

Application of High Molecular Hydrogel in The Treatment of Myocardial Infarction

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Abstract. Myocardial infarction (MI) is the world's leading disabling and fatal disease. Currently, clinical treatment methods mainly include drug therapy, angioplasty, and coronary artery bypass grafting. These traditional treatment methods are difficult to repair damaged myocardial tissue and cannot restore normal necrotic and fibrotic myocardium. Therefore, it is imperative to improve the efficacy of traditional treatment methods and find new treatment strategies. More and more studies have found that stem cell transplantation can repair damaged myocardium, but stem cells transplanted to the affected site undergo oxidative damage, compression loss, and low cell survival and retention rates. At present, there is an urgent need to seek new methods that can effectively repair damaged myocardium and restore cardiac function. In recent years, with the development of regenerative medicine engineering and the continuous optimization of polymer technology and the development of new biomaterials, it has become a reality to create lost or functionally damaged tissues and organs through theoretical methods of biology and engineering, enabling them to have the structure and function of normal tissues and organs. This article will focus on the latest progress in methods for repairing damaged myocardium in myocardial infarction through polymer hydrogel materials.

Keywords: High molecular hydrogel, Myocardial infarction, medical engineering.

1. Introduction

Cardiovascular disease (CVD) is a collective term for heart and vascular diseases, including cerebrovascular disease, coronary heart disease, and deep vein thrombosis. Nowadays, with the improvement of people's living standards and changes in lifestyle, the number of CVD patients is increasing. The American College of Cardiology (ACC/American Heart Association (AHA) myocardial infarction is still the main cause of global incidence rate and mortality. At present, myocardial infarction still poses a serious threat to human health. Therefore, deeper medical research on myocardial infarction is needed, which will provide more effective methods and strong scientific basis for the prevention and treatment of myocardial infarction. For patients with terminal heart failure, the only optional treatment option is heart transplantation, but the donor source is scarce. Therefore, new clinical methods are urgently needed to effectively suppress the occurrence of post infarction heart failure and ischemic heart disease. Since Wichterle et al [1]. prepared methacrylic acid in 1960 β - Since hydroxy acetic acid, hydrogel materials have attracted scientists' interest and carried out a number of studies because of their unique properties and broad application prospects. At present, hydrogels based on natural polymers are one of the research hotspots. Especially in the field of tissue engineering, hydrogels are used as matrices (i.e. scaffolds for cell growth and carriers for growth factors) for the repair and regeneration of various tissues and organs. The research on the synthesis, physical and chemical properties of hydrogel materials and their applications in the fields of biochemistry, physics, medicine, agriculture, forestry, industry and daily necessities are very extensive. The structure and properties of various hydrogels have been studied in depth. At present, there are many therapeutic schemes for myocardial infarction based on hydrogel, and some of them have gone to clinic. This article reviews the progress of polymer hydrogel materials in the treatment of myocardial infarction, which can provide reference for the subsequent medical engineering based on hydrogel.

2. Myocardial Infarction

Myocardial infarction is a common disease in CVD, mainly caused by acute ischemic necrosis of the local myocardium due to coronary artery occlusion. If the myocardium is in a state of ischemia and hypoxia for a long time, it will cause local myocardial cell necrosis or apoptosis. The replacement of necrotic myocardial cells by fibrotic scars can lead to increased wall hardness, abnormal myocardial electrical conduction, and asynchronous cardiac contractions, ultimately leading to complications such as malignant arrhythmia, heart failure, and sudden death. At present, myocardial infarction has become a public health issue that needs to be addressed in emergency situations worldwide, and a comprehensive understanding of the pathogenesis of myocardial infarction and the development of therapeutic drugs is needed.

2.1. Pathological Process of Myocardial Infarction

After myocardial infarction, a very complex pathological process can occur. The main pathological process of myocardial infarction can be simply divided into five overlapping pathological stages: myocardial cell necrosis or apoptosis, inflammatory response, proliferation/repair phase, collagen fiber scar maturation, and ventricular remodeling [2]. Ischemia and hypoxia seriously damage the integrity of blood vessels, promoting inflammatory cell infiltration. If the myocardial ischemia lasts for a long time, a large number of cells will die due to the lack of nutrients and the destruction of oxygen free radicals, activating the apoptosis program and autophagy mechanism of the cells. Necrotizing cells release dangerous signals, such as high mobility group box 1 (HMGB1), calcium A (S100A8), and calcium B (S100A9). HMGB1, S100A8, and S100A9 activate the immune signaling pathway to induce the expression of pro-inflammatory factors such as interleukin-1 (IL-1) and monocyte chemotactic protein-1, ultimately leading to a severe inflammatory response [3]. The activated inflammatory signal promotes adhesion between white blood cells and endothelial cells, promotes the extravasation of inflammatory cells, and eliminates extracellular matrix (ECM) and necrotic cells by infiltrating inflammatory cells in the infarcted area, activating the repair pathways required for scar formation [4].

During the proliferation/repair phase, cardiac fibroblasts (CFs) proliferate and migrate, while transforming into myofibroblasts (MFBs) under the induction of transforming growth factor-1 (TGF- β 1). MFBs are stimulated by TGF- β 1, angiotensin, and aldosterone to secrete a large amount of ECM proteins (such as collagen, fibronectin, and proteoglycans) in the microenvironment of myocardial infarction areas. When a large number of MFBs in the infarcted area undergo apoptosis, the non-infarcted myocardium remodeled at the distal end will experience pressure and volume overload. May cause chronic activation of the local fibroblast population in the non-infarcted area, leading to fibrosis in the non-infarcted area, ultimately leading to ventricular dilation and compensatory cardiac force [5].

2.2. Myocardial Fibers

Myocardial fibrosis refers to the excessive accumulation of collagen fibers in ECM proteins, resulting in an increase in collagen content. This leads to ventricular remodeling, ventricular enlargement, and ultimately affects the diastolic and systolic functions of the heart. Weber divides myocardial fibrosis into reparative fibrosis and reactive fibrosis based on whether there is myocardial cell necrosis, scar formation, etc. Repair fibrosis refers to the process of early myocardial cell necrosis, ECM secretion, and scar formation, which is crucial for preventing ventricular wall rupture after myocardial infarction [6]. However, with the excessive sinking of ECM, the cross-linking of collagen in the dead zone leads to the formation of scars, resulting in different mechanical stresses between the infarcted and non-infarcted areas, leading to interstitial fibrosis and perivascular fibrosis in the infarcted boundary area and distal uninjured myocardium. This process is known as reactive fibrosis. Reactive fibrosis expands ventricular remodeling and affects myocardial electrical conduction, leading to further deterioration of cardiac systolic and diastolic function.

CFs are the main cell types of myocardial fibrosis, including monocytes/giant cells, lymphocytes, and mast cells. These cells regulate fibrosis by secreting inflammatory cytokines, angiotensin, and TGF-B1 [7]. TGF-B1 can induce the conversion of CFs into MFBs, which contain a large amount of ECM proteins and ultimately lead to myocardial fibrosis.

In addition, angiotensin II (AngII) is a soluble substance that rapidly increases in expression in the infarcted area after myocardial infarction, promoting myocardial fibrosis. The mechanism of its action is that Ang binds with receptor (AT1R) to activate downstream effector RhoA/ROCK to function, promoting the proliferation, migration, and ECM synthesis of CFs. In addition, AngII also promotes the expression of collagen in CF through TGF-B/Smads signaling [8]. In the early stage of myocardial infarction, myocardial ischemia and hypoxia can lead to the presence of a large amount of reactive oxygen species (ROS) in the infarcted area. ROS mainly promotes myocardial fibrosis through the MAPK signaling pathway, and in addition, it can also stimulate the expression of TGF-B1 to promote myocardial fibrosis.

2.3. Current Treatment Status of Myocardial Death

The treatment methods for myocardial infarction mainly adopt some routine treatments in clinical practice, such as drug thrombolysis coronary intervention (PCI) and coronary artery bypass graft surgery (CABG). However, cell therapy and factor therapy are still in the research stage..

2.3.1. Routine treatment

After acute myocardial infarction occurs, timely reperfusion is necessary to restore blood circulation. The general myocardial ischemia time is between 20 and 30 minutes, and the myocardium begins to necrosis; After 1 to 2 hours of ischemia, the vast majority of the myocardium undergoes irreversible necrosis, ultimately forming fibrotic scars. During reperfusion, for every 30 minutes of delay, the mortality rate will increase by 10%. At present, the main methods of revascularization in clinical practice include drug thrombolysis, PCI, and CABG.

Drug thrombolysis is mainly achieved by dissolving fibrin with fibrinolytic enzymes, enabling thrombus degradation and recanalization. Thrombolytic drugs, plasminogen activators, can be divided into two types: non-specific and specific. The specificity includes human recombinant alteplase and its derivatives (alteplase, tenecteplase, and reteplase), while the non-specific includes urokinase and streptokinase. These thrombolytic drugs have the advantages of simplicity, non-antigenicity, and ease of operation, making them widely used in the treatment of acute myocardial infarction. However, the time window requirements for thrombolytic therapy are strict, and the likelihood of recurrent myocardial infarction is extremely high [9].

PCI is an effective treatment for early revascularization of myocardial infarction, but patients with a postoperative myocardial infarction risk index higher than 23.05 have a long-term recurrence rate of 7.88% and a mortality rate of 4.98%. In addition, the optimal treatment time for PCI is within 2 hours, and achieving myocardial reperfusion as soon as possible can reduce patient mortality [10].

2.3.2. Cell therapy

At present, research has confirmed the potential of stem cell transplantation for the treatment of myocardial infarction. The main stem cells used for treating myocardial infarction include cortical bone stem cells (CBSCs), mesenchymal stem cells (MSCs), and human cardiac progenitor cells (CPC). Shar et al. used endocardial injection to deliver CBSCs to the dead zone of pigs and found that the collagen fiber scars in the heart were significantly reduced, and the cardiac structure and functional reserve were improved [11].

The proliferative ability of adult mammalian cardiomyocytes is limited, making it difficult for the missing myocardium to regenerate after myocardial infarction. To compensate for the missing myocardial cells, researchers induced stem cells (induced pluripotent stem cells and fetal stem cells) to differentiate into myocardial cells, and then injected them into the infarcted area to supplement the lost myocardial cells by integrating with the host myocardium. Induced pluripotent stem cells derived from monkey fibroblasts were used to differentiate into cardiac myocytes (iPSC-CMs), and then

iPSCCMs were injected into the myocardium of the infarcted monkey heart muscle (allogeneic). It was found that they can electrically combine with the resident heart muscle and improve the systolic function of the monkey heart. Due to the adverse microenvironment such as ischemia and hypoxia, epidemic rejection, and obstruction of blood circulation, the survival rate and residence rate of cells injected into the myocardium are ultimately low, which limits the cell therapy of the heart.

2.3.3. Factor therapy

In the therapeutic effect of stem cells on myocardial infarction, in addition to partially differentiated cardiomyocytes replacing necrotic cardiomyocytes, they mainly exert their effects through paracrine bioactive factors. Therefore, some researchers can achieve good therapeutic effects by using corresponding bioactive factors according to the different pathological stages of myocardial infarction. Myocardial infarction is caused by ischemia and hypoxia. Therefore, the primary issue in treating myocardial infarction is the reconstruction of blood flow in the infarcted area. When myocardial infarction is ischemic for a long time, the supply is needed. Currently, active factors that promote angiogenesis mainly include VEGF, basic fibroblast growth factor (bFGF), acidic fibroblast growth factors (aFGF), angiopoietin-1 (Ang-1), and platelet derived growth factor (PDGF). VEGF plays an important role in angiogenesis, mainly promoting the proliferation and migration of endothelial cells. Proliferation/repair, collagen scar formation, and ventricular remodeling are closely related to myocardial fibrosis during the pathological process of myocardial infarction. Therefore, inhibiting myocardial fibrosis is crucial for the treatment of myocardial infarction. The latest research shows that BMP9 is an endogenous inhibitor of myocardial fibrosis, which binds with BMP to phosphorylate its effector Smad1 and acidify Sad3, thereby weakening the fibrotic effect of TGF-B1.[12].

3. Application of Hydrogel in TheTreatment of Myocardial Infarction

Biomaterials have been widely used for the treatment of myocardial infarction due to their excellent biocompatibility. Biomaterials are mainly used as carriers for cells or factors, thereby increasing the cell residence and half-life of factors. If extracellular matrix patches loaded with mesenchymal stem cells are used for the treatment of myocardial infarction. Secondly, biomaterials can also serve as scaffolds to temporarily replace the degraded extracellular matrix, maintaining the integrity of the ventricular wall. At present, many biomaterials have been used in the treatment of myocardial infarction, mainly including gelatin, hyaluronic acid, fibrin, acellular matrix, and sea acid hydrogel. The sea acid hydrogel is widely used because of its low toxicity, non-immunogenicity, low price, simple and convenient access, preparation and preservation. At present, hydrogels are combined with other materials as carriers to carry cells, proteins, drugs or other cell growth promoting factors to promote the growth and differentiation of transplanted cells. Their application methods include drug delivery systems, injectable hydrogels, polymer microcapsules, etc.

3.1. Polymer Hydrogel

Polymer hydrogel is a new type of functional polymer with 3D network structure obtained by physical or chemical crosslinking, which has great research potential in the field of medical research. Polymer hydrogels contain a large number of hydrophilic groups, which can absorb a large amount of water to swell and maintain a large amount of water without being dissolved. The swollen hydrogel shows a porous structure, and its softness is very similar to that of biological tissues [13]. Moreover, the surface of the hydrogel is not easy to adhere to proteins or cells. It shows good biocompatibility when contacting with biological tissues. A large number of experiments show that polymer hydrogels do not affect the normal physiological metabolism of organisms, and they are biodegradable. Polymer hydrogels have certain mechanical properties due to their three-dimensional network structure. The polymer chain contains a large number of active groups, which provides a basis for gel modification or combination with drugs. Therefore, hydrogels are widely used in drug delivery, tissue engineering scaffolds, wound dressings and other medical fields.

There are several ways to classify hydrogels: (1) According to the network crosslinking mode and structure of hydrogels, they can be divided into physical gel and chemical gel; (2) According to the size of hydrogel, it can be divided into micro gel and macro gel; (3) According to the response of hydrogels to external stimuli, they can be divided into traditional hydrogels and environmentally sensitive hydrogels; (4) According to the source of hydrogel, it can be divided into natural gel and synthetic gel. Natural gel is mainly collagen, fibrin, gelatin, etc., while synthetic gel are mainly polyacrylic acid, polyacrylate, polyethylene oxide, etc; (5) According to the shape of hydrogel, it can be divided into columnar, porous sponge, fibrous, membrane and spherical; (6) According to whether the hydrogel is degradable, it can be divided into degradable hydrogel and non-degradable hydrogel. Most hydrogels are non-degradable, and only a small part of hydrogels such as chitosan and alginate are degradable.

3.2. Drug Delivery System

The drug delivery system is designed as a scaffold structure that carries transplanted cells to increase the local retention rate of transplanted cells or a delivery system for growth factors and drugs. In addition to carrying cells, tissue engineering can be used to arrange cells in a certain spatial order, forming a cell layer structure, which can more accurately act on the lesion area, improve cell retention and survival rates, avoid excessive loss of transplanted cells, improve treatment effectiveness, and reduce treatment risks. In addition, local delivery of proteins, growth factors, and drugs can be achieved. The ideal heart patch should have good biocompatibility and suitable adhesion; Tight intercellular connections enable stem cells to have good proliferation, differentiation, and paracrine abilities; Having a certain extracellular matrix microenvironment; Having a multi-layer structure; Homogeneous arrangement of cells; The mechanical strength and thickness meet the transplantation requirements, and the survival rate of transplanted seed cells in vivo is high [14].

Rodness et al. combined with soluble vascular endothelial growth factor (VEGF) to make microspheres, which can prolong its release, and the myocardial patch can restrain the mechanical force of the heart and prevent the remodeling and expansion related to the ventricle. They made a compact VEGF calcium alginate microspheres chitosan hydrogel patch to deliver VEGF to the damaged myocardium of rats. The results showed that the patch had good in vivo degradation, and magnetic resonance imaging evaluation showed that the heart function of the patch containing VEGF microspheres group was better than that of the single chitosan patch group after implantation in vivo, indicating that the patch containing VEGF had a higher effect on repairing post infarction lesions than the patch alone. [15]

Alginate hydrogels are widely used in the biomedical field due to their good biocompatibility, non-thrombotic properties, low cell toxicity, mild physical gel process and the structural hardness of their hydrogel matrix similar to that of ECM. It can be used as an implant to support the heart in patients with acute myocardial infarction and as a carrier for delivering stem cells and cytokines.

3.3. Injectable hydrogel

Hydrogels are three-dimensional networks of polymers that can release encapsulated drugs, cells, growth factors and other bioactive substances through the combination of swelling, diffusion and dissolution. This process is related to the characteristics of gel, such as the cross-linking density of gel, drug gel interaction, etc. For intelligent hydrogel, it can also change from liquid phase to solid phase according to the ambient temperature, pH value, current and other conditions. Inject the hydrogel solution with bioactive substances or stem cells into the MI area to improve the microenvironment of the lesion, replace the extracellular matrix to fill the defect of the lesion, and help repair the myocardium. Gel materials can be used in vivo and in vitro for in situ tissue regeneration, in vitro for simulating the microenvironment of myocardial tissue to investigate the physiological and biochemical behavior of stem cells, and to build a substitute tissue for myocardial tissue [16]. The research shows that the gel used in myocardial tissue engineering can improve the cell retention rate and survival rate after it carries cells into the animal heart model.

Li et al. obtained temperature sensitive chlorinated chitosan glutathione complex hydrogel through cooling reaction, which can effectively eliminate reactive oxygen species (ROS), radicals and DPPH free radicals in vitro, and has good biocompatibility. It can improve the peroxidation microenvironment in the infarct focus, support the adhesion and survival of myocardial cells, eliminate excessive ROS in the cells, and reduce oxidative stress injury and apoptosis of cells under the condition of high concentration of ROS [17].

3.4. Polymer microcapsules

Microcapsules are semi permeable shells composed of hydrogel matrix, so they also have biocompatibility, biodegradability and adjustable mechanical properties. Although the cells are isolated from the outside world after being encapsulated by microcapsules, due to the porous structure and high hydrophilicity of the hydrogel, the transport of cells and extracellular nutrients and the exchange of metabolites, physical, chemical and biological modifications, and the recombination with extracellular matrix proteins, skin and growth factors can enable cells to proliferate, migrate and differentiate in the matrix; At the same time, it can also prevent the entry of extracellular macromolecules or immune cells, preventing cells from being attacked by the immune system. However, microcapsules also have problems such as difficulty in in-situ localization and uncertain long-term survival ability. At present, the materials used for microcapsule preparation mainly include PLGA, sodium alginate, fibrinogen, and chitosan.

Blocki et al. solved the problem of poor retention of myocardial cells injected into the myocardium by loading mesenchymal stem cells into microcapsules and injecting them into the inner wall of the infarcted heart. The microcapsule system is composed of low concentration agarose, ECM protein, collagen, and fibrin, and dextran sulfate is added to mimic the aminoglycan in ECM to ensure cell survival. Research has found that microcapsule materials can slowly degrade in the body. The results of in vivo magnetic resonance imaging with cell labeling showed that the residence time of the cell loaded microcapsules injected into the myocardial infarction area of rats was significantly longer than that of the cell suspension group [18]

4. Summary

In conclusion, polymer hydrogels, with their excellent performance and characteristics, have made a lot of research progress in the specific treatment and application of myocardial infarction, which is worthy of further exploration by researchers. At the same time, the mechanical strength of polymer hydrogels is poor, the water absorption rate and swelling rate are low, the biocompatibility needs to be improved, and the sensitivity and response time of sensitive hydrogels have room for improvement. Although the current hydrogel preparation technology still focuses on improving the performance defects such as water absorption, mechanical strength and biocompatibility, the future polymer hydrogel should have both excellent performance and sensitive response ability, making it an excellent material that can be applied in different fields.

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