Review

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Tailored-Biomaterials Based Potential Strategies for Cardiovascular Disease

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Cardiovascular disease is a significant health concern worldwide, and varied effective treatment and prevention methods have been developed. Among these, tailored biomaterials-based strategies such as stents, scaffolds, patches, and drug delivery systems have emerged as a promising avenue. These devices are designed to match the mechanical and biological mechanisms of the cardiovascular system, ensuring optimal performance and compatibility. By effectively treating or preventing cardiovascular diseases, these devices have the potential to improve patient health outcomes significantly. They can restore blood flow by addressing blocked arteries and regenerate damaged cardiac tissue by delivering bioactive agents or cells directly to the affected area in a targeted, sustained, and controllable manner. Therefore, the objective of this article is to summarize the available evidence on these tailored biomaterial-based tunable cardiovascular devices. This knowledge can help to transform cardiovascular medicine for the treatment or prevention of cardiovascular disease and restore cardiac function to improve patients' quality of life.

Keywords: biomaterials; biomaterial-based cardiovascular devices; tailored auxetic effects; tuned deformation mechanisms; controlled drug delivery

Introduction

Cardiovascular disease remains a significant cause of illness and death worldwide, resulting in around 17.3 million deaths annually, which can increase to 23.6 million by 2030. This disease affects patients and significantly strains healthcare systems globally, with an economic burden of approximately $239.9 billion annually estimated only in the United States For treatments and management of this ailment, the current biomaterial industry, generating an impressive $88.4 billion globally and growing at a compound annual rate of 15%, has led to the development of various biomaterial-based cardiac support devices [1–3]. These include implantable cardioverter-defibrillators, artificial blood vessels, heart valves, and devices placed by angioplasty procedures, such as stents, scaffolds, patches, and drug delivery systems [4–12]. These devices, integrating hydrogels, bioconjugates, and nanomaterials in various biomaterials, including metals and polymers, have shown remarkable progress in fighting against cardiovascular disease to improve patient's quality of life [13–17].

They have certain limitations when utilized in the human body, such as inadequate matching of their mechanical and biological mechanisms with native tissue. However, their tunable capacity with unique properties that allow them to act as switches, self-fold or self-unfold, and targeted and sustained release of cells or drugs at the diseased site has shown to overcome these challenges [18]. Architectures of geometrical patterning on biomaterials, which tailor their mechanical and biological behavior, are known as auxetic biomaterials is one of these approaches. These materials are designed to withstand the conditions of the native tissue and have shown significantly enhanced efficacy in treating various cardiovascular ailments efficiently [19]. Their versatile applications extend across various biomedical domains [20–22]. The distinct characteristics of auxetic materials, encompassing enhanced mechanical strain, tensile forces, shearing forces [23], and electrical conductivity [24], enable them to replicate the natural stretching and compression of cardiac tissue. This imitation facilitates dynamic cardiac tissue functions such as tuning mechan-

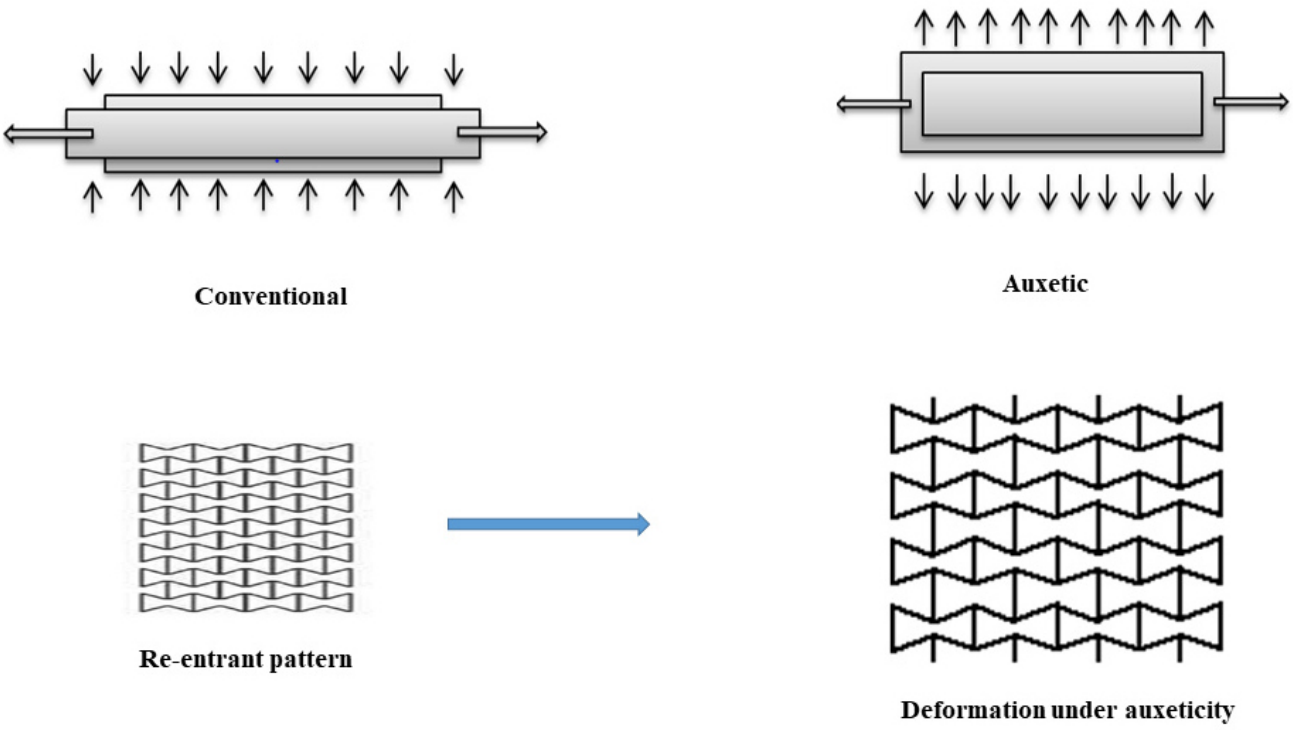

Fig. 1. Simultaneous expansion in all directions of an auxetic biomaterial with a geometrically patterned structure. Drawn using PowerPoint and SolidWorks.

ical strength, flexibility, and unique deformation mechanisms akin to natural tissue [25]. Evidence also shows that specific biological tissues have auxetic-like behavior, rendering tailored auxetic biomaterials ideal for interacting with the human body [26–29]. Moreover, the indications that embryonic stem cells in the pluripotent state possess nuclei with auxetic characteristics [25] and that utilizing auxetic scaffolds for vascular differentiation from Human Pluripotent Stem Cells has been revealed to promote endothelial differentiation [30]. It is worth noting that current research findings predominantly involve conceptual prototypes within controlled laboratory environments. Progress in this domain necessitates thoroughly exploring the potential and challenges critical for transitioning from experimental models to practical applications [31].

Hence, this article aims to present a comprehensive overview of the pivotal roles played by various tailored auxetic biomaterials in treating and preventing cardiovascular diseases. Specifically, the spotlight is on metals and polymers-enabled auxetic cardiovascular devices, comprising stents, cardiac patches, scaffolds, and drug delivery systems individually or encapsulated with biological substances at macro to nanoscale levels [32]. Comprehending the enhanced capabilities of these tools in addressing obstructed arteries, restoring blood flow, and repairing cardiac tissue damage and regeneration may be valuable in evaluating the potential benefits of this biomaterial-enabled therapy in cardiology.

Role of Tailored-Biomaterials in the Interventional Treatment of Cardiovascular Diseases

Biomaterials, including metals and polymers, have been indispensable for various implantable and angioplasty-processed cardiovascular devices for almost a century [4,5,22]. Because of their high tensile strength and corrosion resistance, metals such as stainless steel, titanium alloys, and cobalt-chromium alloys are commonly used for making stents, grafts, stylets, and heart valves [4,5]. On the other hand, owing to their excellent biocompatibility, polymers such as polyolefins, polyamides, polytetrafluoroethylene, polyesters, and polyurethanes are widely utilized in bioabsorbable stents, scaffolds, cardiac patches, drug delivery systems, annuloplasty rings, and smaller arteries hemodialysis membranes as well as pacemaker leads [13–16]. A range of natural and synthetic polymer scaffolds and patches have been developed to replicate the fundamental characteristics of the cardiac extracellular matrix and establish a suitable microenvironment that enhances cell viability and regenerates damaged tissues [33,34]. Combined with stem and progenitor cells, they have been shown to significantly augment the cardiac tissue's regenerative potential [35–38]. Also, polymers are processed into nanocarriers and hydrogels for drug delivery, leading to considerable regenerative approaches for treating cardiovascular disease [39–41]. Their compelling potential in enhancing drug delivery through various

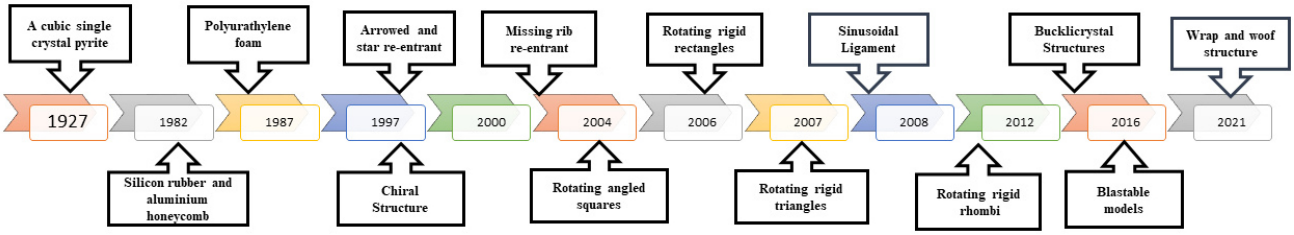

Fig. 2. Milestones in developing tailored structures for auxetic materials. Drawn using PowerPoint.

modes of administration, including injection, oral dosing, and scaffolds, is notable [42,43]. Notably, polymers combined with bioprosthetics available in homografts, porcine valves, and bovine or porcine pericardium have been shown to have their restorative capacity for cardiac function efficiently [5–7].

Since stretching longitudinally, most biomaterials contract transversally (Fig. 1), which mismatch with the heart's structural features that exhibit transverse expansion when subjected to axial tensional force [36,44,45]. This deformation mechanism of the biomaterials cardiovascular devices has been exposed and limited by inadequate flexibility, elongation, and poor cellular access [44–46]. On the other hand, tailored (auxetic) biomaterials promote the deformation mechanism of expanding in multiple directions simultaneously when stretched and returning to the original after removal of stretching (Fig. 1) provides cardiovascular devices such as stents, scaffolds, and patches to simulate the physiology and mechanics of the heart during the remodeling process [47–50]. Under auxetic effects, tuned mechanical properties such as compressive strength, elastic modulus, resistance to shear, indentation, and synclastic curvature have been shown to augment the compatibility of these devices to the demanding mechanics of the cardiac tissue, and replicate the motion and mechanical properties of the human heart in a three-dimensional micro-environment [19,31,51,52]. In this regard, tailoring of a variety of auxetic patterns such as reentrant structures, rotating units, chiral structures, sliding bars systems, fibril/nodule buckling-induced structures, crumpled structures, and Miura-folded structures have been specified on a variety of material, including metals and polymers [53,54] using various techniques. These include additive manufacturing, 3D bioprinting, bio-ink printing, textile techniques, electrospinning and micromachining, microfluidics, and gas foaming [46,50,55]. Fig. 2 depicts the key milestones in developing auxetic materials over the decades [56], and diverse functionalities of auxetic cardiovascular devices are described in the following next sections, which may be essential in exploring better cardiovascular medicine.

Auxetic Stents in Treating Cardiovascular Disease

Due to critical conditions, including atherosclerosis, hypertension, diabetes, genetic defects, and aging, arterial blockage, contraction, twisting, elongation, tortuosity, kinking, and curving, have been known to result in cardiovascular diseases such as coronary heart disease and peripheral artery disease. The effects of these diseases can significantly impede the heart's ability to pump an adequate supply of blood through the vessels and arteries, eventually leading to severe outcomes, including heart attack and stroke [57]. The advanced stages of coronary artery disease can cause plaque build-up on the inner surface of an artery, resulting in significant narrowing and blockage, a condition known as atherosclerosis [58]. Balloon angioplasty, which involves the insertion of a catheter to place a stent in the affected blood vessel, has proven effective in treating blockages for restoring blood flow by reducing the risks, such as elastic recoiling and restenosis while strengthening the artery wall [59–63].

Over the past five decades, metals, metal alloys, titanium, platinum, polymer, and plastic stents in various forms, coated or uncoated, bioabsorbable, balloon-expandable, and self-expandable, have been developed. Selecting an appropriate stent is crucial and varies, depending on the patient's symptoms, the local deposition of plaque and fatty substances, and potential side effects [64–68]. Clinically, they have shown significant promise in treating arterial blockages. However, the suboptimal design of stents has led to complications such as stent thrombosis and in-stent restenosis, resulting in high failure rates of arterial stenting attributed to inadequate stent expansion, incomplete stent apposition, and stent fracture [63,69]. Several factors, including design optimization, choice of materials, fabrication method, surface functionalization, and implantation procedure, can be responsible for optimizing stent designs [70–73]. Since the inefficiency of stent designs has been found to cause the high failure rate of arterial stenting [60,62,63,66]; auxetic architectures have been shown their efficacy for developing novel stenting structures to overcome challenges with existing stents [74–79]. It is worth noting that the performance of auxetic stents relies heavily on the unit cell of the geometrical pattern rather than the biomaterial itself. Furthermore, the mechanical

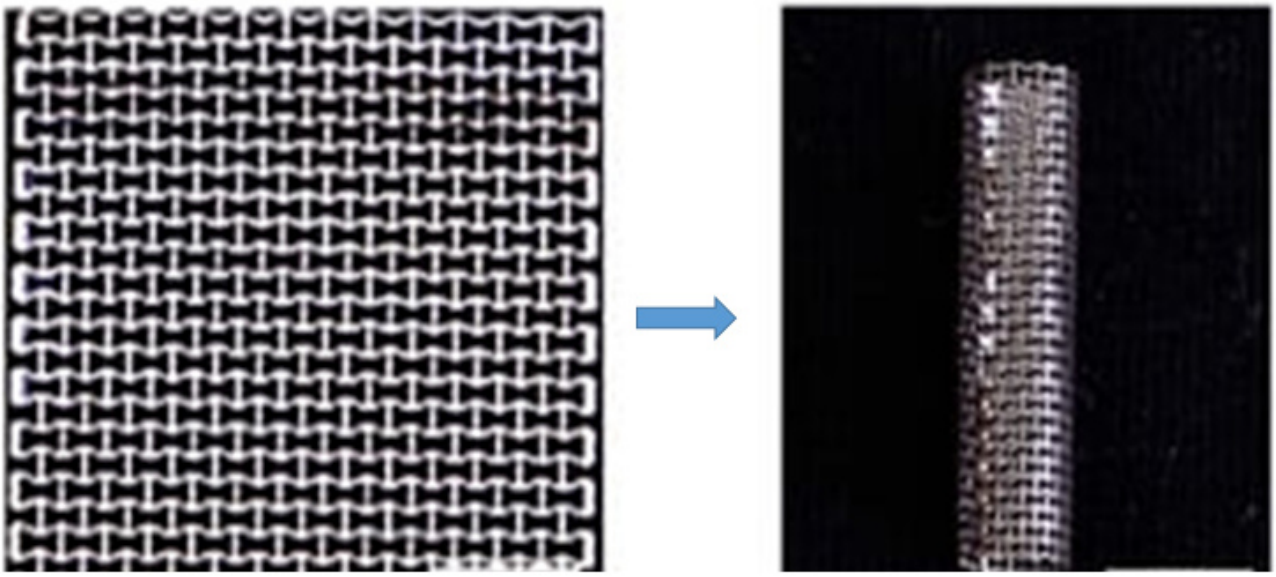

Fig. 3. A stainless-steel metal plate designed with a repeating unit-cell pattern using femtosecond micromachining and a laser-welded auxetic stent. Figures from author's own fabricated samples arranged in PowerPoint.

characterization of stents is crucial in promoting efficient functional recovery of blood vessels and arterial endothelium. They are subject to wall shear stresses and cyclic circumferential strain induced by pulsatile blood flow, which cause concurrent axial and transverse expansion or contraction. In this context, auxetic stents have been recognized as a potential solution that may better integrate with native tissues. Their efficacy has been conducted mechanically, numerically, and analytically [74,80]. Various auxetic stents, such as an auxetic-chiral pattern, a model of a rotating square system, and arranged hexagonal honeycomb structures, have been shown to improve mechanical performance and deformation mechanisms [74,77–83]. Implementing the topology of the repeating unit on a stent's structure has been shown to significantly improve safety and achieve high hemodynamic performance and low foreshortening, which is essential for the safe and successful implantation of stents [79]. It should be noteworthy that stent undergoes diverse mechanical loadings such as bending, longitudinal compression, buckling, and torsion on the implantation site from the pulsation of the heart or body movement or pressures of the surrounding vessels and blood flow in addition to repetitive deformations caused by patient' routine activities. In this regard, several auxetic designs have been probed to optimize strut thickness for mechanical capacity, buckling, twisting, gripping, and deformation ability of stents [19,75,84–87]. The mechanical capability of a high-precision femtosecond micromachined auxetic stainless steel stent of reentrant cell geometry (Fig. 3) under mechanical loadings through *in vitro* mechanical and finite element analysis has been performed. This stent demonstrated higher capability when subjected to bending, superior performance at elevated levels of twisting angles, appropriate buckling, and physiologically relevant mechanical conditions like longitudinal contraction and radial strength. Additionally, the noteworthy characteristic of transverse expansion or contraction in response to uniaxial tension or compression exhibited by auxetic stents has resulted in exceptional strength with reduced surface coverage, rendering them highly suited for deployment in relevant applications. Their enhanced radial expansion capability while reducing axial expansion has resulted in efficient gripping to arteries and reduced stent migration [85,87]. Furthermore, the potential of 4D-printed reentrant honeycomb structure polymer auxetic stents in treating vascular stenosis has also been brought to the forefront. The efficacy of auxetic stents has been noticed for axial and radial compression, three-point bending, fluid-structure interaction, and stress distribution during deformation, suggesting that they can effectively expand within a simulated narrow blood vessel, and making them promising in treating vascular stenosis [88]. Since the presence of non-degradable metal stents within blood vessels has become increasingly apparent as a significant risk factor for chronic damage to vessels and intimal smooth muscle cell proliferation, ultimately leading to restenosis, biodegradable polymer stents have emerged as a promising alternative to reduce the risk of restenosis and minimize chronic damage to vessels [89]. In this viewpoint, a micromachined biodegradable electrospun polymer microfiber tubular structure (Fig. 4) has been reported to

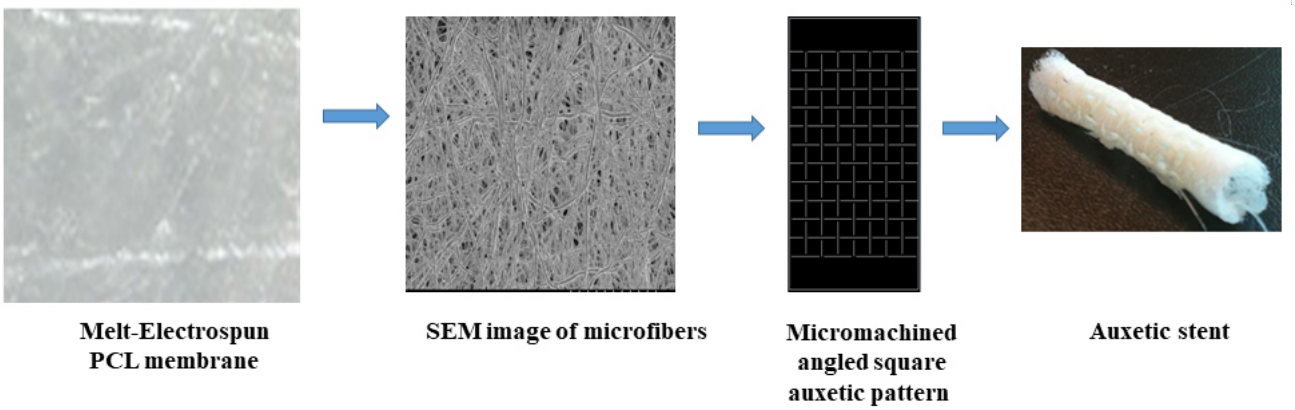

Fig. 4. A schematic representation of a microfiber sheet of electrospun poly-ϵ-caprolactone created an auxetic stent. Figures from author's own fabricated samples, created using SolidWorks and arranged in PowerPoint.

exhibit enhanced deformation mechanisms and mechanical strength [18], indicating that auxetic stents hold potential for clinical application but require *in vivo* animal studies or clinical trials to verify their efficacy.

Overall, the use of biomaterial-based auxetic stents has exhibited considerable promise in facilitating a more individualized approach to treating blockages and restoring blood flow, offering a customized shape, tuned mechanical properties and functionalities, in addition to the ability to enhance radial expansion while reducing axial expansion, making them a promising option for deployment. It could be a noteworthy development in interventional cardiovascular medicine. However, comprehensive scrutiny of their design and manufacturing would yield valuable insights for optimizing their performance and unlocking their full potential in treating cardiovascular diseases, such as atherosclerosis.

Auxetic Cardiac Patch for Cardiac Regeneration

In light of the limited regenerative capacity of the human heart, cardiac patches represent a promising avenue for repairing and replacing diseased heart tissues [42]. Through the delivery of bioactive factors, vesicles, cells, insulin-like growth factor-1, and drugs to the infarcted region of the heart, cardiac patches of natural and synthetic biomaterials or biological materials have emerged as a promising strategy for cardiac regeneration [43,90–97]. Since the ideal biomaterial for cardiac tissue regeneration should be able to closely mimic the heart vessels and withstand the stresses generated by the heart function, auxetic cardiac patches are adaptable in size, shape, and mechanical strength capacity to cater to each patient's unique needs [98–100]. When stretched, their expansion in all directions allows them to conform to the shape of the heart tissue [91]. By incorporating various designs, including reentrant honeycomb or angled squares, these patches have been observed to exhibit a deformation mechanism that matches the movements of healthy heart tissues more effectively than unpatterned cardiac patches [101]. In addition, auxetic patches have been found to stimulate cell proliferation and display higher metabolic activity than traditional patches. Notably, in myocardial infarcted rats auxetic cardiac patches were found to have an anisotropic electrical conductivity that aligns with the longitudinal axis of cardiac tissue to adapt heart movements better than traditional patches [52]. In particular, the unique deformation mechanism of the auxetic surface of patches during systole and the expansion in all directions under stress mimics the complex characteristic of the heart contracting longitudinally and transversely, which is noteworthy to make these patches specifically significant in treating myocardial infarction [23]. Compared to control patches they have better cell attachment and the ability to regain their original structure after each unloading cycle. They exhibit strains and stresses similar to the native cardiac muscle during diastole and systole due to their potential for electroconductivity for regenerating cardiac tissue. Moreover, their anisotropic mechanical properties and anisotropic ratio of effective stiffness have been shown to align with the heart's directionally dependent mechanics. Furthermore, they can replicate the intricate three-dimensional structure of the natural cardiac extracellular matrix-cell attachment profiles and, thus, have been shown to preserve cellular viability and function and create a favorable microenvironment for cardiomyocyte cell culture [101,102]. It is noteworthy that these patches hold the potential to enhance the contractility, calcium handling, and transverse-tubule formation of induced pluripotent stem cell-derived cardiomyocytes. Moreover, the patches have been observed to enhance cardiomyocyte functioning for up to 14 days, which indicates their potential for cardiac tissue regeneration [101]. Auxetic electrospun nanofiber membranes have shown their capability to withstand mechanical stresses. Their efficacy, in this regard, noticed from observations was shown that an angled solid square geometry on electrospun polymer nanofibrous membranes coated with gold nanoparticles retained their shape when subjected to

small tensile loads, resulting in a tenfold increase in tensile capacity compared to traditional nanofibrous patches. Indeed, it has also been uncovered that the total elongation capacity of thick membranes was significantly reduced (almost six-fold) compared to thin ones, indicating a reduced ability to deform because of increased thickness. It is noteworthy that these auxetic patterned membranes as cardiac patches can potentially treat infarcted regions of varying thicknesses according to patients' requirements and support cardiac regeneration [103].

The above observations emphasize the potential of using auxetic cardiac patches as a solution to the limitations of conventional cardiac patches to develop more effective treatment options for cardiovascular disease. However, it is necessary to conduct more research to thoroughly understand this approach's potential and implementation in clinical settings.

Auxetic Scaffolds and Drug Delivery in Cardiovascular Disease

Scaffolds play an indispensable role in cardiac tissue engineering, acting as a synthetic or biological platform for cell growth and development. They promote tissue formation and replicate the structural and mechanical properties of native tissue. However, synthetic scaffolds pose challenges due to their lack of organic components in the extracellular matrix, which obstructs cell penetration and recolonization of the scaffold. In contrast, biological scaffolds derived from animal (xenografts) or human (homografts) tissue provide a more favorable environment [104–108]. A variety of biocompatible polymers, including polyethylene glycol-diacrylate and poly-ϵ-caprolactone, have been used to construct various auxetic geometries, such as chiral, reentrant, and rotating diverse shapes, like square, rectangular, hexagonal as a multilayered and tubular scaffold to acknowledge their potential in cardiac tissue engineering, repair, and regeneration [109–111]. Whether utilized solely for support or as carriers for growth factors, cells, and drugs, these scaffolds have shown promising results in enhancing heart function [112]. Their exceptional porosity strength and increased flexibility make them ideal for regulating cell migration and inhibiting a phenotype change in vascular smooth muscle cells compared to non-auxetic scaffolds [109,113,114]. For instance, by cultivating vascular smooth muscle and endothelial cells on different layers of a multilayered scaffold, auxetic scaffolds have been observed to prevent a phenotype change in vascular smooth muscle cells and optimize co-culture conditions. Additionally, enhanced cell proliferation and metabolic activity have led to the expression of specific markers for vascular differentiation [115]. Also, the potential for vascular differentiation from stem cells revealed elevated expression levels of vascular markers like vascular endothelial-cadherin and cluster of differentiation 31 (CD31) in the auxetic scaffold have been indicated compared to the non-auxetic scaffold. Furthermore, the effect on the level of the α-actinin cardiac biomarker was minimal [116]. Likewise, auxetic scaffolds have improved cell adhesion and growth, which is noteworthy in cardiovascular regeneration. Notably, the proliferation of mouse fibroblasts has indicated these scaffolds' efficacy in enhancing cellular activity within a controlled environment [80]. Moreover, these scaffolds have demonstrated biaxial expansion/compression behavior as one or multiple cells apply local forces and move the structures, potentially impacting cardiac tissue regeneration [111].

Furthermore, it is well known that various biomaterial-based systems, such as micro or nanoparticles, liposomes, polymer capsules, and micromachined constructs, are employed to deliver drug-delivery therapeutic loads [117–119]. While minimizing side effects, these systems achieve enhanced solubility, accurate targeting, prevention of premature degradation, permeation of barriers, and reduction of dosage [117]. Since the intricate nature of the body's circulatory pathways and organs, drug delivery within the body necessitates precise drug encapsulation packages with multifunctional attributes [120]. Essential attributes include material composition, surface functionalization, reconfigurability, manufacturability, and structural parameters, encompassing monodispersity, size, shape, porosity, and reservoir wall thickness [121]. Also, the composition of drug delivery systems governs their toxicity, biodegradability, and compatibility with diverse therapeutic loads. Moreover, the dimensions and properties of these systems significantly influence their capability to traverse biological barriers, circulation times, semi-permeability for immunoisolation, and the spatial and temporal aspects of drug release. Furthermore, surface chemical functionalization determines immunocompatibility, cellular targeting, and uptake while incorporating optoelectronic elements, which is imperative for imaging, remote communication, and on-demand delivery [122–124].

Notably, the capability for reconfigurability provides the systems with stimuli-responsive and intelligent behaviors, and manufacturability is integral for practical considerations [125,126]. Incorporating these attributes within a single fabrication presents challenges, limitations, and potential for enhancements in the synthesis setting. Specifically, stimuli-responsive auxetic drug delivery systems have shown remarkable efficacy in treating cardiovascular ailments, such as atherosclerotic plaque and myocardial injuries [127–129]. Auxetics are known for their distinctive ability to enable directional release, in contrast to isotropic drug release, thus holding promise for the potential of drug delivery systems [88,127–130]. Likewise, the porous morphology and an increase in pore size in response to uniaxial loading are associated with a significant volume change acting as molecular sieves, entrapping a particle and releasing it in response to pore size changes after directional loading make auxetic scaffolds more suitable for controlled drug delivery. The efficacy of a rotating square-designed auxetic

construct with adjustable pore sizes has been indicated to achieve tunable drug delivery characteristics and for localized delivery of antiproliferative drugs through pores on the tubular surface. The drugs were also efficiently distributed into the adjacent arterial tissue, ensuring effective delivery to the target site. Furthermore, biomaterials that exhibit auxetic features have the potential to regulate nutrients and therapeutic agents released from matrix systems in response to specific stimuli due to their capacity for shape memory and deformation mechanisms unique to the microenvironment. Stimuli-responsive micro-scale multifaceted folded auxetic surfaces and cages represent cutting-edge advancements in multidimensional metamaterials. Their proven compatibility with biological and electronic systems [22] positions them as up-and-coming intelligent drug delivery systems for cardiovascular treatments.

These observations emphasize the potential of customizing biomaterial drug delivery systems with auxetic effects; this approach offers a promising avenue for developing encapsulants that embody the multifaceted attributes necessary for a controlled drug delivery system. The precise and controlled drug release of auxetic scaffolds makes them a promising strategy for developing novel drug delivery systems, marking a significant step forward in cardiovascular disease treatment [130,131].

Conclusion

Since the use of tailored biomaterials for treating cardiovascular disease can significantly influence therapeutic approaches. This comprehensive article presents an overview of auxetic cardiovascular devices, encompassing stents, patches, scaffolds, and drug delivery systems, to promote cardiac regeneration and reinstate heart function. Understanding their ability to replicate cardiac tissue's mechanical and deformation mechanisms, as expounded within this review article, holds potential for advancing cardiovascular disease treatment. Nonetheless, it is essential to acknowledge that the practical implementation of auxetic patterning in these devices for cardiovascular disease treatment remains in the theoretical phase. However, optimizing parameters like porosity, stiffness, load-bearing capacity, and tailored geometrical patterns is crucial before mass production. Furthermore, the constraints associated with manufacturing techniques such as electrospinning, 3D printing, and femtosecond laser cutting, which possess micro- and nanoscale patterning capabilities and the intricate geometry of auxetic devices, contribute to elevated production costs. Hence, technological advancements in manufacturing are imperative to render these devices feasible for the biomedical device industry. In this context, integrating 4D printing or printing mechanisms directly into the design phase can enable the customization of auxetics for particular cardiovascular implantable devices, potentially advancing shape-morphing capabilities. Moreover, applying auxetic geometries on biohybrid materials populated by cells is a viable consideration, presenting the potential for cardiac regeneration. Continued exploration of the potential of auxetic biomaterials can advance cardiovascular disease treatment and improve patient outcomes.

Availability of Data and Materials

Not applicable.

Author Contributions

SKB, HM, JT, DGR, AM, NC, MBGJ and SMW, made substantial contributions to the conception and design, or acquisition of data, or analysis and interpretation of data. SKB was involved in drafting the manuscript. All authors revised it critically for important intellectual content. All authors gave final approval of the version to be published. All authors participated sufficiently in the work to take public responsibility for appropriate portions of the content. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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