Original Article

# Cardiac Patch Of Myocardial Infraction: A Review

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## Abstract

One of the most prevalent cardiovascular diseases, myocardial infarction (MI) is a life-threatening condition caused by damage to the myocardium caused by a blockage in one or more of the coronary arteries. Researchers are eager to discover novel strategies for delaying the progression of myocardial injury in order to repair the damaged myocardium in MI. Cardiac patches, which are scaffolds that are layered on top of the heart, have been shown to have a significant curative effect in the treatment of MI. They have the ability to deliver a variety of bioactive cells or factors, enhance cardiac function, and provide mechanical support for the site of an infarction. For use in cardiac patches, biomaterials with certain mechanical and biocompatibility properties have received a lot of attention. This review focuses on recent developments in these biomaterial-based cardiac patches, which can be divided into two categories based on the materials they are made of: (i) natural materials and (ii) synthetic materials. Each type's major benefits and current difficulties are discussed, as is a brief overview of potential research directions.

**Key Words:** Cardiac Patch, Mayocardial Infraction(MI), Scafflod Fabricating, Material, Gelatin

## INTRODUCTION:

A group of conditions known as cardiovascular diseases (CVDs) affect the pathological growth of the heart and blood vessels.Cardiometabolic, behavioral, environmental, and social risk factors account for the majority of their causes [1].The term "cardiovascular diseases," which encompasses conditions of the heart and blood vessels, has emerged as a serious threat to human health [2] and is anticipated to cause up to 20 million deaths worldwide by 2030[3].One of the most common cardiovascular diseases, myocardial infarction (MI) is brought on by a blockage in one or more coronary arteries. This prevents oxygen and nutrients from reaching the myocardium, kills cardiomyocytes (CMs), makes it difficult for the heart to contract simultaneously, and ultimately causes sudden death or life-threatening heart failure [4].In China, the MI mortality rate increased by 42.23–62.72 percent between 2002 and 2016 [5].CVDs are currently the leading cause of death worldwide, causing one-third of all deaths in 2019 and significantly increasing healthcare and disability costs[1,6].According to the World Health Statistics 2020 report, the death rate from cardiovascular diseases topped all noncommunicable diseases in 2016 (43.66% vs. 21.95%)[7].Therefore, the development of cardiovascular treatment methods is urgently required to maximize therapeutic efficacy and reduce adverse effects.Current myocardial infarction (MI) treatment strategies, which include reducing the initial insult and preventing downstream maladaptive pathways, significantly reduce cardiovascular morbidity and mortality.Arrhythmias and heart failure continue to be common outcomes of the remodelling process following acute MI, increasing cardiovascular morbidity and mortality[8].

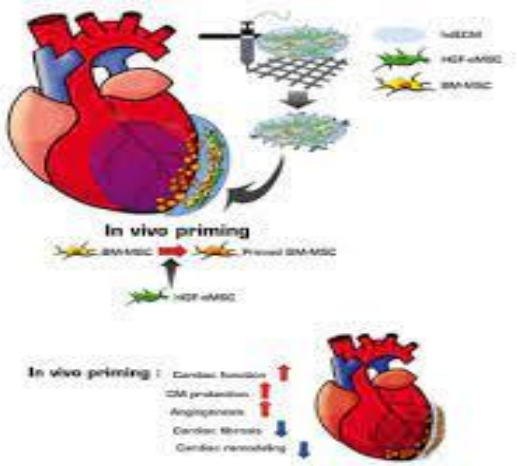


**Figure 1 :** Cardiac Infraction

## ARCHIVE:

About 635,000 Americans suffer a new coronary heart attack each year. A new coronary heart attack is the first myocardial infarction (MI) that necessitates hospitalization or leads to death from coronary heart disease. Another 155,000 individuals have silent MIs, and another 300,000 individuals experience recurrent attacks[9]. 36% of MI survivors will face an increased risk of developing heart failure in the future[10,11].To reduce the size of an existing heart scar, there is currently no approved treatment [12].Stem cell therapy is intended to enhance the treatment options available to MI survivors. It aims to reduce the size of the scar, re-establish viable myocardium, and halt detrimental cardiac remodelling[13].

## DNA QUANTIFICATION OF MYOECM :

Before and after decellularization, samples of heart tissue (10 mg) were digested overnight at 60°C with papain (0.2 mg/ml;Sigma-Aldrich).Following the manufacturer's instructions, the Quant-IT Picogreen dsDNA Assay (Thermo Fisher Scientific, Waltham, MA) was used to check the DNA content of the samples. Using a fluorescence spectrometer, samples (100 l) were read at 538 nm with an excitation at 485 nm. Samples contained 418.8  27.33 ng of DNA per mg of tissue (n = 8) prior to decellularization, and samples contained 17.66  3.869 ng of DNA per mg of tissue (n = 8) after decellularization [48].

## CELL-BASED PATCHES:

Cardiomyocytes (CMs) are terminally differentiated cells that have limited ability to recover heart function after cardiovascular diseases[23,24]. Cells from many different sources have been studied to both replace lost cardiomyocytes in the native heart and to stimulate cardioprotective events via paracrine signaling after their implantation in order to repair or restore the myocardium[25]. Both of these strategies are necessary for repairing or restoring the myocardium. Angiogenesis, activation of endogenous progenitor cells, decreased cardiomyocyte apoptosis, and reduction of fibrosis are just a few of the regeneration processes that can be sparked by the transplanted cells, which also provide cells that aid in tissue repair [25].Skeletal myoblasts (SMs), mesenchymal stem cells (MSCs), and human induced pluripotent stem cells (hiPSCs) have been extensively used in cardiac patch fabrication to treat MI at preclinical and clinical studies[48] in light of the availability of cell sources, the technical possibility of isolating and differentiating cells, and ethical considerations.

## SCAFFLOD FABRICATING:

The synthetic cardiac patch's scaffold is designed to resemble natural ECM.A structure that is permeable and enables efficient transfer of nutrients and waste, mechanical support for tissue replacement and regeneration, and a setting that encourages cell migration, integration, proliferation, and differentiation in order to produce the desired therapeutic effect can all be included in the scaffold [49].Chemical compositions, physio-mechanical properties like stiffness, and 3D geometry of the scaffold control how cells interact with their environment and how much medication is released[50].Natural, synthetic, or composite materials based on biology can be used to make scaffolds. Natural materials like alginate, collagen, and fibrin are examples of substances that stimulate biological activity but require laborious purification and repeatability procedures. On the other hand, although synthetic materials like PU and PLGA are typically simple to synthesize, stable in structure, readily available from a variety of sources, and inexpensive to prepare, they require functionalized modifications in order to adhere to native or transplanted cells or provide the desired biological signal [51]. Even though they came from different places, these two kinds of materials are compatible and can be used for a lot in heart regeneration. As shown in Table 1, extremely effective and intricate cardiac patches made of interwoven fibers have been manufactured using a variety of designs and procedures, despite the lack of a universal or ideal method[52,53] .

**Table 1.** Common Techniques For Engineering Cardiac Patches

| Techniques | Advantages | Disadvantages |
|---|---|---|
| Decellularized extracellular matrix | Matain ECM composition and its organization | Residual cellular debris causes immune rejection |
| Electrospinning | Highly versatile; minic the anisotropy and nano-micron scale fibrous topography of myocardium | Lack biological complexity of the native cardiac ECM |
| 3D bioprinting | Precise control of the geometry; creation of complex porous networks that permit efficient nutrient delivery | Limited bioinks |
| Hydrogels | Easy to be fabricated and delivered | Lack biological complexity of the native cardiac ECM; low mechanical properties |
| Scaffold free cell sheets | Maximize cell numbers and survival; better integrity with the host; without suturing | High cost; cell sourcing selection; long culture time; difficulty in storage and transportion of cell sheets |

## MATERIALS REQUIRED FOR THE FORMULATION OF CARDIAC PATCHES:

### *Synthetic Materials*

Synthetic materials with stable physical and mechanical properties have demonstrated the potential to meet clinical requirements by taking advantage of reproducible synthesis processes [26].Polymers like poly(vinyl alcohol) (PVA),

poly(lacticco-glycolic) acid (PLGA), poly-(L-lactic) acid (PLLA), and polyurethanes (PU) have been extensively studied for tissue engineering [27]. A synthetic polymer patch with strong mechanical properties can be used to create a linker between cells and the host myocardium [28].In cardiac stem cell therapy, the difficulty of efficiently delivering secreted factors to the MI region remains. This possibility exists with the microneedle patch for drug delivery. Using biocompatible PVA, a cardiac stromal cell-encapsulated microneedle patch (MN-CSCs) was recently made using a micromolding technique [29]. Microneedles allowed cells to pass through the host myocardium and produce more paracrine substances to restore heart function. Due to their high mechanical strength, acellular epicardial patches exhibit excellent therapeutic efficacy in aiding in the reconstruction of damaged cardiac tissues. A viscoelastic adhesive patch was able to reverse LV remodelling in models of acute and subacute MI in rats[30].This patch was made from transparent hydrogel that has a low dynamic modulus and is crosslinked ions. Using finite-element simulations at the "gel point," which contributes to the harmony between fluid and solid properties, this acellular epicardial patch was created. Synthetic cardiac patches are superior to natural ones for therapeutic purposes due to their lack of biomolecules or cells, long-term preservation, consistent quality, and ease of manufacture.

### *Natural Materials*

Collagen, fibrin, alginate, hyaluronic acid, gelatin, and decellularized extracellular matrix (ECM) are examples of natural substances that are more biocompatible than synthetic ones[31].These materials still possess the structure necessary to replicate the original cellular milieu, regardless of whether they originate from in vivo sources or are found naturally. Particularly, biologically produced materials enable enhanced therapeutic function by providing treatments with additional protection against immune inflammation [32].Collagen is the natural substance that is used to make cardiac patches the most frequently and is mostly found in cardiac ECM. Due to its low antigenicity and chemotactic properties, collagen can mimic the environment of a tissue for cells[33].Electrospinning, which requires electricity to charge, is the most recent method for creating collagen patches. Electrospun nanofibrous collagen scaffolds can be seeded with a variety of cells, including iPSCs and MSCs[34].Due to paracrine signaling and force transmission (DCM), collagen scaffold patches show potential therapeutic efficacy in treating both MI and dilated cardiomyopathy. The production of cardiac patches made of conductive collagen has developed into a trend. With the addition of conductive components like carbon nanotubes, metal nanoparticles, and graphene oxide, online monitoring of tissue statures can be accomplished [35].In addition, natural substances derived from other in vivo sources, such as alginate, fibrin, and HA, demonstrate therapeutic potential for upcoming clinical trials.

**Table 2 :** Summary Of Natural Materials Used For Cardiac Patches

| Material | Delivered cell or bioactive factor | Biological results |
|---|---|---|
| Protines collagen | N.A.<br>CMs<br>MSCs<br><br>ADSCs<br>VEGF | Fibrosis↓, myocardial remodeling ↓, angiogenesis↑, contractility↑<br>Vascular density↑, infraction size↓, LV dilation↓. Wall thickness↑, heart function↑<br>Angiogenesis↑, wall thickness↑, myocardial remodeling↓, perfusion↑, contractility↑<br>Fibrosis↓, vascular density↑, LV function↑<br>Vascular density↑, LV function↑ |
| Fibrin | N.A.<br>CMs<br><br>HiPSC-cardiac cells (CMs,ECs, SMCs)<br>hESC -vascular cells (ECs, SMCs)<br>MSCs<br><br>HUVECs<br><br>ATDPCs<br>IGF-1<br><br>CSCs and ECs | Myocardial remodeling↓, heart failure↑<br>Infraction size↓, wall thinning↓, myocardial remodeling↓, heart failure↑<br>Apoptosis↓, vascular density↑, infarction size↓, wall stress↓, cardiac function↑<br>Angiogenesis↑, apoptosis↓, perfusion↑, cardiac function↑<br>Apoptosis↓, infraction size↓, angiogenesis↓, wall thickness↑, cardiac function↑<br>Cardiomyocyte proliferation↑, neovascularization↑<br>Angiogenesis↑, morphology↑, cardiac function↑<br>Myocardial metabolism↑, arteriole density↑, infraction size↓, wall stress↓, apoptosis↓, LV function↑<br>Cardiomyocyte mitosis↑, angiogenesis↑, inflammation↓, apoptosis↓, cardiac function↑ |
| Gelatin | bFGF<br>CMs | Microvascular density↑, LV function↑,<br>Myocardial remodeling↓, wall thickness↑, cardiac output↑, blood vessel density↑, fibrosis↓, LV function↑ |
| Polysaccharides<br>Alginate | <br>CMs<br>HESCs and hEBs HMSCs | LV dilation↓, HF progression↓, heart function↑<br>Scar thinning↓, LV dysfunction↓<br>Infraction size↓, microvascular density↑, EF↑ |
| Chitosan/ Calcium silicate | CMs | Infraction size↓, angiogenesis↓, cardiac function↑ |
| Hyaluronic acid | ADSCs | EF↑, LV function↑ |
| Cellulose | AD-MSCs | Fibrosis↓, myocardial remodeling↓, angiogenesis↑, apoptosis↓ |
| Decellularized tissues | N.A.<br><br>ASCs<br>MSCs<br><br>Mesenchymal stromal cells<br>CSC- secreted factor Bfgf | Wall thickness↑, angiogenesis↑, heart function↑<br>Vascular formulation↑<br>Inflammation↓, apoptosis↓, cell proliferation↑<br>Angiogenesis↑, myocardial protection↑, wall thickness↑, heart function↑<br>LV dilation↓, heart function↑<br>Angiogenesis↑, heart function↑<br>Myocardial remodeling↓, contractility↑ |

## CARDIAC PATCH CLINICAL TRIALS:

In these tests, cells were injected without any support material. However, biomaterials, both with and without cells, have been used in other clinical trials previously. Chachques et al. carried out the MAGNUM trial, which was the first such clinical study. and treated infarct patients with a patch made of BMMNCs seeded onto a collagen I matrix. In particular,

250-28 million BMMNCs were injected into a number of infarcted heart sites, and a patch of the same number of BMMNCs and a collagen I matrix was sutured onto the epicardium on top of the scarred area. According to Chachques et al., the patch therapy improved LV filling, increased scar thickness, and ejection fraction.2007).Later on, the same group compared their injection/patch method to BMMNC injection alone, and they found that the injection/patch group significantly improved ventricular filling when compared to cell injection alone (Chachques et al.).2008).Cor-Matrix®, a cell-free, porcine SIS-derived ECM, was used in the subsequent cardiac patch clinical study. Cor-Matrix® was used to repair cardiac and vessel defects in 37 congenital heart patients in the initial human studies (Scholl et al.2010).In 11 patients, it was then demonstrated to be a clinically viable option for repairing LV complications following MI (Yanagawa et al.).2013).Cor-Matrix® has also been tested as an epicardial patch in rat and pig models of MI, and it has been found to speed up myocardial recovery from MI (Mewhort et al.).2014;Mewhort and co2016).The Cor-Matrix® epicardial patch was also used in a clinical trial on eight MI patients undergoing coronary artery bypass grafting (Fedak 2017), but the results have not been made public. In the AUGMENT-HF trial, Algisyl, an injectable calcium alginate hydrogel, was administered to patients with advanced heart failure as an additional acellular therapy. During the left anterior limited thoracotomy, 12 to 15 injections of algisyl were given to the LV wall. The 6-minute walk test distance and VO2 showed statistical improvement at 12-month follow-up (Anker et al.).2015;Mann and co.2016).Finally, patients with ST-segment elevation MI were treated with the bioabsorbable scaffold known as IK-5001 in the PRESERVATION clinical trial. According to Frey et al., a pilot study involving 27 patients demonstrated that the IK-5001 could be used safely and effectively in patients with ST-segment elevation MI. At the six-month follow-up, there were no IK-5001-related adverse events.2014).Later, a larger study with 201 similar patients was conducted, but the results showed that IK-5001 implantation did not reduce LV remodeling or improve LV function at six months follow-up (Rao et al.).2016).These clinical studies demonstrate the potential for promising preclinical work to be effectively translated into clinical settings and demonstrate the viability of using tissue-engineered constructs to improve cardiac function in failing hearts [48].

## CLINICAL APPLICTIONS OF CARDIAC PATCHES:

Clinical applications of cell therapy for heart repair are subject to numerous restrictions [13-15].First, cells must be carefully maintained prior to transplantation to maintain viability and functionality[13]. As a result, living cells cannot be considered a generic therapeutic product. Cell treatment is costly in terms of labour and material expenses. Because the mechanisms of action of cell therapy products are still unknown, it is difficult to define product release criteria .These issues are made even more difficult by the fact that some undifferentiated cells may undergo uncontrolled cell growth after transplantation or turn into tumors [14,15]. Immunogenicity is another issue when using allogeneic cells. Although autologous cell transplantation offers a number of advantages [16], the process of producing these cells is time- and cost-intensive due to the fact that each patient's cells are a distinct batch [14].Additionally, cell death is not the primary cause of such a rapid loss of cells following transplantation [19], but rather the active heart's "washing away" of the cells from the delivery point[20,21]. Cell retention and engraftment are extremely low regardless of the administration method [17,18]For the purpose of myocardial regeneration, a variety of scaffold materials infused with stem cells have recently been developed.

## CHALLENGES AND FURTHER DIRECTION:

Even though pre-clinical heart repair experiments have shown that cardiac patches work well, there are still problems before they can be used in the real world [36]. The improved delivery efficiency of cardiac patches is advantageous to therapeutic integrations, but the majority of cardiac patches must be implanted through open-chest surgery. Everyone is aware that patients with MI may not recover from damage and inflammation caused by surgery, which causes patients who are experiencing psychological distress to panic[37].Therefore, it is essential to apply cardiac patches using minimally invasive techniques. A strong back support should be provided by new fabrication technologies and materials in addition to the implantation method. More expensive technologies like 3D printing and photoetching are strongly recommended for patch fabrication [38]. The next generation of cardiac patch biomaterials would have stronger mechanical properties and shape memory. Despite being verified in animal models [39], the biocompatibility of existing cardiac patches is still significantly below satisfactory and unable to meet the clinical requirement. The ability of patches to integrate with the myocardium of the host makes it possible, on the one hand, to increase cardio-myogenesis and angiogenesis at the wounded heart. Tissue adhesion following cardiac patch transplantation, on the other hand, frequently occurs and has serious side effects that must be addressed[40].It is an immune reaction given that patches still contain foreign materials. This would be the most important issue to address prior to the actual use of cardiac patches. Tissue adhesion has been found to be significantly reduced by surface modification[41], which may be suitable for polymer cardiac patches. Biodegradation must also be taken into consideration in order to prevent immunological rejection from persisting after treatment[42].This kind of improvement necessitates the use of biodegradable materials and has little effect on the duration of the therapy.

## CARDIAC CELL-INTEGRATED MN PATCHES:

Stem cell therapy has gained popularity as a treatment for now-curable diseases over the past two decades. Stem cell-secreted regenerative factors are used to encourage endogenous repair of damaged myocardium as one such treatment [43]. Stem cells are typically delivered via epicardial patches, intravascular infusion, or muscle injection. The injected methods are only capable of poor cell retention because the majority of injected cells do not function [44,45].Tang and co. introduced an inventive "MN cardiac patch" that, in order to improve the integration of the epicardial patches with the host myocardium, combined a fibrin gel encapsulated with cardiac cells on the base with a biocompatible polymeric

(poly(vinyl alcohol)) MN patch with a conical shape.Fig.2a and b)[46].This patch's porous structure may serve as a conduit for communication between the transplanted cardiac stromal cells (CSCs) and the host myocardium, in contrast to conventional cardiac patches (Fig.2c).This MN-CSC patch may improve cardiac function and demonstrate necessary biosafety in both rat and porcine models when applied to the myocardial infraction location following ligation of the left anterior descending artery. The MN cardiac patch-treated rats in the rat model had healthier tissues and fewer tissues with fibrosis than the untreated rats. from the Based on the clinical study, we discovered that the cardiac patch has a significant and sufficient effect. Additionally, we discovered that patients are willing to use the patch because it does not cause inflammation. Heart patch operations seem to be more popular with doctors in other countries. It performs better than the drug. Additionally, this patch has no adverse effects on the heart. and eosin staining, also known as H&E), and improved heart performance from the left ventricular ejection fractions, also known as LVEFs, three weeks later (Fig.2d and e).

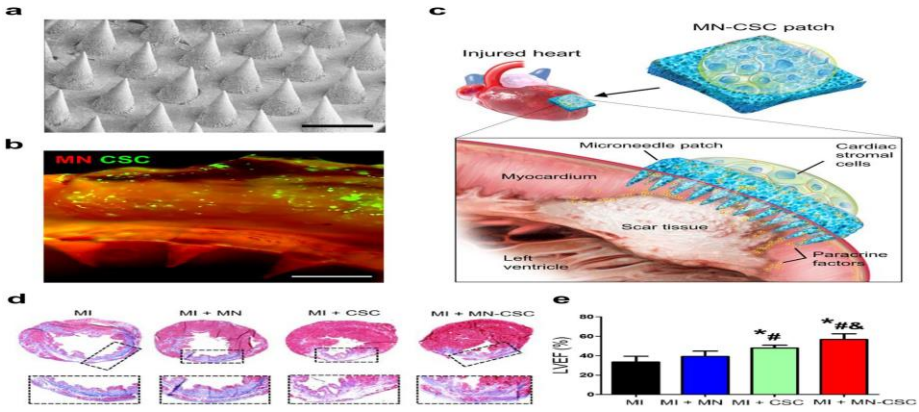


**Figure 2:** Miocroneedle Therapy

## CONCLUSION:

Based on the clinical study, we discovered that the cardiac patch has a significant and sufficient effect. Additionally, we discovered that patients are willing to use the patch because it does not cause inflammation. Heart patch operations seem to be more popular with doctors in other countries. It performs better than the drug. Additionally, this patch has no adverse effects on the heart.

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