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Review Article

Biomaterials in Regenerative Therapy for Cardiovascular Diseases: A Review

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Abstract

Loss of cardiac function is caused by the physical damage that a cardiovascular disease inflicts on the heart. While medications can help reduce symptoms, treating the underlying cause of an injury by repairing damaged tissues will benefit patients more in the long run. Cardiovascular surgeons use various techniques, in addition to heart transplants, to repair damaged heart tissue, including the ventricular septal wall and valves. Damaged cardiac tissues are replaced and repaired using a wide range of biomaterials. The two primary types of biomaterials are natural and synthetic. Metals and polymers are among other examples of synthetic materials used in cardiovascular applications. Natural materials come from biological sources, including tissues taken from animals or donated by humans. To maximize the prospects and reduce the negative aspects of both synthetic and natural materials, a new class of composite materials has emerged. These materials give a variety of new and better options for a permanent or a more persistent cure of cardiac diseases. The present and future uses of biomaterials in cardiovascular therapy are reviewed in this article. This study is done to further elaborate and highlight the uses of different materials in regenerative therapy. Its main objective is to focus on commonly used biomaterials and to compare them in different parameters. Regenerative therapy is the future of modern medicine and many new methods are being studied on daily for advancement in regenerative therapy. This study focuses on different cardiac diseases and how different materials as a medium of regenerative therapy improve these conditions.

Keywords: Biomaterials, cardiac repair, regeneration, stem cells, tissue reconstruction.

1. Introduction

In the current world, various forms of cardiovascular diseases such as hypertension, stroke, heart failure, and arrhythmias— along with other diseases —critically impact a person's life and overall well-being. It is becoming a global challenge to overcome these diseases (Li 2023). In 2021 the approximate number of patients suffering from cardiovascular diseases globally was 20.5 million and the predicted cardiovascular death rate of any given year over the ensuing hundred years in any country was estimated to be about 1.05% (Oleg Gaidai 2023b). Symptoms of cardiovascular diseases vary from patient to patient (Corrine Y. Jurgens 2022) and can be caused by various factors such as smoking, diet, unhealthy lifestyle, obesity, and diabetes. (Dahlöf 2010, R. Nangia 2016). Coronary artery disease most commonly arises as a result of cholesterol buildup in the coronary artery or due to damage of the arterial lining causing a decrease in blood supply to the heart (Peter Libby 2005, Valentin Fuster 1992). Hypertension is persistently alleviated blood pressure often caused by the

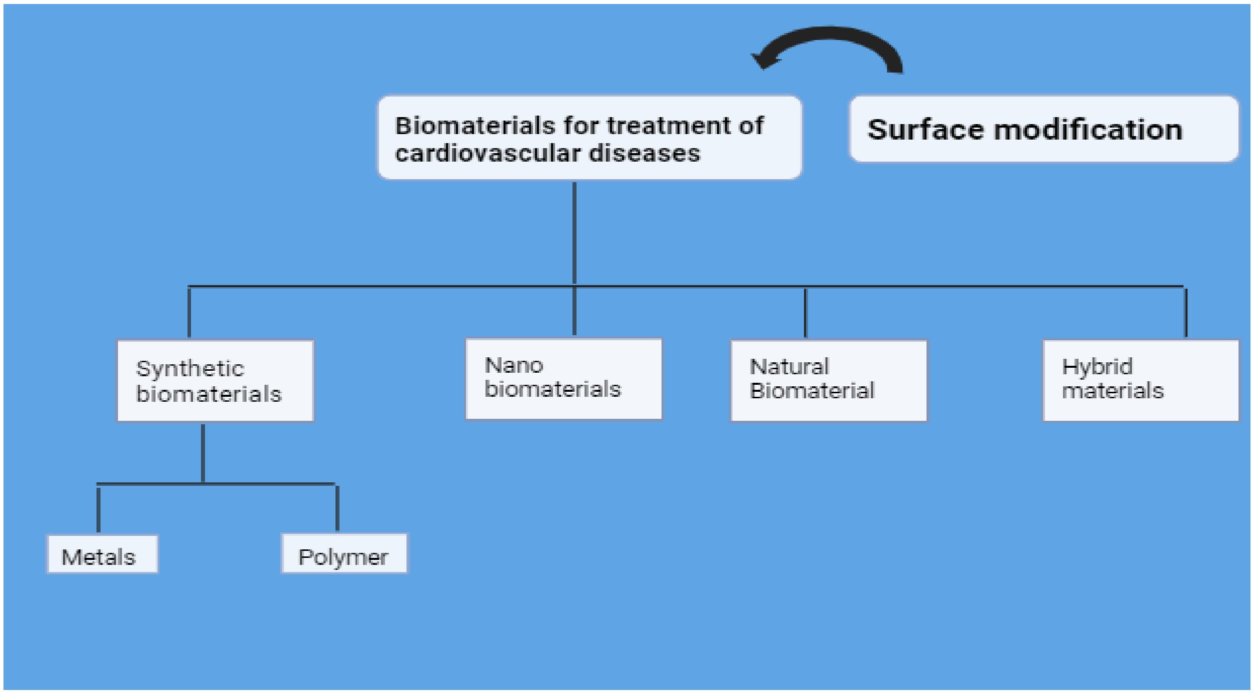

Figure 1. Biomaterials used for the treatment of cardiovascular diseases.

narrowing of blood vessels or due to any defect in the blood pressure regulation mechanism (Jan A. Staessen 2003, Franz H. Messerli 2007). Stroke is commonly caused by blood-circulation blockage due to a blood clot (Feske 2021) or rupture of a blood vessel (Arturo Montaño 2021, Eric E. Smith 2005); furthermore, they are among major reasons for incapacity and demise (Mendis 2013, Charles Ellis 2010). A number of cardiovascular conditions can result in heart failure, which further exacerbates cardiovascular disease burdens. Besides peripheral artery disease, arrhythmias, and other cardiovascular diseases contribute to this global health problem. Not only do cardiovascular diseases manifest in various forms, but they are also difficult to treat due to their sudden onset and chronic nature. In order to cure and cope with the difficulties of cardiovascular diseases engineers have innovated many biomaterials that are used as regenerative therapy(Yunbing Wang 2022). Hence an elaborate study is done in this review article that gives information and detail about the use of different biomaterials in cardiovascular disorders. For heart valves and stents, biomaterials based on metals, including alloys based on titanium and cobalt-chromium, provide mechanical support and resistance from corrosion (K. Sangeetha 2018, Muhammad Asad 2023). Benefits of biomaterials made up of polymers include enhanced biocompatibility (Adrian JT. Teo 2016, Daniel Salthouse 2023), regeneration of tissue (B.L. Seal 2001), and replication of the cardiovascular system's extracellular matrix (ECM) (Joseph M. Aamodt 2016). Bioprosthetic valves and allografts are biocompatible natural materials(Christine E. Schmidt 2000, Diana Elena Ciolacu 2022a), whereas biomimetic and physical surface modifications increase performance and biocompatibility, decreasing thrombosis, inflammation, and improving endothelialization (Megan Douglass 2022, Amisha S. Raikar 2023). In terms of biomedical devices, new developments such as biodegradable stents provide short-term support for weakened or constricted blood vessels, hence lowering the risks of serious cardiovascular events (Tingzhang Hu 2018). Additionally, metal stents—like those made of zinc (Yi Qian 2020)—can replenish necessary metal elements in a patient while offering (David Hernández-Escobar 2019). A review of advancements in biomaterials recently is given in Figure 1.

2. Different Biomaterials Used as Therapy in Cardiovascular Diseases

Different types of materials are used along with different mechanisms in order to regenerate cells of the heart or to improve the current state of any cardiac disease. These biomaterials are usually mixed with the stem cells grown outside the body and then injected into the heart with other biomaterials as shown in Figure 2.

3. Natural Biomaterials Used for Cardiovascular Diseases

In the area of cardiovascular tissue regeneration and repair, natural biomaterials have shown great promise (Andrea S. Theus 2019). Natural biomaterials have intrinsic biocompatibility and functional characteristics, similar to those of the native ECM of the heart, and vascular tissues. They are derived from biological sources as opposed to synthetic ones (Qasim A. Majid 2020). Biological materials can be designed to have specific functionality (Xu Xue 2021b). To maintain the matrix and limit its breakdown, penta-galloyl glucose is applied, after porcine-derived ECM is used to create tissue-engineered mitral valve scaffolds (Tahera Ansari 2020). These scaffolds appear to be a viable alternative for mitral valve replacement due to their enhanced mechanical qualities and longevity. Some natural materials are written below.

3.1. Bioprosthetic Valves

The critically damaged heart valves must be replaced. Metal mechanical valves or bioprosthetic valves derived from animal or human donors are typically utilized. Blood clots can occur from blood's propensity to stick to the metal in mechanical valves. As a result, those who have mechanical valves will always need to take anticoagulant drugs (Eikelboom JW 2012). One benefit of natural tissue valves over mechanical valves is that they rule out anticoagulants. Tissues from cows or pigs are commonly used as sources for biological valves (McGregor CG 2011). Porcine valves normally survive 8–15 years, while bovine valves typically last 15–20 years. The primary cause of variations in commercial valves is the variance in the standards provided by manufacturers, which encompass several aspects like hemodynamics, implantation technique, and saturability. Patients who have mechanical valves implanted must continuously take an anticoagulant medicine (e.g., Coumadin®; Bristol-Myers Squibb), even though mechanical valves composed of titanium or carbon are stronger and survive longer than biological valves (usually up to 25 years). The lifespan of a replacement valve is significantly influenced by age. Due to their increased activity and metabolism, children and younger patients use up replacement valves more quickly than older patient (Weber A 2012). Patients who are older than 65 or 70 usually have bioprosthetic valves, whereas younger patients usually get mechanical valves. Patients in their middle years may choose any kind of valve, but research suggests that bioprosthetic valves are a better option for them, since they are more likely to endure the rest of their lives without the need for anticoagulant drugs (Chikwe J 2010).

3.2. Pericardium

The fibroserous sac that envelops the mammalian heart is called the pericardium. It has been utilized for a very long time in cardiac repair for pericardial closure, valve repair, and reconstruction (Inoue H 2009). The most prevalent sources of xenogeneic pericardium are pigs, cows, and less frequently, horses. Large patches of tissue from various sources are available for specific configurations with numerous cardiovascular applications. Its elastic qualities enable it to adapt to intricate anatomy. Collagen fibers make up the majority of its composition. Pericardial tissue exhibits consistent suture retention and excellent

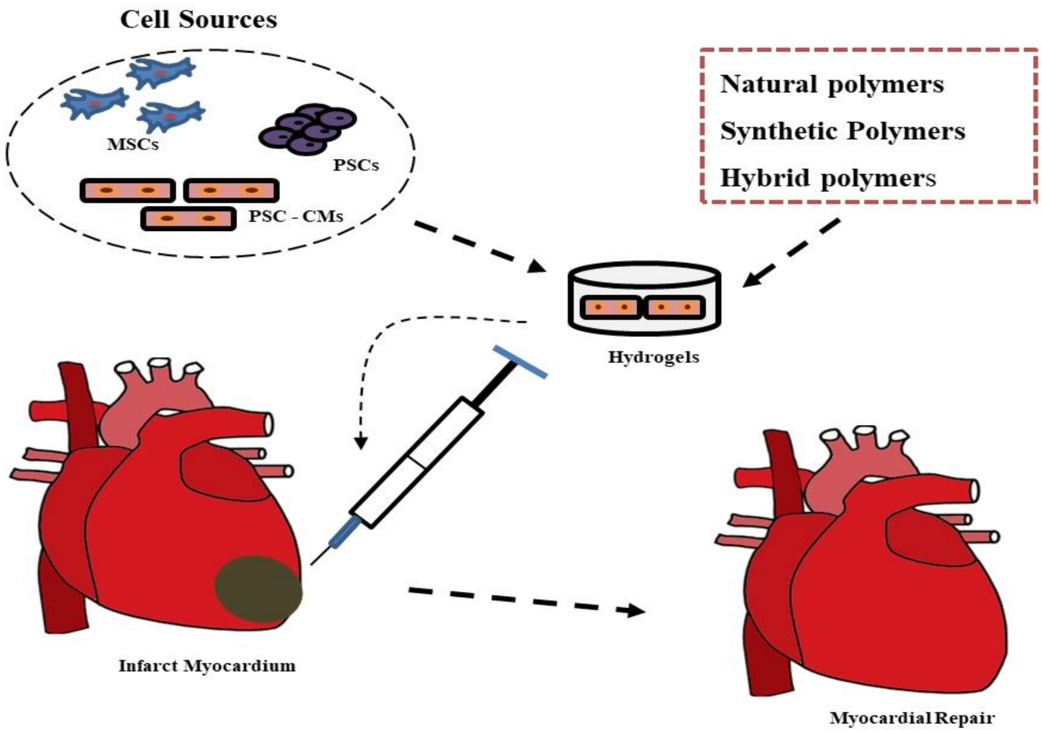

Figure. 2. Common method of using biomaterials as regenerative therapy.

handling properties. Furthermore, it is naturally resistant to infection and non-thrombogenic (ASM 2009).

3.3. Vascular Tissue Engineering *in situ* Driven by Biomaterials

Recent years have seen tremendous progress in the field of cardiovascular tissue engineering, with an increasing emphasis on *in situ* regenerative techniques. *In vitro* culture and conditioning phases are more laborious and tediously protracted in traditional tissue engineering procedures. In order to develop viable substitutes for injured or diseased cardiovascular tissues, like blood arteries, and heart valves robust techniques are needed (Chrysanthi-Maria Moysidou 2021). Nevertheless, a significant obstacle to accurately reproducing these dynamic tissues' intricate structure and mechanical characteristics, through *in vitro* engineering, has been their intrinsic complexity (Shantanu Pradhan 2020). *In situ,* tissue engineering provides a more practical and affordable method, which has become a pivotal technological advancement. This approach uses readily available, biodegradable, and cell-free scaffolds designed to promote endogenous regeneration within the functional zone right away (Xiuting Wang 2022). The fundamental idea of *in situ* tissue engineering is to make use of the host's innate ability to repair wounds and regenerate itself. This is accomplished by leveraging the interaction among resident tissue cells, stem/progenitor cells, and immune cells within the environment created by the implanted scaffold (Rebecca D. Bierman-Duquette 2022, Liangbin Zhou 2023).

3.4. Biomaterials in Restoring Cardiac Tissues

Autologous grafts, which are biomaterials derived from the tissues of the patient, have also been investigated for cardiovascular uses (Tristan Mes 2022). Among these is the application of patient-derived pericardial tissue (Mingze Sun 2022) that is utilized to fabricate heart valve replacements on demand or patch up congenital cardiac abnormalities (Carmen Kiper 2020). Bioprosthetic valves are frequently utilized in cardiovascular applications; these valves are typically obtained from pig or cow sources (Diana Elena Ciolacu 2022b). These valves are superior to mechanical heart valves because of their biocompatibility and durability (Williams et al. 2021). Glutaraldehyde cross-linking is one chemical process that can be utilized to increase the bioprosthetic valve stability and robustness (Tao Yu 2021). The possible use of decellularized porcine small intestine submucosa (DPSIS), as a scaffold for cardiac repair, is another example. Small intestinal submucosa (SIS) is gathered from the submucosa layer of the pig small intestine, which is rich in collagen, elastin, glycosaminoglycans, growth factors, and numerous other vital ECM components (Huimin Xiao 2023). The natural ECM structure is preserved, whereas cellular components are eliminated through the decellularization process (Xuewei Zhang 2022). This SIS-ECM scaffold was proven to have strong hemostatic properties, resistance to calcification, and the ability to promote tissue remodeling and revascularization following implantation (Frederick J. Schoen 2020). In animal trials, SIS emulsion injection into the heart resulted in an increase in angiogenesis and an improvement in cardiac function, suggesting potential benefits for SIS-based treatments of myocardial infarction. Furthermore, in chronic ischemia conditions, SIS scaffolds implanted with mesenchymal stem cells derived from bone marrow have shown encouraging outcomes in rebuilding heart tissue and function (Yun Jiang 2023). After being implanted, the DPSIS demonstrates tissue regeneration potential by promoting the formation of new tissue composed of myofibroblasts and small blood vessels (Pawan Kc 2019, Simranjit S. Pattar 2019). Compared to mechanical valve replacements, bioprosthetic valves offer better hemodynamic performance and biocompatibility. Bioprosthetic valves are a favored option for many patients, particularly those who are elderly, as they do not require lifetime anticoagulation medication like mechanical valves do (Evangelia Sigala 2023). Nevertheless, there are still issues with bioprosthetic valve endurance, such as the possibility of structural degradation over time. The pericardium is another well-known natural biomaterial utilized in cardiovascular therapy (Ali Fatehi Hassanabad 2023). The xenogeneic pericardium has been widely used for a variety of cardiac repair and reconstruction treatments. It is primarily obtained from bovine, porcine, and horse sources (Ekaterina A. Grebenik 2020). The natural collagen structure and elastic qualities of the pericardial tissue are preserved, while cellular components are removed and mechanical characteristics are improved by cross-linking, and decellularizing the tissue. Heart tissue healing, valve replacement, and pericardial closure have all been accomplished with decellularized pericardial patches. When compared to synthetic materials, pericardial grafts have shown improved host tissue response, less adhesion formation, and increased resistance to infection (Alessandra Costa 2019).

For cardiovascular applications, autologous tissues—such as a patient's own valves or pericardium— are the best natural biomaterials. Because these tissues are autologous, they offer the highest degree of biocompatibility and functionality. However, the scarcity of autologous tissues and the additional surgery needed to harvest them may be significant drawbacks (Jamie L. Hernandez 2022, Xu Xue 2021a, b).

4. Synthetic Biomaterials Used in Cardiovascular Diseases

Synthetic biomaterials are materials created artificially with the goal of improving, substituting, or repairing biological tissues and organs in biomedical and pharmaceutical applications (Satyavrata Samavedi 2014). These materials are designed with certain biological and physical characteristics in mind that allow them to be used in conjunction with the human body without a significantly negative impact (M. Sai

Bhargava Reddy 2021). Treatments for heart conditions employ ceramics far less frequently. Strength and durability are the primary advantages of synthetic materials, but there may be drawbacks due to biocompatibility problems. When it comes to synthetic materials, toxicity is a critical factor, particularly when it comes to biodegradable materials, which can release potentially hazardous breakdown products into the body. Chemically inert materials have provided a useful basis for implantable materials, enabling coating-based medication administration or stand-alone applications. The most commonly used synthetic biomaterials are:

4.1. Expanded Polytetrafluoroethylene

Because of its performance and convenience of use, expanded polytetrafluoroethylene (ePTFE) has become a standard material in cardiovascular applications. In the business world, this material is most commonly referred to as Gore-tex®. Using this material, Gore Medical produces cardiovascular products for vascular grafts, pediatric shunts, and general heart repair (Hamed Amani 2019). A fluorocarbon polymer is what gives ePTFE its sheets; they are created through extrusion. A microporous, elastic layer in the middle is encircled by two layers of polymer fibrils to form a three-layer polymer (Oleg Gaidai 2023a, b). The resulting structure offers resistance to dilatation and a high strength-to-weight ratio. Low thrombogenicity, decreased hemostasis, and restenosis rates, less calcification, and biochemically inert qualities are all encouraged by the chemical composition (Saha SP 2011). Furthermore, it has been demonstrated that ePTFE has strong resilience to inflammation and allergic reactions (Verbelen 2010). Because of the previously mentioned qualities, ePTFE has proven to be a great choice for shunt creation (Doble M 2008), reconstruction (Miyazaki T 2011), valve repair (Ando M 2009), and even covering implanted devices to reduce inflammation. However, since ePTFE is a synthetic material, it may provoke immunological reactions and thrombosis.

4.2. Polyethylene Terephthalate

Maquet Cardiovascular produces Dacron®, or polyethylene terephthalate (PET) is a thermoplastic polymer whose chemical inertness enhances its biocompatibility. Although this material can be produced in various ways, it is usually utilized in cardiovascular applications as knitted or woven vascular grafts. The effectiveness of pre-lining PET vascular grafts with endothelial cells has been investigated. This strategy has enhanced graft performance in animals (Shayani V 1994), but low patency rates were observed in human clinical trials as compared to autologous grafts (Jensen N 1994). PET grafts are being utilized more frequently than ePTFE grafts, yet recent data indicates that ePTFE has certain benefits, including reduced thrombogenicity. The use of either biomaterial depends on the specifications needed to replace or repair a particular cardiovascular tissue.

4.3. Metals

Because of their strength and biocompatibility, chemically nonreactive metals have been employed for a variety of medicinal applications for several decades. Biocompatible metals that are frequently utilized include gold, silver, stainless steel, and titanium. Metals are utilized in stents, which are devices used in the cardiovascular field, to open blocked arteries. Stents have traditionally been made of titanium and stainless steel, but because of their increased strength, more recent stents have been made of cobalt-chromium or platinum-chromium alloys (O'Brien BJ 2010). Owing to the form memory, nitinol stents constructed of an alloy of titanium and nickel in the past were renowned in the market, but their usage has since been discontinued because of nickel allergy (Rigatelli G 2007). Heart valve replacement is another common application for metals. Metals like titanium and stainless steel are used to make mechanical replacement heart valves (van Putte BP 2012). However, patients with mechanical valves have an increased risk of blood clot development; they will need to use anticoagulants for the rest of their lives. Individuals who are unable to use anticoagulants are left with no other choice except to use natural tissue valves.

4.4. Polyurethane

Polyurethanes (PUs) are classified as reaction polymers. When an isocyanate group combines with a hydroxyl group, PU is produced. PU can also be made into a more robust thermoplastic that is used in medical environments. PU made of thermoplastic offers excellent elasticity, transparency, and shear strength. The exploration into PU, as a substrate in cardiac stem cell treatment, includes *in vitro* studies on the effects of patterned PU substrates on the phenotype of stem cell-derived cardiomyocytes (Parrag IC 2022).

5. Conclusion

To sum up, the scientific community is paying close attention to customizing biomaterials to tackle the challenges imposed by cardiac tissue engineering and regeneration. The management of cardiac injuries can be completely transformed by the creative combinatorial application of electrically conductive materials, stem and/or progenitor cells, bioactive chemicals, and natural and synthetic polymers. Adopting an interdisciplinary approach, a number of recently developed cardiac patches, hydrogels that may be injected, formulations based on extracellular vesicles, and biomaterial scaffolds have already shown promise in both *in vitro* and *in vivo* testing. To guarantee technological transfer to the clinical setting, further research and optimization of the suggested strategies are still needed.

6. Future Directions

In order to maximize the performance of implantable materials overall, future research should concentrate on optimizing composite materials to fully utilize the best blend of natural and synthetic biomaterials. The present conundrum of having to choose between synthetic or natural tissues and giving up the advantages of one material over the other may be resolved by composite biomaterials. Additionally, more should be done to boost stem cell survival and retention through the use of biomaterials. This can result in the routine use of tissue regeneration methods, which would provide the best remedy for the restoration of damaged cardiovascular tissue. Stem cells will become more prevalent in the field of cardiovascular therapy as it advances. In-depth research is being done to improve stem cell survivability and proliferation after transplantation; these solutions most likely involve the use of biomaterials. With the innumerable efforts made in this direction, material development could reach a breakthrough and result in a more specialized list of effective materials combined with the right stem cells. Although tissue replacement and repair have proven to be an effective therapeutic option, tissue regeneration is the next major goal to pursue in fully restoring a damaged heart's function.

Conflict of Interest

The authors declare that they have no conflicts of interest to disclose.

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Study Approval

There are no animal/human subjects involved so, this study requires no institutional or ethical review board approval.

Consent Forms

NA.

Authors Contributions

MA conceptualized the study and wrote the final manuscript, SGN, SS, CJ, and QA helped with the literature search analysis and writing the first draft, MA, EA, and MT did the literature search and review of the studies, and MA supervised the whole project and wrote the final manuscript.

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