondary corrected 8-year patency rates reaching 96% [33].

Besides sealing the porous wall of woven blood prosthesis, collagen coating can also act as a drug delivery medium, allowing the controlled drugs to release at the implant site. The main causes of graft failure include thrombosis, intimal hyperplasia, and implant infection [24, 34, 35]. Incomplete endothelialization of vascular grafts is an important cause of thrombosis and intimal hyperplasia, because the endothelium, as a barrier between blood and subendothelial thrombogenic tissue, plays a vital role in regulating local coagulation function [36, 37]. Therefore, drug delivery of vascular collagen coatings is mainly aimed at anti-thrombosis, promoting vascular graft endothelialization, and preventing infection [37, 38]. Due to the thrombogenic nature of collagen, cross-linking with anticoagulants (such as heparin [39, 40] and nitric oxide [41]) or tailoring the platelet activation site of collagen [42] is an indispensable design when contacting with blood. In addition, loading collagen with endothelial cell growth factors such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) to promote the process of graft endothelialization is also an important method to prevent graft thrombosis and intimal hyperplasia [43]. Perioperative graft infection is another common cause of vascular graft failure and patient mortality, which often requires resection of the blood vessel prosthesis to control infection [44, 45]. Collagen-based vascular prostheses containing antibiotic constituents (such as antibiotics and antimicrobial peptides) as well as prophylactic perioperative systemic administration of antibiotics are one of the solutions to reduce the risk of graft failure related to graft infection [46, 47]. This is demonstrated by a prospective cohort study which showed collagen graft

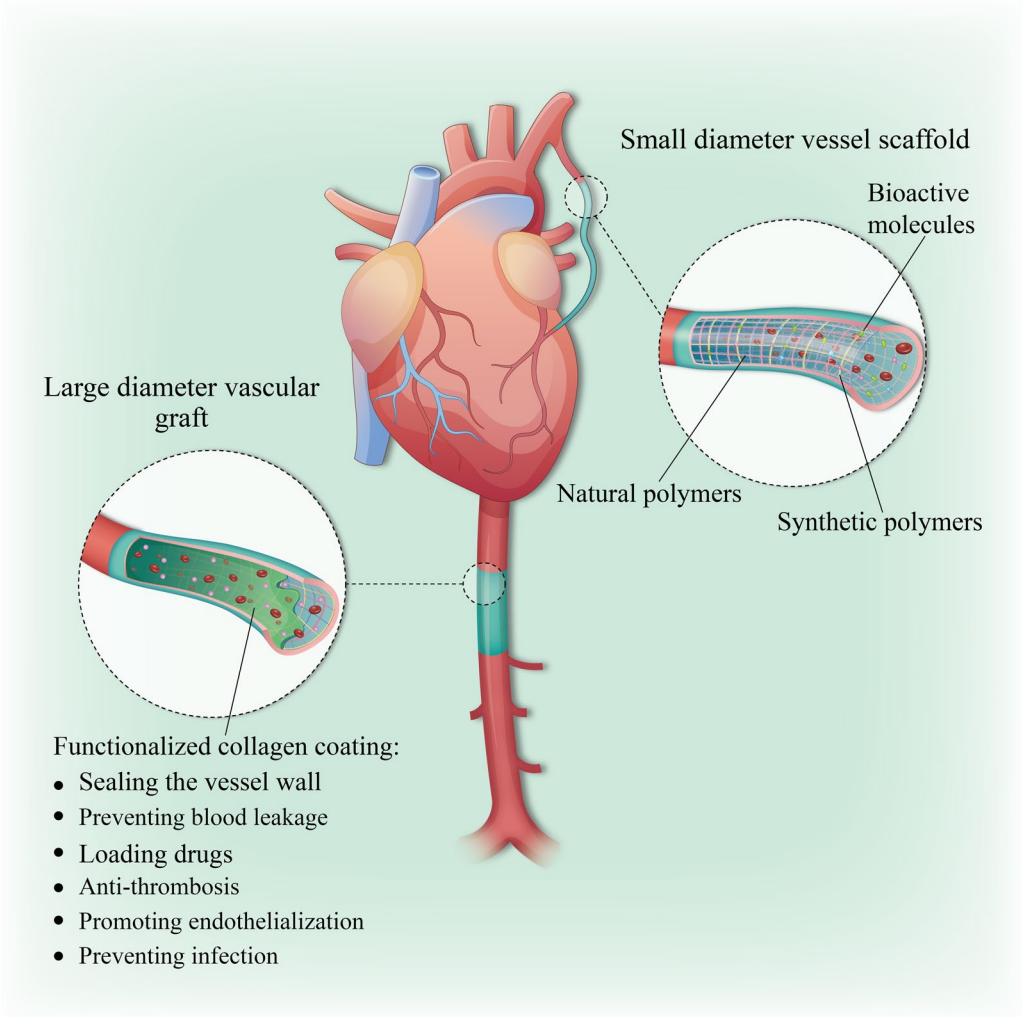


Fig. 2 Application of collagen materials in vascular tissue engineering. Collagen materials are mainly used as functional coatings of large/medium diameter blood vessels and vascular scaffolds of small diameter blood vessels

with gentamicin sulphate (Collatamp (®)) significantly reduced surgical site infection and days of hospitalization [48]. However, due to the denaturation of collagen in the environment of high temperature, strong acid and alkali, the reaction conditions of its crosslinking with antibiotics require to be relatively mild, thus limiting its ability to load antibiotics. Considering the adverse consequences of vascular graft infection, researchers have further proposed to functionalize the collagen coating with novel polymers, such as poly-catecholamines, to improve the antibiotic-binding ability of vascular prostheses [49]. The results showed that poly (L-DOPA)-coated grafts bound six times more gentamicin than pristine collagen-sealed vascular graft and maintained the original properties of the prosthesis [50]. However, the antibacterial advantages of polycatecholamine coatings still need to be confirmed by in vivo studies.

In short, with the development of vascular tissue engineering, large and medium diameter blood vessels (inner diameter > 6 mm) woven with synthetic materials (such as polytetrafluoroethylene and dacron) have been successfully used in the clinical practice of vascular transplantation, such as aortic and iliac artery, which is characterized by high blood flow and low-resistance. The collagen in large and medium diameter blood vessels mainly acts as sealing and functional modifications as mentioned above.

2.2 Collagen-based tissue engineering in small diameter vessels

Partly due to the low blood flow and high shear stress, thrombosis as well as intimal hyperplasia in the small diameter vascular prostheses (inner diameter < 6 mm) hampers the long-term patency rate and limits their

clinical application [51]. These include coronary arteries and extremity arteries, which suffer from a high prevalence of arteriosclerosis stenosis [52]. The patency rate after 2 years reached 90% for the saphenous vein graft while only 32% for the expanded polytetrafluoroethylene (ePTFE) graft in coronary artery bypass grafting (CABG) [23]. Due to the unique hemodynamic characteristics, small-diameter vascular grafts have more stringent requirements for biocompatibility, especially to avoid inflammation and thrombosis after implantation, and to accelerate the process of endothelialization [53].

Currently, mainstream strategies for small blood vessel bioengineering include self-assembled cell sheets and scaffold-guided vascular tissue engineering [54, 55]. The former is the assembly of cultured human cell sheets in vitro, while the latter employs polymers (natural or synthetic) or decellularized matrix to construct vascular scaffolds, which then recruits cell before or after implantation [25]. As a natural polymer material with excellent biological properties and the main component of vascular ECM, collagen is one of the mainstream materials for small diameter vascular scaffolds [55]. However, native collagen has defects such as insufficient mechanical strength, rapid degradation rate, and thrombogenicity. Researchers have attempted to solve these problems by modifying collagen structure and mixing other materials. Chemical cross-linking agents (such as glutaraldehyde, formaldehyde, and genipin) as well as ultraviolet radiation can improve the mechanical properties of collagen to a certain extent and manipulate its degradation rate, but the residues of these agents are prone to produce cytotoxicity and affect scaffold remodeling [56]. Alternatively, combining collagen with other natural or synthetic polymers is another commonly used tissue engineering strategy.

2.2.1 Collagen-natural polymer composite scaffolds

Silk fibroin (SF) is a natural fiber spun by silkworm and has excellent mechanical properties [57]. Previous studies have mixed fibroin with collagen to complement their mechanical and biological advantages with each other and the results showed collagen-fibroin composite scaffold well-performed in the tensile, compression, and mechanical test, along with improved porcine smooth muscle cells proliferation [58–60]. To improve the viscoelastic properties of collagen scaffolds, some studies have blended elastin with collagen to better biomimetic vascular function. Elastin-collagen scaffold constructed by Alan et al. showed the resistance to long-term deformation/creep and modulation of smooth muscle cell (SMC) phenotype toward a contractile state [61]. In addition, composite scaffold made of collagen and chondroitin sulfate [62] or hyaluronic acid oligosaccharide [63–65] could promote endothelialization and reduce thrombosis in small diameter vascular scaffolds, which may further translate to improved long-term patency. Moreover, another study tactfully introduced hyaluronic acid oligosaccharides scaffold loaded with Apyrase and 5'-nucleotidase (5'-NT) into the collagen scaffold, which can convert the strong platelet activator ADP to adenosine and reduce the accumulation of platelets, thereby reducing the risk of thrombosis [66].

2.2.2 Collagen-synthetic polymer composite scaffolds

Synthetic polymer materials (such as polyurethane, polydioxanone polycaprolactone et al.) have controllable mechanical properties, broad availability, excellent operability, and adjustable degradation, which can complement the merits of collagen [67, 68]. Collagen-synthetic polymer composite is expected to produce vascular scaffolds with outstanding biological and mechanical properties. Martin et al. constructed collagen-polylactic acid hybrid scaffold through circular interweaving of electrochemically arranged collagen filaments and polylactic acid, which significantly improved the mechanical properties of blood vessels (with bursting strength = 1.89 ± 0.43 MPa, suture retention strength = 10.86 ± 0.49 N), with compliance (3.98 ± 1.94%/100 mmHg) comparable to that of human coronary arteries, and in vitro human umbilical vein endothelial cell (HUVEC) proliferation experiments showed no cytotoxicity [69]. Another study blended collagen, elastin, and polyurethane to construct a hybrid scaffold by rotary jet spinning, and the results showed improved hydrophilicity, enhanced thermal stability (up to 324°C), and no cytotoxicity [70].

In addition to hybridization of polymer materials, the structural bionic design of scaffolds can further improve their mechanical properties. To better simulate the morphological structure and mechanical properties of natural blood vessels, researchers tried to build multi-layer vascular scaffolds using different preparation methods and manufacturing materials [27]. Michael et al. utilized the polycaprolactone, elastin, and collagen to construct a three-layered electrospun scaffold, with the intimal layer (98: 2: 0 PCL-ELAS-COL) providing initial stiffness and the anchoring of endothelial cells, the medial layer (45: 45: 10, 55: 35: 10, or 65: 25: 10 PCL-ELAS-COL) decreasing stiffness, and the adventitial layer (70-0-30 PCL-ELAS-COL) preventing rupture and attracting cells from outside of the graft. The results showed that the modulus (2.0–11.8 MPa) and compliance (0.8–2.8%/100 mmHg) data of this composite multi-layer scaffold were all within the range of the autologous artery, suggesting its excellent biomimetic ability [71].

2.3 Translational applications of collagen-based vascular tissue engineering scaffolds

Although multiple studies have claimed to construct vascular scaffolds with mechanical properties similar to autologous arteries, and proved their biocompatibility through HUVEC or SMC cell culture in vitro [71–73], from the perspective of clinical translation, the long-term patency rate in vivo after implantation is the ultimate standard of its practicality [74]. Several animal models have been used to evaluate the in vivo performance of collagen-based vascular prostheses, mainly in terms of long-term patency, mechanical function, and histological remodeling, with promising results [75–77]. Bryan W. Tillman et al. constructed an electrospun polycaprolactone-collagen scaffold (inner diameter = 5 mm) seeded with endothelial cells (ECs) on the lumen as well as SMCs on the external surface of the scaffolds, and tested its in vivo stability in rabbit aorto-iliac bypass model. The results of this study showed that the cellularized polycaprolactone-collagen scaffold was resistant to platelet adhesion and maintained structural integrity and mechanical properties (e.g. tensile strength) stable, with blood patency rate reached 87.5% (7/8) after four weeks of implantation [78]. Another study from China constructed electrospun hyaluronic acid/collagen nanofibrous scaffolds (inner diameter = 3 mm) which consisted of a thin "intima" and a thicker outer "media", mimicking the structural of native arteries. After cellulizing the intima and media layer of the scaffold with ECs and SMCs, respectively, the vascular graft remained patent and structurally intact during the six-week rabbit carotid artery replacement experiment. Furthermore, histological evaluation of the retrieved graft showed the vascular remodeling process by newly formed ECM and endogenous cells while not inflammatory infiltration, suggesting that the implanted prosthesis was being integrated in situ by circulatory system [79]. The same research group also implanted a cellular electrospun PCL-collagen vascular prosthesis (inner diameter = 4.75 mm) into the sheep carotid artery [76]. The results showed that the vascular graft remained structural intact and patent after 6 months of implantation, without intimal hyperplasia and thrombosis. Remodeling of the implanted prosthesis produced a new continuous intimal layer (ECs), and the porous micro-fibrous outer layer also had infiltration of newly formed SMCs.

Nevertheless, significant interspecific differences between flow dynamics, inflammatory response, vascular structure, clotting tendency, and injury healing process require us to be cautious when transferring the animal experimental results to humans [80, 81]. In the development of clinical transformation of collagen-based tissue engineering vascular graft, more strategies such as manipulations of the scaffolds pore size, modifications with biologically active molecules, are used to improve the cells residence and functionalization, and finally the integration ability of the graft [23, 82]. So far, there are no commercial small diameter vascular tissue engineering prostheses used in clinical practice, and more in vivo animal studies are needed to further confirm their long-term safety and effectiveness, so as to fill the gap between laboratory research and clinical translation.

3 Collagen-based hydrogels for cardiac disease treatment

As a three-dimensional hydrophilic polymer network, hydrogel has been increasingly explored for the treatment of heart diseases (especially myocardial infarction and heart failure) due to its unique biocompatibility, cardiac extracellular matrix simulation and other advantages [83–85]. Myocardial injection of hydrogel can exert pleiotropic effects: 1. provide mechanical support for the ventricular wall, increase the wall thickness, reduce the ventricular stress, and limit the contractile tension, so as to improve cardiac function; 2. exert its therapeutic effects by mimicking the cardiac extracellular matrix microenvironment; 3. act as drug/cell delivery systems to load stem cells and/or bioactive molecules/drugs for sustained and controlled release at the lesion site to promote myocardial regeneration, anti-inflammation, and reduce pathological remodeling (Fig. 3) [85–87]. The ideal injectable hydrogel for the treatment of heart diseases should have the following characteristics: (1) biocompatibility and low toxicity: no rejection inflammation after injection, and can provide a beneficial microenvironment for cardiac cell adhesion and growth; (2) injectability: remain liquid when injected, and quickly form gel after injection to avoid leakage; (3) appropriate stiffness: provide suitable mechanical support while not hampering the normal myocardial contraction; (4) degradability; (5) electrical conductivity: not interfere the electrical conduction and synchrony of normal myocardium [88, 89]. As the most abundant component of cardiac extracellular matrix, collagen (collagen I and III) is utilized as one of the main ingredients for injectable hydrogels due to its excellent biological properties, adjustable mechanical properties, and thermal sensitivity which allow its jellification upon injection at 37 °C [89, 90].

3.1 Injectable collagen hydrogel per se for cardiac disease

Myocardial infarction (MI) is an acute worsening phenotype of coronary heart disease, which is characterized by occlusion of coronary blood flow, loss of myocardial cells, thinning of the ventricular wall, and pathological collagen deposition, eventually leading to cardiac enlargement and heart failure [91]. Injection of

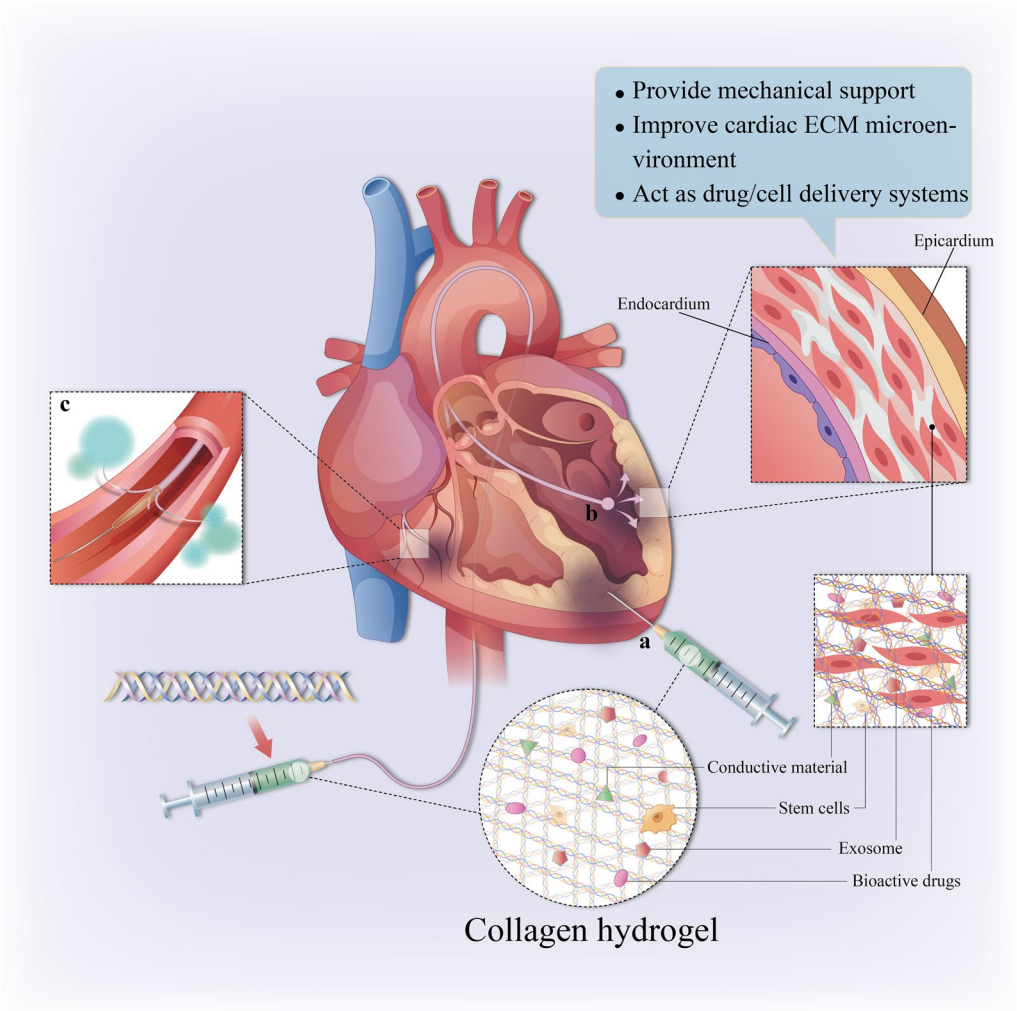


Fig. 3 Injectable hydrogels for the treatment of heart diseases. Injectable hydrogels can be administered in the following ways: **a**. myocardial injection in thoracic surgery or under the echocardiographic guidance; **b**. transcatheter endomyocardial injection; **c**. intracoronary myocardial injection. Injectable hydrogels can exert the cardiac protective effect by providing mechanical support, improving the heart microenvironment, and loading cells/bioactive drugs

hydrogel after MI might provide mechanical support for the ischemic ventricular wall and reduce the pathological remodeling, which may improve the prognosis of MI. McLaughlin et al. crosslinked the recombinant human collagen I/III hydrogel by chemical crosslinkers and investigated their performance in C57BL/6 mice after 1 week of MI. Their results showed that collagen I and III hydrogel were retained at the injection site for 7 and 2 days, respectively, and this "bionic matrix" significantly attenuated post-MI pathological remodeling and improved cardiac function and morphology, contributing to higher vessel density and lower myocyte loss [92]. MI goes through different pathophysiological stages, from necrotic and inflammatory phases to proliferative and maturation phases, which may lead to discrepant curative effects of hydrogel injection [93, 94]. Hence, another study further explored the temporal therapeutic difference of collagen hydrogel injection after MI. Blackburn et al. constructed rat tail derived collagen I hydrogel and examined its efficacy of administration at 3 h, 7 days and 14 days after MI. The results proved that 3 h delivery group gained the optimal cardiac function (assessed by %LVEF), higher vascular density, lower degree of inflammation, whereas administration at 14 days post MI seemed no therapeutic effect, indicating early stage after MI as the therapeutic window of hydrogel injection [95]. The possible explanation may be that hydrogel injection can reduce the initiation and development of pathological remodeling after MI, but cannot reverse the already remodeled heart in late stage. Besides the administration time, another study addressed the dose–response

relationship of collagen III hydrogel in the treatment of MI. The research results suggested that a single collagen hydrogel injection at 3 h after MI reduced scar size, inflammation, and improved cardiac function, while extra injections at 1 and 2 weeks did not provide additional benefit. Interestingly, increasing the collagen concentration in the hydrogel from 1 to 2% extinguished the positive efficacy [96], which suggested that more is not the better, and the appropriate injection timing and dose are the key to efficacy of hydrogels.

The coordinated contraction of the heart depends on the ordered electrical conduction of healthy cardiocytes. Various heart diseases, such as myocardial infarction and amyloid cardiomyopathy, could lead to progressive loss of myocardial cells and disruption of cardiac conduction pathways, thus inducing arrhythmia and cardiac contraction desynchrony [97]. Although collagen hydrogels themselves are less conductive, a wide variety of conductive biomaterials including conductive polymers (e.g. polypyrrole [98, 99]), carbon nanomaterials (e.g. graphene [100] and carbon nanotubes [101]), and metal-based compounds (e.g. gold nanoparticles [102]), can be incorporated to construct conductive hydrogels. In this case, the conductive hydrogel can bridge the electrical signal between healthy and scarred myocardial tissue, restore the electrocardiosignal conduction in the scar area, and improve the contractile coordination of the diseased heart [103]. In vitro experiments have shown that the conductive collagen hydrogel can improve the arrangement and assembly of cardiomyocytes and promote the generation of sarcomere and electrical coupling, thereby improving the beating performance of the engineered heart tissue [101, 102, 104]. Qian et al. constructed a polypyrrole gelatin-based conductive hydrogel (with a conductivity of $5.52 \pm 0.37 \times 10^{-4}$ S/cm) and injected it into myocardial scar tissue in rat acute MI model [98]. The results showed that the conductive hydrogel reduced the resistivity and increased the conduction velocity of fibrous tissue in the infarcted area, made it harder to induce arrhythmia, and improved the cardiac function of the MI rats [98].

3.2 Collagen hydrogel as a vehicle for cardiac cell/cell free therapy

Various cardiac diseases are accompanied by the irreversible loss of cardiomyocytes characterized by the very low regenerability [105]. In this scenario, researchers hope to reverse the pathological process and improve the prognosis of heart disease by exogenous supplementation of stem cells (such as mesenchymal stem cells) with the properties of self-renewal, proliferation, differentiation plasticity, and immunoregulation [106]. In practice, however, due to the unsuitable inflammatory microenvironment and mechanical contraction of the diseased heart, the injected stem cells have a very low long-term survival rate (no cells survive in the infarct scar and survival rate < 1% in infarct border region after 24 h [107]) and fail to differentiate into mature functional cardiomyocytes, hindering its clinical translation [108–110].

Nevertheless, porous collagen-based hydrogels can mimic cardiac extracellular matrix and provide a favorable microenvironment for the retention, proliferation, differentiation, and mature of stem cells at the injection site [94, 111], which may improve the problem of poor intramyocardial stem cells transplantation and bring the dawn of cardiac cell therapy [112]. Chen et al. established Transglutaminase collagen-based hydrogel as a biological scaffold for adipose-derived mesenchymal stem cells (ADSCs) delivery. The in vitro co-culture experiments of ADSCs with the hydrogel showed that ADSCs could survive and proliferate in the collagen-based hydrogel for up to 4 weeks, and gradually migrated to the edge of the hydrogel. In vivo experiments showed that ADSCs could survive at least 42 days after injection in the hydrogel group, while less than 28 days in the PBS-ADSCs group. The prolongation of ADSCs residence in myocardium significantly improved left ventricular ejection fraction (LVEF), reduced left ventricular diameter, attenuated myocardial fibrosis area and pathological remodeling at 4 weeks after MI [113].

The promising results of animal experiments have actively promoted the clinical translation of hydrogel-loaded stem cell therapy. A cardiac surgery team from China evaluated the efficacy and safety of the human umbilical cord-derived mesenchymal stromal cell laden collagen hydrogel in patients (n = 50) with chronic ischemic heart disease receiving elective CABG [114]. No serious adverse events such as malignant arrhythmia, systemic infection, stroke, anaphylaxis, hospitalization for heart failure, cardiac perforation or pericardial tamponade were observed during the 12-month follow-up. Compared with the cell-only injected group (infarct size percentage = + 5.19%) and control group (infarct size percentage = + 8.59%), the percentage of infarct size defined by cardiac magnetic resonance was slightly reduced in the collagen-stem cell group (infarct size percentage = − 3.10%) while no significant difference in LVEF among the groups. The marginal improvement in infarct size but not in the LVEF from this phase 1 clinical trial was probably due to the selection of patients -CABG significantly restored the cardiac blood supply and increased LVEF, thus possibly masking the differences between the collagen-stem cell group and the control groups. The clinical evidence of this collagen-hydrogel loaded stem cells suggests that we should further improve the

biological performance of hydrogel to increase the survival and retention of the stem cells, explore the potential beneficiaries and the timing of injection, admiration dose of stem cells, and expand the clinical sample size to verify its long-term efficacy and safety [107].

In addition to using hydrogels as a vehicle for exogenous stem cell delivery, another idea is to utilize hydrogels loaded with stem cell "homing factors" (such as histone deacetylase 7 derived phosphorylated 7-aminoacid peptide) to mobilize and recruit autologous stem cells in situ at the injection site to participate in cardiac injury regeneration [115]. Moreover, studies have shown that the pro-cardiac tissue repair function of stem cell therapy relies more on the paracrine of soluble factors and bilayer phospholipid membrane vesicles, namely extracellular vesicle (EV), rather than their differentiation capacity [116, 117]. These advances shift the research focus from stem cell therapy to a novel cell-free strategies using stem cells derived exosomes to treat cardiovascular diseases [118, 119]. However, low target site retention and poor vesicle stability after systemic administration limit their efficacy. Due to the excellent release kinetics, hydrogels combined with EVs may facilitate their clinical translation [120]. Prieto et al. developed an alginate-collagen hydrogel as hADSC-EV delivery system for longer EVs retention in MI lesion [89]. The results showed that the alginate-collagen hydrogel released EVs continuously for at least 7 days at the injection site, which was hopeful to improve the prognosis of myocardial infarction.

3.3 Collagen hydrogel as a cardiac drug delivery system

Problems with traditional systemic administration include insufficient drug accumulation in target organs (inefficiency), excessive distribution in healthy tissues (toxicity), and the short half-life of some bioactive drugs. Collagen hydrogels are promising drug delivery systems that can restrict the drug to the injection site (high drug retention in situ), with modifiable drug release kinetics (slow and controlled sustained release) and reduced non-target organ side effects. So far, various studies have attempted to use hydrogels loaded with short peptides [115, 121], small molecule chemicals [122] and cytokines [123–125] to treat heart diseases, such as myocardial infarction and heart failure [126].

Reis et al. constructed a chitosan-collagen hydrogel loaded with angiopoietin-1 derived peptide, and injected it into the peri-infarction/infarct area of MI mice. The results showed that the hydrogel remained in situ for almost 3 weeks and continuously released the peptide, without rejection inflammation. The hydrogel injection significantly reduced scar size as well as post-infarction cardiac function [121].

3.3.1 Collagen hydrogel with on-demand release kinetics

In addition to sustainably releasing drugs until gel degradation, hydrogels can transform the release kinetics into a disease-responsive manner through synthetic design, achieving better spatiotemporal properties of drug delivery [127, 128]. The inflammatory microenvironment in the early stage of MI is characterized by the persistent overexpression of reactive oxygen species (ROS) and matrix metalloproteinases (MMPs) and a weakly acidic environment, which promotes pathological remodeling and deterioration of cardiac function after MI [129–131]. Therefore, collagen hydrogels can utilize the unique microenvironment after MI as a trigger for drug release to achieve environmentally responsive on-demand release. Dai et al. constructed an on-demand drug release hydrogel by grafting the recombinant protein "GST-TIMP-bFGF" to GSH-modified collagen hydrogel through specific binding between GST and GSH (Gel-GSH-GST-TIMP-bFGF), in which TIMP peptide acted as a competitive substrate for MMPs, and bFGF was an anti-fibrosis and pro-angiogenic growth factor [124]. The overexpressed MMPs at the infarction site promoted the hydrolysis of TIMP and release of bFGF. This kind of disease-responsive spatiotemporal growth factors delivery ensured that the release of bFGF was confined in the infarct focus while not the normal cardiac tissue, which could further improve drug efficacy and reduce toxicity. Another study utilized the disintegrable feature of borate ester bond in ROS and acidic environment, and established a borate ester bond-based MI reactive rhCol III-hydrogel [122]. Combined with anti-inflammatory/antioxidant drug curcumin, this hydrogel could on-demand release the curcumin and rhCol III by degrading in the acidic and ROS microenvironment of MI, which in turn inhibited the oxidative stress, inflammatory response and apoptosis as well as promoted the recovery of cardiac function after MI. This on-demand release kinetics is promising to improve drug therapeutic efficacy and reduce off-target toxicity [132].

3.3.2 Strategies for improving drug loading capacity of collagen hydrogel

In addition to improving the release kinetics of collagen hydrogels, another key translational problem is how to increase the drug loading capacity. The enhanced drug loading combined with the sustained release kinetics can highly prolong the drug release duration and reduce the frequency of drug delivery, which is particularly crucial for cardiac drug delivery, because the myocardial injection of hydrogels is usually an invasive and risky procedure [133]. The drug-loading ability of the native collagen hydrogel is largely dependent on the swelling properties, electrostatic association and hydrogen bonding between the hydrogel

and the hydrophilic drugs [134], which is usually inadequate for long-term drug administration, especially for hydrophobic molecules, antibodies, and nucleic acids [135]. Nanoparticles (NPs) possess many ideal properties for drug delivery, such as high prominent drug loading capacity, high stability, manipulatable release curve, and multi-environmental response (like thermo-responsive, pH-sensitive, high glucose sensitive et al.) [136, 137]. The integration of hydrogels with nanoparticles (termed as nanogel) can further diversify their drug loading, especially for hydrophobic molecules [138, 139]. Roshanbinfar et al. developed a nanogel based on collagen type I and branched polyethyleneimine (bPEI)-coated AuNPs. Positively charged bPEI-coated AuNPs can bind to a variety of negatively charged drugs and growth factors, and the release process can be customized by controlling the degree of ionic interaction [102]. Besides polymeric nanoparticles, liposomes, micellar and dendrimers can be used as drug carriers to further optimize the drug loading performance and release kinetics of hydrogels [139]. More research is needed to demonstrate the role of these modified collagen hydrogels in the treatment of heart disease.

3.4 Collagen hydrogel for cardiac disease—gaps in clinical translation and future outlook

As mechanical support materials and drug delivery systems, collagen hydrogels have gained promising results in multiple preclinical studies, but their clinical translation still faces the following problems:

(i) Administration strategies and injection location: Current mainstream cardiac hydrogel delivery strategies include direct epicardial injection, trans-endocardial delivery, and intra-coronary administration. Direct epicardial injection owns the best location control but requires invasive surgery procedures, and is usually used in preclinical (small animal) research or in combination with open chest surgery like CABG; trans-endocardial or coronary delivery can be performed on the basis of transcatheter procedures, but both require exquisite interventional skills and carry the risk of exposing the hydrogel to the circulation, which could lead to vascular embolism. Moreover, intra-coronary administration cannot always reach the target location, limited by the distribution of available coronary vessels. Transthoracic ultrasound-guided myocardial puncture may be a minimally invasive and feasible method [140, 141].

(ii) Differences between experimental animal models and clinical diseases: In preclinical studies, hydrogels are often injected shortly after MI modeling, while in actual clinical practice, AMI patients are rarely treated in such a timely manner. Furthermore, emergency catheter-based restoration of coronary flow is currently the preferred treatment for AMI, while hydrogel may be used as a complementary therapy after vascular recanalization. Therefore, further studies are needed to explore the timing of hydrogel injection after MI and its additional value after revascularization.

(iii) Lack of "brakes": Collagen hydrogels provide a long-term sustained-release platform for local drug delivery to the heart. However, the high retention of hydrogels at the injection site also means it is difficult to remove them after injection, which is necessary when cytotoxic injury, hypersensitivity reaction, and injection site infection occur. A hydrogel that is difficult to remove manually after injection is just like a bicycle on the road without brakes.

(iv) Narrow spectrum of treatable cardiac diseases: At present, most studies of injectable hydrogels for cardiac diseases focus on coronary heart disease with high morbidity rate, including MI, ischemic cardiomyopathy, and concomitant heart failure, with less research on other diseases such as dilated cardiomyopathy. This is mainly due to the fact that injectable hydrogels are primarily a topical treatment. The above-mentioned coronary artery diseases are easy to model (by coronary ligation), and exist clear disease-targeted injection areas (diseased coronary artery distribution areas), while for diseases with diffuse involvement such as dilated cardiomyopathy and myocarditis, topical injection of hydrogel maybe out of focus. Theoretically speaking, even if the hydrogel indeed improves the local myocardium at the injection site, the functional difference between the injected and the non-injected myocardium could easily lead to uncoordinated myocardial contraction and deterioration of the overall cardiac function. For such non-ischemic cardiac diseases, more studies are needed to improve the injection strategy of hydrogels (such as injection site distribution) and to find key disease intervention targets.

In summary, collagen hydrogels have the potential for clinical translation, but more research is needed to explore their injection strategies (timing, dosage, and route of injection), improve experimental models to be more relevant to clinical practice, and develop a "withdrawal" mechanism to deal with post-injection adverse events.

4 Collagen patch for cardiac disease treatment

The engineered cardiac patch is the tissue-like biomaterial scaffolds with/without cells and/or bioactive factors, which is manufactured through tissue engineering-based

methodologies, including decellularized extracellular matrix, electrospinning, 3D bioprinting, and cell sheets [142]. It is typically designed to be attached to the epicardium to repair myocardial damage (adhesive dressings) or be sutured to cardiac defect (cardiac patches) [143, 144]. Similar to the aforementioned cardiac hydrogel, the ideal cardiac patch scaffolds should meet the following characteristics: (1) excellent biocompatibility and suitable biodegradability to integrate into the patients' natural heart tissue; (2) adequate mechanical stiffness and compliance that accommodate the heart beat; (3) biomimetic conductivity to allow the sequential conduction of electrical excitation in the heart for synchronous myo-contraction [145, 146]. As the main components of the cardiac ECM, collagen possesses superior biological properties to mimic the cardiac ECM microenvironment and adjustable mechanical properties to withstand the cyclic cardiac contraction stress, which renders it a popular choice as biomaterial for cardiac patch scaffold [3, 147]. The main applications of collagen patches in vivo include: as an epicardial dressing by loading cells/bioactive molecules; as a patch for reconstruction of heart and large vascular defect (Fig. 4).

4.1 Collagen patch as epicardium dressing for the heart

Collagen patches can be placed in the epicardium of the diseased myocardium to act as stem cells and/or drug vehicles to promote the regeneration and repair of the damaged heart tissue. Collagen cardiac patch can be divided into cell-based patch and cell-free patch.

4.1.1 Collagen patch for cardiac cell/cell free therapy

Cardiomyocytes are terminally differentiated cells and have the low regenerative capacity, which limits its ability to restore cardiac function when cardiomyocytes pathologically lost [148]. Collagen patches can provide biomimetic microenvironment for stem cell growth and differentiation, and increase the retention of stem cells in the lesion site, which are functionalized as biological carriers for cardiac cell therapy, especially in MI and heart failure [149, 150]. Currently, human induced pluripotent stem cells (hiPSCs), mesenchymal stem cells (MSCs), cardiovascular progenitor cells, and skeletal myoblasts (SMs) etc. have been extensively incorporated in the cardiac patch fabrication at preclinical and clinical studies [151–153]. Yang et al. used decellularized extracellular matrix as a scaffold for cardiac patch, and loaded hiPSCs-derived cardiovascular progenitor cells (hCVPCs) and cardiomyocytes (hCMs) to construct a cell patch for MI C57 mice [154]. The results showed that the heart patch well supported the growth and retention of hCVPCs and hCMs, which together attenuated cardiac functional deterioration, ventricular dilation, and scarring size at 28 and 90 days after implantation [154]. Another study prepared a bio-scaffold by coaxial electrospinning of poly (CL-co-TOSUO)/collagen /shell nanofibers and seeded bone marrow MSC to construct the cardiac cell patch [155]. The results of this study showed that the collagen cell patch possessed well mechanical properties (elongation at break > 300%) as well as high survival rate of transplanted MSC after 5-weeks implantation (survival rate 15 ± 4%), and significantly promoted angiogenesis and improved cardiac function after MI(LVEF: 40.8 ± 3.2% in cardiac patch group *vs.* 29.8 ± 3.2% in control group) [155].

Accumulating evidence suggests that the cardioprotective effects of stem cells are mainly mediated by its paracrine cytokines [156]. Therefore, in addition to delivering stem cells directly, the cardiac collagen patch can load stem cell-derived exosomes to promote endogenous regeneration and repair of myocardium. Using hybrid electrospinning method, Fu et al. prepared COL-/PCL hybrid nanofibers as a patch scaffold, and loaded mixed nanoparticles of TGF-β3 and human umbilical cord MSC exosomes to form collagen nanopatches (Exo@TGF-β3@NFs). The results of in vivo experiments showed that the implantation of Exo@TGF-β3@NFs for 4 weeks significantly reduced the infarction size and fibrosis of AMI rats, and improved left ventricular ejection fraction [157]. Another study demonstrated the additional benefits of MSC derived exosome-laden collagen patches during CABG in a chronic myocardial ischemia porcine model, which suggested that exosome patches can further improve cardiac function even on the basis of revascularization [158].

Various bioactive molecules, such as angiopoietin-like protein 1 (Ang-1), granulocyte colony-stimulating factor (G-CSF), Substance P (SP), can recruit endogenous stem/progenitor cells [159–161]. Therefore, in addition to exogenous delivery of stem cells or exosomes, collagen patches can load these stem cell "homing factors", mobilize and recruit endogenous stem/progenitor cells to the lesion site, and provide a habitable environment for the recruited stem/progenitor cells, which in turn promotes in-situ repair of cardiac tissue [160, 162]. Kong et al. incorporated SP (stem cell homing factor) and insulin-like growth factor 1 (stem cell growth supporting factor) into the type I collagen/polycaprolactone (PCL) electrospun patch, and evaluated its in vivo performance in AMI rats. The results showed that this homing factor ladened collagen patch significantly increased the number of stem cells in the infarct area (nearly fourfold than the saline control group), increased ventricular wall thickness and vascularization, and improved cardiac function post MI [163]. In addition to conventional stem cell homing factors mentioned above, another study covalently

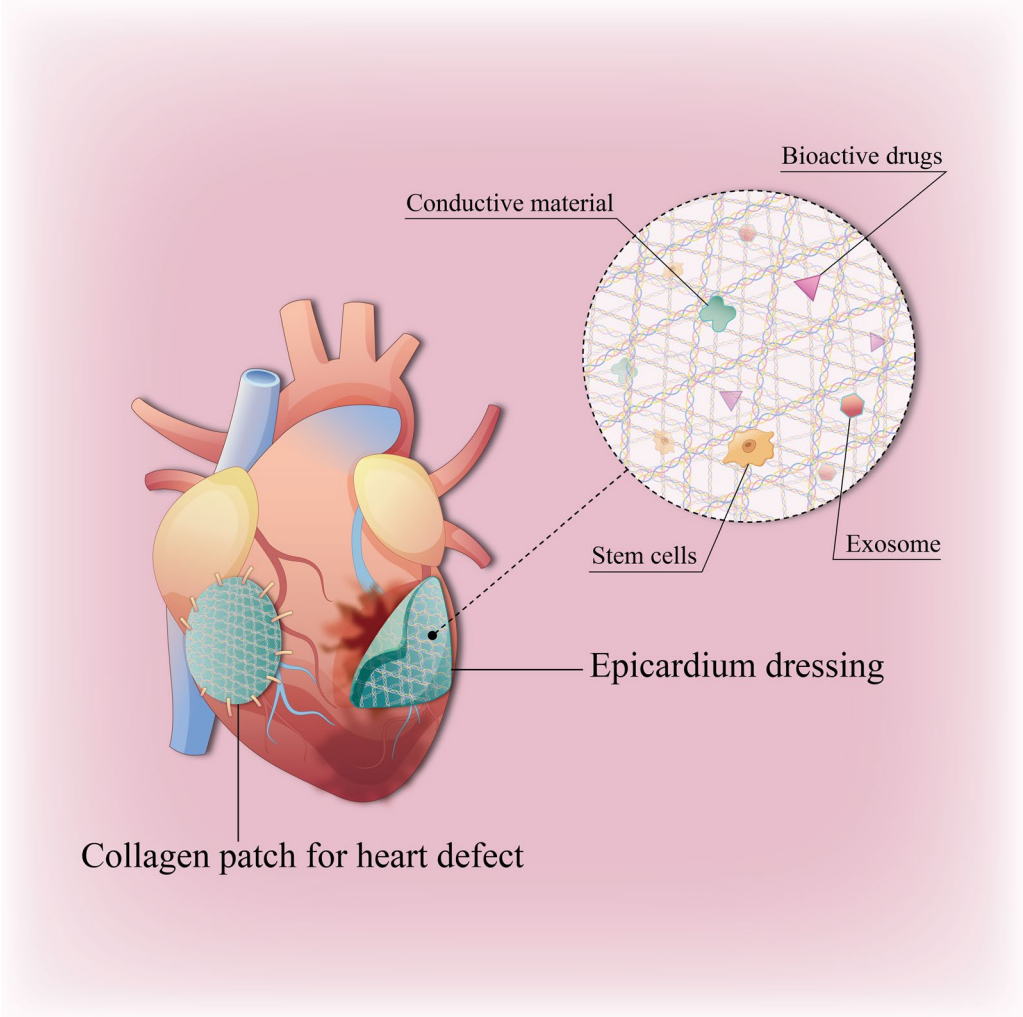


Fig. 4 Collagen patches for the treatment of heart disease. Collagen materials can be used as epicardial dressings or mending patches for cardiovascular defects

combined collagen scaffolds with the stem cell specific antibody (anti-Sca-1 monoclonal antibody) to construct a stem cell capturing collagen patch, which could enrich autologous stem/progenitor cells into the functional patches at wound sites to promote damage repair [164].

4.1.2 Collagen patch as a local drug delivery system for the heart

Collagen patches can serve as a carrier for intrapericardial local delivery of various bioactive molecules, such as proteins, growth factors, and RNA [165, 166]. The application of fol-listatin-like1 (FSTL1) via an epicardial patch had been confirmed to stimulate the cell cycle entry and the division of pre-existing cardiomyocytes and improve cardiac function and survival in mouse and swine models of MI [167]. However, epicardial patch as a drug delivery agent confronts the process of drug diffusion loss from the patch to the myocardium, and the delivery efficiency may be inferior to direct intra-myocardial injection of hydrogel.

4.1.3 Conductive collagen patch for heart diseases

A variety of heart diseases can perturb the bioelectrical activity of the myocardium, which further affects cardiac contraction and function. Collagen patches can integrate conductive substances, such as conductive nanomaterials, conductive polymers, and ionic electrolytes, to enhance electrical conductivity and improve electrical coupling of damaged myocardium [168, 169]. Leite et al. introduced conductive polyaniline into a biodegradable stent patch composed of collagen, silk cellulose and hyaluronic acid (COL-SF) through plastic compression to construct a conductive heart patch, which can improve the pathological remodeling of rat heart after MI [170].

Another study utilized PPy to increase the conductivity of a type I collagen heart patch (up to 0.06 S cm^{-1}) and showed excellent cardiomyocyte compatibility in vitro [171]. Although conductive heart patch has achieved initial results in promoting heart regeneration and cardiac function recovery, the optimal conductance parameter is still under exploring, because mismatched conductivity is not conducive to the coordination of cardiac electrical activity [172, 173].

4.2 Collagen patch for the heart and large vascular defect repair

Traditionally, decellularized animal/human-derived pericardium and synthetic polyesters (such as PCL, PGS, PLGA, PU) are the mainstream materials to repair cardiac/large vascular defects [146]. Despite easy access, these materials still face the following shortcomings for clinical use [174–176]: (1) inability to continue to grow with the development of the heart, and often need to be replaced by secondary surgery; (2) mismatched mechanical properties with surrounding tissues and lack of contractility, which may lead to ventricular aneurysm and abnormal cardiac output function; (3) immune response: inflammation, calcification, and fibrotic changes at the transplant site; (4) lacking conductivity: it may lead to the formation of an electrical reentry ring around the implanted patch, which can induce arrhythmias such as atrial flutter after cardiac surgery. Therefore, tissue engineering biomaterials are investigated to make up for the current shortage of cardiac patch materials. Due to the aforementioned biological properties, collagen is one of the potential materials for use in cardiac defect patches [145]. However, additional modifications, including improving electrical conductivity and reducing thrombogenicity, are necessary for collagen patches when used in surgical cardiac repair [142]. For example, conducive nanoparticles can enhance the electrical and mechanical properties of collagen [177, 178], and heparin can inhibit thrombosis [179]. Kaiser et al. prepared a chitosan/collagen/polyurethane composite patch through co-electrospinning technology and evaluated its blood compatibility in vitro [180]. Further studies are needed to explore and improve the ability of tissue-engineered cardiac collagen patches to integrate into myocardial tissue.

In brief, cardiac collagen patches can act as epicardial dressings to directly deliver stem cells and drugs for treatment of heart diseases such as myocardial infarction and heart failure. In addition, collagen patches may have potential as heart/large blood vessel repair materials, but their performance in vivo needs to be further evaluated and improved. Finally, the delivery of cardiac patch may be the major obstacle in its clinical transformation. Thoracotomy or thoracoscopic surgical placement is quite traumatic. Qiu et al. have constructed a carbon nanotube fibrin patch with shape-memory behavior, and can restore the membrane shape after injection into the epicardium, which may be a breakthrough in minimally invasive heart patch delivery [181, 182].

5 Collagen-based hemostatic materials

Hemorrhage is a vital but intractable clinical problem, accounting for at least 40% of deaths after injuries [183], increasing the incidence of postoperative complications and the risk of surgical failure [184–186]. Effective approaches to control hemorrhage are urgently required in the medical field [187]. Traditional hemostatic materials such as gauze have limited hemostatic ability and need to be completely removed after hemostasis due to their non-biodegradability [188]. Therefore, the development of novel hemostatic materials and technologies has received extensive attention [189]. Clinically, the ideal hemostatic material should possess the following properties: (1) rapid hemostasis; (2) biocompatible, self-biodegradable, and conducive to wound healing; (3) economical [190]. Physiologically, hemostasis requires the participation of the vascular endothelium, circulating platelets, and coagulation factors [10]. Collagen is a major component of the basement membrane and ECM of blood vessels, responsible for mediating platelet adhesion, activation, and congregation as well as stimulating factor XII to initiate endogenous coagulation cascade [10]. The excellent thrombogenicity and biodegradability of collagen make it an ideal hemostatic material. At present, collagen-based hemostatic products mainly serve as topical hemostats, including collagen powder, sponge, hydrogels, and collagen-based vascular closure devices (VCDs) (Fig. 5) [191–193].

5.1 Collagen hemostatic sponges and hydrogels

High porosity of collagen sponge increases the contact areas between platelets and hemostatic materials, which promotes platelet adhesion, activation, aggregation and in turn shortens hemostasis time [194–196]. Clinically, collagen-based powder and sponge can be applied directly to the bleeding surface, especially for the wide areas of parenchymal bleeding, irregular cavities, and lacerations, where conventional hemostasis methods such as compression are difficult to handle [195, 197]. Microfibrillar collagen hemostat (MCH, trade name Avitene) is one of the representative products in collagen powder and sponge, which is made of purified bovine corium collagen by biological enzyme and/or organic acid extraction technology [198, 199], with a bio-absorption time

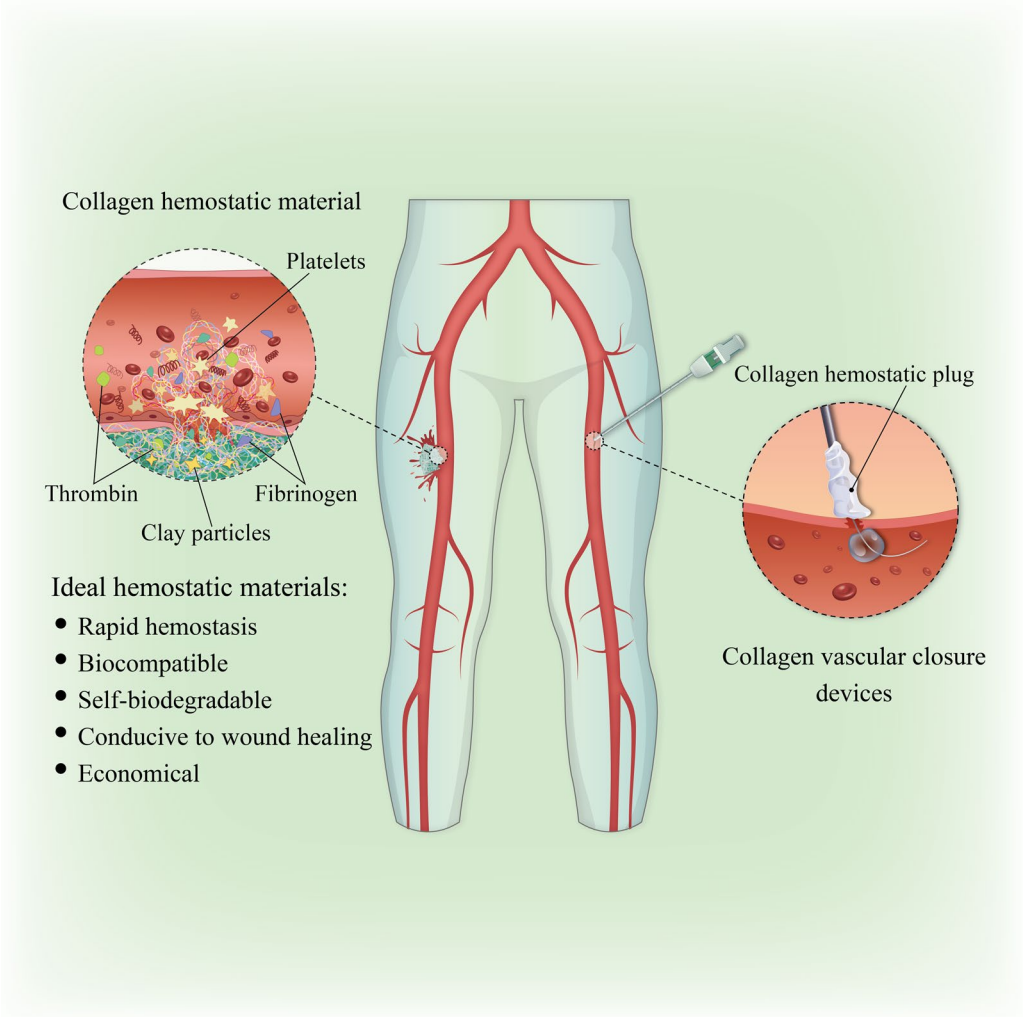


Fig. 5 An overview of collagen-based hemostatic materials. Collagen can be combined with other procoagulant substances to form composite hemostatics for hemostasis in surgery or percutaneous interventional surgery

of approximately 8 weeks [195]. Wilkinson et al. verified the hemostatic ability of MCH in a skin incision model, where MCH were immediately applied on the manmade skin defect and obviously reduced the hemostasis time (1 min in MCH group vs. 15.7 min in the control group) [200]. However, considering the risk of animal-derived collagen carrying infectious diseases and inducing immune responses [201], genetically engineered human collagen has been developed as novel biocompatible hemostatic material [202].

Furthermore, in addition to powder and sponge form, collagen-based hydrogels possess better stretchability and tough adhesion, and have been proved to have good hemostatic efficacy and great potency as surgical sealants and hemostats [190, 203]. Sun et al. assembled recombinant human collagen and tannic acid through the intermolecular interaction force to construct an excellent surgical sealing hydrogel with properties of fast gelation time (within 10 s), clotting time (within 1 min), and strong viscosity (adhesive strength > 250 kPa) [204]. Besides well hemostatic efficacy, collagen-based hydrogels can comprehensively promote wound healing by accelerating wound angiogenesis and collagen synthesis, while reducing inflammation, oxidative stress, postoperative adhesions, and infections [205–210].

5.2 Compound collagen hemostats

The hemostatic capacity of the collagen-only materials is limited, so researchers usually combine collagen (the initiator of the coagulation reaction) with other hemostatic materials like clay, thrombin as well as fibrinogen (the enzymes and substrates of the coagulation reaction), to further enhance its hemostatic efficacy [194, 211]. The clinical translation of these products is well established,

and commercial compound collagen hemostats (for example, Tisseel, Evicel, Tachosil) are widely used to control ongoing diffuse parenchymal hemorrhage and cardiovascular surgeries [212–215]. For instance, Santos et al. evaluated the hemostatic effect of Tachosil (a collagen sponge coated with thrombin and human fibrinogen) in sealing 7–0 needle stitches holes on the femoral arteries of rats and the results showed that Tachosil treated group had a significantly shorter average hemostatic time than those with gauze compression (65.63 ± 39.49s vs. 181.25 ± 67.49s) [213].

5.3 Collagen vascular closure devices in hemostasis after transcatheter interventions

Apart from the use in surgery, collagen-based hemostats also play a role in hemostasis at the vascular puncture site of transcatheter intervention [192]. As the rapid development of percutaneous procedures, traditional puncture hemostasis methods such as manual compression (MC) and restricted activity have multiple limitations: time-consuming, inadequate hemostatic capacity, patient discomfort, and increased risk of deep venous thrombosis [216, 217]. Therefore, collagen hemostats-based vascular closure devices have been developed as an alternative to traditional puncture site compression, especially in large bore arteriotomies [218]. Commercial VCDs such as Angio-Seal and Vascade Vascular Closure System mainly act as a passive approximator that deploys a collagen hemostatic plug over the vessel puncture port [192]. The implanted collagen plug could promote platelet accumulation and coagulation at the vascular defect site, while swelling during this process and sealing the blood vessels by mechanical compression [219]. Previous clinical studies have shown that collagen VCDs can significantly reduce the incidence of hematoma, and shorten the time to hemostasis and ambulation after percutaneous vascular procedures, which is conducive to the turnover and recovery of patients [220–222], with negligible risk of infectious complications (0.6% in VCDs vs. 0.2% in MC) and thrombotic complications (0.3% in VCDs vs. 0% in MC) [192]. Modifications of the collagen plug, such as coupling with thrombin, may further shorten the hemostasis time and reduce the risk of embolism [223].

6 Conclusion and prospect

Collagen possesses excellent biological properties and has become a vital tissue engineering biomaterial for the treatment of cardiovascular diseases. With the development of bio-manufacturing technology (such as blend electrospinning and 3D printing), collagen can be used as a functional coating of large and medium diameter vascular graft and a scaffold for small diameter tissue engineering vessels, which provide an additional therapeutic option for vascular transplantation. Collagen alone or combined with other biomaterials, could form injectable hydrogels as well as cardiac patches, which further laden stem cell or bioactive drugs for the target treatment of heart diseases such as myocardial infarction, ischemic cardiomyopathy, and heart failure. In addition, collagen's thrombogenicity makes it an excellent hemostatic biomaterial. Collagen-based sponges, hydrogels as well as vascular closure devices have been widely used in surgical and interventional procedures. More studies are needed to improve the feasibility of delivery (minimally invasive or even non-invasive), biosafety, and intrinsic properties of collagen (such as mechanical properties, electrical conductivity, drug loading capacity and release kinetics) to promote the clinical translation of more collagen-based tissue engineering products.

Abbreviations

ECM	Extracellular matrix
VEGF	Vascular endothelial growth factor
bFGF	Basic fibroblast growth factor
HUVEC	Human umbilical vein endothelial cell
SMC	Smooth muscle cell
PCL	Polycaprolactone
MI	Myocardial infarction
ADSCs	Adipose-derived mesenchymal stem cells
LVEF	Left ventricular ejection fraction
CABG	Coronary artery bypass grafting
EV	Extracellular vesicle
ECs	Endothelial cells
ROS	Reactive oxygen species
MMPs	Matrix metalloproteinases
NPs	Nanoparticles
MCH	Microfibrillar collagen hemostat
MC	Manual compression
VCDs	Vascular closure devices

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Author contributions

ZXH, YX, and JY equally contribute to the article. ZXH and KL designed the intellectual framework of this review. ZXH, YX, and JY wrote the initial manuscript. KL contributed to the critical discussion, manuscript revision and figure design. YMH and YXH participated in manuscript revising and literature filtration. All the authors approved the final version of the manuscript.

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Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Competing interests

On behalf of all authors, the corresponding author states that there is not any conflict of interest.

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