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Technologies for intrapericardial delivery of therapeutics and cells

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ABSTRACT

The pericardium, which surrounds the heart, provides a unique enclosed volume and a site for the delivery of agents to the heart and coronary arteries. While strategies for targeting the delivery of therapeutics to the heart are lacking, various technologies and nanodelivery approaches are emerging as promising methods for site specific delivery to increase therapeutic myocardial retention, efficacy, and bioactivity, while decreasing undesired systemic effects. Here, we provide a literature review of various approaches for intrapericardial delivery of agents. Emphasis is given to sustained delivery approaches (pumps and catheters) and localized release (patches, drug eluting stents, and support devices and meshes). Further, minimally invasive access techniques, pericardial access devices, pericardial washout and fluid analysis, as well as therapeutic and cell delivery vehicles are presented. Finally, several promising new therapeutic targets to treat heart diseases are highlighted.

Contents

Abbreviations: 8-isoPGF2alpha, 8-isoprostaglandin F2alpha; ACE, angiotensin converting enzyme; ANP, atrial natriuretic peptide; AT1, angiotensin II type I; AUC, area under the time-concentration curve; bFGF, basic Fibroblast growth factor; BNP, brain natriuretic peptide; EL, endoluminal; EPCs, endothelial progenitor cells; ET-1, endothelin-1; FDA, Food and Drug Administration; FGF, fibroblast growth factor; H-FABP, heart-type cytoplasmic fatty acid-binding protein; HGF, hepatocyte growth factor; HVJ, Hemagglutinating Virus of Japan; IC, intracoronary; IL, interleukin; IPC, intrapericardial; IV, intravenous; IVUS, intravascular ultrasound; LAD, left anterior descending; LVADs, left ventricular assist devices; MI, myocardial infarction; MSCs, mesenchymal stem cells; MW, molecular weight; nDS, nanochannel drug delivery system; NP, nanoparticle; OK-432, picibanil; PCADK, poly(cyclohexane-1,4-diyl acetonedimethylene ketal); PEG, poly(ethylene glycol); PEI, polyethyleneimine; PK, pharmacokinetics; PLGA, poly(lactide-co-glycolide); RAA, right atrial appendage; SG, Swan Ganz; VEGF, vascular endothelial growth factor.

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1. Introduction

The pericardium offers a well-contained, easily accessible space during surgery. It consists of two closely connected anatomical structures, an external sac of fibrous connective tissue, referred to as fibrous pericardium, and an internal serous portion, composed of a parietal and visceral layer, forming the pericardial space. Between these two layers exists the pericardial fluid, which aids in minimizing friction from the beating heart [1,2]. While the composition of normal human pericardial fluid is complex, the volume is directly analogous to the subject size. In adult humans the pericardial fluid volume is approximately 15–35 ml [1]. The pericardium plays an important role in the regulation of several myocardial processes. Its major functions also include adequate cardiac positioning, separation of the mediastinum from the surrounding tissues, protection against ventricular dilatation, maintenance of low transmural pressure, and facilitation of ventricular interdependence and atrial filling [3].

The delivery of drugs and cells into the pericardium has proved to be of great value. Studies, as highlighted in this review, have demonstrated that intrapericardial, as opposed to intravenous administration, has improved pharmacokinetics profiles as well as greater drug distribution within the heart tissue.

Here, we focus on the most recent developments in the field of drug delivery to the heart with particular emphasis on using the pericardial sac as an access point to increase bioavailability throughout the entire organ. First, we introduce the advantages of local drug delivery to the heart and highlight strategies to provide drug in boluses or in a sustained fashion to the pericardium. Second, we present factors in the pericardial fluid that have been identified and can act as markers to provide insight into cardiac health. Finally, we discuss the use of micro and nanoparticles to encapsulate drugs and sustain their levels within the desired therapeutic window in the heart, for a prolonged duration. Intentionally, this review does not go into depth about targeted immunotherapeutic or endothelial approaches to reduce inflammation and adverse cardiovascular events, which have been broadly presented in the literature [4–6].

2. Local drug delivery

Treating the pericardium directly and locally allows for drug perfusion to the entire heart. Efficient and localized delivery of agents to the pericardium could be beneficial for the treatment of numerous cardiovascular diseases. Some examples include using the pericardial space as a drug delivery reservoir to administer heparin-binding growth factors to induce angiogenesis in chronic myocardial ischemia [7], antiarrhythmic agents for atrial fibrillation [8,9], and streptokinase for purulent pericarditis [10]. Localized drug delivery to the pericardium, however, has been considered invasive, where the pericardium is often left open after surgery [11]. Intrapericardial (IPC) delivery has also been limited because the pericardial volume is relatively small and difficult to access by standard pericardiocentesis without invasive surgery or risk of cardiac injury [12,13]. Approaches are emerging to overcome these limitations and there is demand for less invasive cardiac procedures. With the prevalence of heart failure increasing, and it continually ranking as the leading cause of morbidity and mortality worldwide [14], intrapericardial delivery may provide a bridge to transplantation therapy to assist patients and improve quality of life.

Targeted local drug delivery is considered more advantageous over systemic approaches such as oral and intravenous (IV) administration. Common problems with oral and IV delivery approaches include patient variability, broad therapeutic window, ingestion/absorption in the blood stream, and whole body drug exposure, which can result in undesired off-target side effects. Local delivery is preferred due to increased drug concentration to the target tissue, minimization of adverse systemic effects, reduced quantity of drug needed, reduced variability, and increased therapeutic half-life. Additionally, the low solubility of some therapeutics requires treatments based on a local delivery approach. Recent reports have demonstrated these advantages when applied to the heart [15–17]. For example, local intrapericardial administration of sodium nitroprusside was shown to abolish cyclic coronary flow variations in dogs at a smaller dose and with higher percent success rate, yielding a safer and more effective approach than when administered intravenously [18]. This is worthy of attention as nitric oxide donor therapeutics administered *via* the venous system could be detrimental. Amiodarone, a drug used for managing supraventricular arrhythmias, was continuously infused intrapericardial for 72 h in adult sheep, and the drug concentrations in cardiac biopsy specimens, along with its active metabolite, desethylamiodarone, were similar to, or higher than, those reportedly observed in patients taking long-term oral amiodarone [19]. This report is further significant, as while amiodarone is a powerful and effective antiarrhythmic and its use is increasingly more wide-spread, it carries the risk of severe extracardiac side effects due to systemic toxicity, such as pulmonary fibrosis, hepatic toxicity, and clinical thyroid disease [20]. There are also cases in which patients have a diminished local blood supply, for example in occlusive coronary artery disease, whereby systemic administration of substances to the heart or coronary circulation would be hampered [21]. Advantages of intrapericardial delivery include short term dosing to rapidly achieve therapeutic levels in the heart while minimizing systemic drug distribution, thereby decreasing the risk of systemic complications as well as reducing the amounts of drug needed and limiting exposure to livers and kidneys, typical sites for drug metabolism.

Intrapericardial delivery may be one approach to overcome drug induced liver toxicity. Lazarous et al. [22] demonstrated that IPC administration produced the highest level (~20% recovered) of retained basic fibroblast growth factor (bFGF), an angiogenic peptide, in the heart, when compared with four other routes of injection: left atrial, Swan Ganz (SG), IV, and intracoronary (IC) into the left anterior descending (LAD) coronary artery, which all had drug recovery levels equal to or lower than 5%. It was also noted that with the exception of IPC delivery (3%), all other methods led to a large fraction (11–40%) of bFGF found in the liver, which can result in liver fibrosis. This is also significant because increased myocardial exposure to a therapeutic of interest, such as bFGF, should result in improved efficacy. In another study involving use of the same select agent of interest, bFGF, agent washout time was compared between endoluminal (EL) and IPC local delivery [23]. It was found that the average time following IPC delivery for washout was slower (approximately 3.4 times) than EL delivery. Because of the

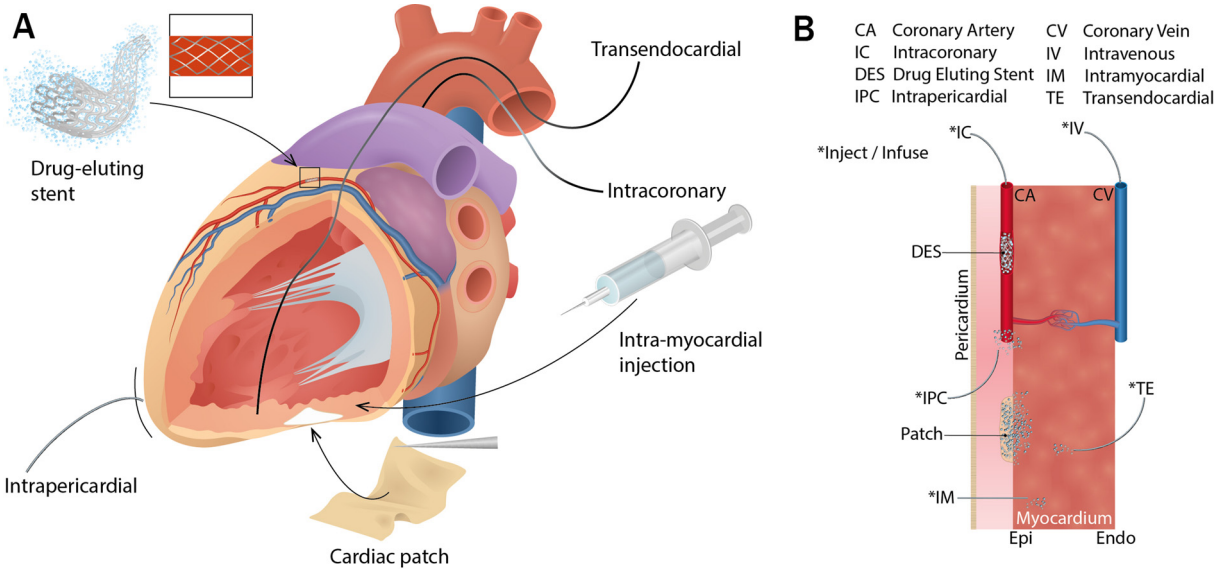

Fig. 1. Current clinical approaches for therapeutic delivery to the heart: (A) schematic and (B) stylized versions. Note that IC infusion is not chronic.

importance in establishing drug pharmacokinetics within the myocardium, mathematical models [24,25] are also being developed and employed to determine drug washout rate, permeability of pericardium and epicardium boundary, and effective drug diffusion constant. Sustained drug levels due to increased residence time as a result of pericardial delivery further demonstrates its advantages over other routes of administration.

3. Current strategies for IPC drug delivery

Direct, local injections and pumps to the pericardium are currently the main methods for therapeutic delivery. Besides these common methods of injections and/or infusions through catheters (*e.g.* transendocardial, intracoronary, and intrapericardial), other clinical approaches to deliver drugs to the pericardium include drug-eluting patches, and stents, as seen in Fig. 1A. Drugs can perfuse from local sites to other tissues in the heart depending on the delivery approach (Fig. 1B). Intrapericardial injection is a good approach when, for example, an injection of agents into the coronary artery may not reach an infarcted area due to conjugation with the extracellular matrix at the site of coronary lesion [26]. Injection is also typically performed for treatment of pericardial effusion accumulation. It is used for treatment with corticosteroids in patients with recurrent uremic pericarditis or connective tissue disease, particularly lupus erythematosus, which encounter life threatening effusions. For procedures where a needle or catheter is needed to be safely placed, patients are required to have sufficient fluid in the pericardium [27]. Possible complications with direct injection include altered efficacy depending on whether the treatment, such as cellular delivery, are administered to viable myocardium or hypoperfused and/or infarcted myocardium [28] and needle-induced microtrauma. Although these complications can lead to trauma, the ability to precisely administer through a direct approach, may be leading physicians to continue to prefer this method.

In a research setting, intrapericardial injections have been reported as particularly difficult procedures to perform in small rodents [29], limiting the spectrum of *in vivo* models of cardiovascular diseases and leading researchers to favor larger animal models. Richardson et al. [13] utilized a porcine model and tented the pericardium with suture to form a reservoir for drug or saline delivery. They showed that the therapeutic effect of IPC-administered metoprolol was sustained approximately twice as long as the IV group, which was considerably reduced after just 1 h. They also noted negligible detectable amounts of metoprolol within the plasma when given IPC. Such preclinical studies demonstrate the advantages of localized IPC drug delivery and provide a foundation to advance current clinical strategies for pericardial access and drug administration.

4. Sustained IPC delivery

4.1. Catheters and pumps

4.1.1. Catheters

Catheterization alone has been used to treat malignant pericardial effusion through fluid drainage and prolonged intrapericardial injection of therapeutics. For example, co-delivery into the pericardium of an antineoplastic, such as cisplatin [30] or picibanil (OK-432) [31], with various antibiotics or radioactive compounds, can help patients can achieve a longer-lasting response to treatment with better control over local disease progression. Furthermore, treatment techniques utilizing catheters that allow for bi-directional fluid exchange are advantageous as they provide physicians an alternative to partial or complete pericardial removal. When coupled with a pump, this combination can allow for both therapeutic administration and fluid sampling in a more continuous and long-term fashion.

4.1.2. Osmotic pumps

Drugs of various molecular weight (MW) and physical and chemical properties can be dispensed continuously and at controlled rates through the use of an osmotic pump coupled to a catheter. These pumps typically consist of an inner drug reservoir, separated from an osmotic compartment by a rigid piston or flexible bladder. As fluid from the body is absorbed into the osmotic compartment, the increased pressure acting on the piston or bladder exerts a force that pushes the drug solution out of the drug reservoir, into the body, through a delivery orifice [32]. Different dosing rates can be achieved by varying the formulation and concentration of agent in the reservoir. Hermans et al. [21] coupled pericardial catheters with subcutaneously implanted osmotic minipumps to compare the pharmacokinetic profiles of various compounds that were either continuously infused or administered as a bolus. The authors showed that when macromolecules or steroids are infused into pericardial space for seven days, it results in relatively high pericardial fluid concentrations and low plasma concentrations as compared to bolus injections. Overall, they concluded that if substances are infused into the pericardial space, their concentration in pericardial fluid will be relatively high, due to low clearance of the substances in the pericardial fluid compared with higher clearances in the

blood. This slow clearance of agents or entrapment into pericardial space through the use of catheters can be leveraged to prolong treatment. Van Brakel et al. [33] performed a similar subcutaneous implantation of osmotic minipumps coupled to pericardial catheters to demonstrate the efficacy of sustained IPC infusion of the antiarrhythmic drugs, sotalol and atenolol for seven days. They observed antitachycardiac effects at doses 10- to 30- times lower when compared to IV delivery. As another example, Landau et al. [34] successfully implanted osmotic pumps in a subcutaneous pocket in the neck of rabbits for continuous infusion of bFGF into the intrapericardial space through use of a catheter for up to four weeks. However, the use of these pumps have been criticized as bulky and burdensome, requiring special placement and anchoring, tubing attachment, priming, and incubation time to activate drug infusion. Additionally, after implantation the pump positioning needs to be checked and patency maintained.

4.1.3. Other pumps

Aside from osmotic pumps, pericardial catheters have also been coupled with peristaltic pumps. Dave et al. [35] used a peristaltic pump to perfuse lactated Ringer's solution into the pericardial space of rabbits without a net accumulation of fluid. This procedure was done to cool the pericardial space to reduce myocardial infarct size and minimize necrotic damage, offering cardiac protection during coronary bypass surgery. Although reports of intrapericardial administration with programmable syringe pumps are more difficult to find, use of these pumps have been reported for IV [36] as well as IC infusion [37] and are advantageous for delivering drugs with short half-lives [38].

While it is clear that an IPC catheter-pump combination system is advantageous in that it can provide continuous and sustained heart encompassing therapeutic administration, it should be noted that IPC infusion does not allow for specific heart chamber-targeted drug delivery because the drug will diffuse into the atrium as well as the ventricular epicardium [39]. Further, drug clearance from the pericardium is likely dependent on a number of molecular properties including solubility and MW; for example, a smaller MW results in a more rapid clearance [40]. Despite these shortcomings, pumps have still proven to be promising systems for controlled drug delivery.

5. Localized tissue delivery

5.1. Patches

Myocardial patches offer another approach for the delivery and retention of agents, such as stem cells [41,42] and growth factors [43,44] for cardiac repair, or medications for the treatment of cardiac arrhythmias or endocarditis [45,46]. Patches are especially advantageous as a pericardial substitute after cardiac operation for complete closure of the pericardium [47]. Myocardial patches are typically composed of gel, collagen, or other biocompatible materials. Bovine pericardium is one example of a patch material commonly used after arteriotomy in cardiovascular surgery and has several advantages compared with prosthetic systems, including superior biocompatability, easy handling, less suture line bleeding, and possibly reduced rates of infection [48]. Cardiac patches can provide mechanical restraint, preventing dilatation associated with ventricular remodeling [49]. Patches also allow for customizability for a variety of cardiovascular applications and conformity to complex anatomy [50]. Vashi et al. [51] evaluated the CardioCel® scaffold, a commercial material derived from bovine pericardium that is stabilized *via* the ADAPT® process, which includes low concentration glutaraldehyde and other steps to eliminate calcification after implant. Calcification of pericardial grafts post implantation is attributed to glutaraldehyde processing and causes valve failure, limiting durability. The researchers showed that the CardioCel® material was suitable for the attachment, growth, and delivery of human bone marrow mesenchymal stem cells and that the substrate has the potential to act as a template for cell propagation and new tissue formation. Guldner et al. [52] nanocoated pericardial grafts with titanium to prevent immune reactions and calcification. The titanium coating significantly reduced antibody deposits and the immune response of glutaraldehyde-fixed pericardium, offering a method to prevent immunorejection and increase durability. While patches placed on the epicardium can be effectively utilized to deposit intrapericardial stem cells and improve the perfusion and microvascular density of scar tissue [53], it should be noted that in an infarcted heart, blood supplies to the implanted patch from the surrounding tissue might be significantly reduced or completely shut off, which may negatively influence myocardial remodeling. Limitations with patches include burst release kinetics immediately after application, followed by a decay tail in drug concentration, which can reduce patch efficacy over time. Also, patch degradation products might cause local inflammation and/or fibrosis after application. Continual development of cardiac patches as well as improvements in their integrity and biodegradability may with time increase their success for clinical application.

5.2. Drug eluting stents

Drug eluting wafers, stents, and drug coated balloons can provide local delivery of agents into the arterial wall. These are considered endoluminal local delivery approaches and have been found to be limited by short residence time, as well as highly variable deposited agent concentration [23]. They are also associated with relatively rapid washout of the agent from the target vessel [54]. Drug may be absorbed into the stent material itself, similar to a sponge, where release occurs due to diffusion or material degradation, chemically bonded to the surface and released as the result of a chemical or biological action, or the drug may be physically coated. Stent elution pharmacokinetics (PK) of Biolimus A9, a rapamycin derivative specifically developed for local delivery to the coronary arteries, have been reported in the NOBORI PK study [55] and the Stealth PK study [56]. These studies examined two different biodegradable poly-lactic acid stent platforms implanted in patients with coronary artery disease: Nobori coronary stents, where abluminal (vessel contact) drug coating was achieved by spray coating, and the BioMatrix II stent, abluminally coated using a unique automatic micropipette coating process. Abluminal stent coating is performed so that lipophilic Biolimus A9 is directly released into the vessel wall and minimal drug is distributed into peripheral circulation. When compared to other drug-eluting stents, both studies showed relatively low systemic drug exposure, with the Stealth PK Study demonstrating higher maximum and greater area under the time–concentration curve (AUC) Biolimus A9 concentrations. Further, in the Stealth PK study after 9 months, 100% of the patients were free of major adverse cardiac events; thereby demonstrating promising clinical application warranting further evaluations. While many people with heart problems have been successfully treated with drug-eluting stents, which helps prevent the use of more-invasive procedures, their deployment is not without risk. For example, they can result in complications such as inflammation and localized coronary artery aneurysms adjacent to the stent [57]. Thus, clinicians and patients alike must carefully balance the associated risk with potential therapeutic benefit.

5.3. Cardiac support devices and meshes

Cardiac support devices coupled with slow release therapeutics offer another approach to enhance therapeutic effects and prolong delivery. Such support devices may consist of a mesh net, composed of polyglycolic acid [58] or polyester [59,60], placed over the ventricular epicardium, similar to a woven polyester jacket. Their function is to reduce diastolic ventricular wall stress and prevent left ventricular dilatation. When coupled with a slow-release synthetic prostacyclin agonist ONO-1301 in a canine model, the hybrid therapy elicited a greater reversal of left ventricular remodeling than either treatment alone, suggesting the potential of this strategy for the clinical treatment of

ischemia-induced heart failure [58]. Meshes may also be tailored to particular heart anatomy and structurally and electrically integrated to deliver electrical impulses to improve cardiac function in models of heart failure. Made from silver nanowires embedded in a rubber polymer, an electric mesh fabricated by Park et al. [61] was shown to act as an epicardial defibrillator and regulate heart beating patterns in rodents. While pacemakers deliver electrical stimulation at only specific places in the heart, this approach provides a more comprehensive coverage to the entire heart.

5.4. IPC gene delivery

Intrapericardial delivery is being explored as a mode of delivery for gene transfer. For example, recombinant genes can be used to enhance myocardial collateral blood vessel function, which may represent a new approach to the treatment of ischemic cardiovascular disease [62]. Atrial fibrillation could also be treated or prevented through site specific gene transfer, as conventional antiarrhythmic drug therapy is often inadequate with atrial fibrillation reoccurrence in ~50% of patients within 1 year of treatment [63]. Typically, plasmid DNA encoding for factors, such as VEGF for treatment of angina, have been performed *via* direct myocardial injection [64]. Since the effect of blood flow can hamper localized vector uptake in the vessel wall [65], delivery of gene products into the pericardial space provides an alternative approach for efficient gene therapy. Vector delivery directly into the pericardial sac allows for diffusion of the gene products or their metabolites into the epicardium as well as sustained release due to the natural closed reservoir structure, which restrains rapid elimination of the gene vectors [66]. Some researchers have critiqued this approach, citing minimal vector penetration beyond the epicardial layer [63]. Others, however, have proven larger diffusion of transgene activity, reaching up to 40% of the myocardium, by injecting a mixture of collagenase and hyaluronidase together with the virus into the pericardial sac [67]. Pericardial gene transfer was performed by Woody et al. [68] in adult dogs to more widely distribute the delivery of recombinant adenovectors over that achievable through direct injection. The researchers found high-efficiency transduction of the pericardial sac and epicardial tissue as well as the ability of this tissue to secrete recombinant protein products locally. However, it should be noted that the tight junction of pericardial cells has led some researchers to hypothesize that the pericardium acts as an anatomical barrier to gene transfer, deterring further investigation [67,69,70]. Additionally, due to safety, efficacy, and ethical issues, gene transfer therapy has not been further implemented beyond early-phase clinical trials, such as the CUPID study [71]. Re-evaluating current vectors, delivery systems (such as liposome mediated transfer discussed in a later section), targets, and endpoints may help make gene transfer a more effective therapeutic approach.

5.5. Minimally invasive access to the pericardium

Minimally invasive access to the normal pericardial cavity can be achieved through subxiphoid, transatrial, and transvenous approaches. Instead of a thoracotomy, a small incision below the xiphoid processes can be made to drain pericardial fluid (pericardiocentesis) or access epicardial substrate, such as subepicardial myocardial fibers for ventricular tachycardia. The subxiphoid approach is considered relatively safe in the presence of a pericardial effusion, however, when effusion is not present, there is fear of myocardial puncture and coronary artery laceration, such that it is not commonly attempted. According to Laham et al. [72], percutaneous *subxiphoid access* to insert a catheter for fluid delivery volumes as large as 50 ml can be safely and rapidly achieved to a non-fluid-filled pericardium without delivery related myocardial damage. This can be performed by advancing an epidural introducer needle gently under fluoroscopic guidance with a continuous positive pressure of 20–30 mmHg by saline infusion using an intraflow system. Positive pressure is used to push the right ventricle away from the needle's path. An increase in the saline flow indicates entry into the pericardial space, which is then confirmed under fluoroscopy through use of diluted contrast. Following confirmation of successful entry, a soft floppy-tip 0.025″ guidewire can then be advanced and the needle exchanged for an infusion catheter [72]. This approach was used on 42 patients where no long-term follow-up complications were detected [73]. Subxiphoid access, however, can be considered challenging for electrophysiologists because of this risk of right ventricular puncture.

An alternative to access the normal pericardial space is percutaneous *transatrial access*. Drug delivery or fluid sampling of the normal pericardial space can also be achieved by piercing the right atrial appendage (RAA) [74,75]. This procedure was performed by Scanavacca et al. [76] for epicardial mapping and ventricular tachycardia ablation in a swine model. Puncture of the RAA was also demonstrated in swine by Kumar et al. [77] for intrapericardial administration of the nitric oxide donor, nitroglycerin, for protection against myocardial ischemia-induced arrhythmias. Closure of the puncture can be achieved using a patent foramen ovale closure device [76] to prevent cardiac tamponade or spontaneous formation of a fibrinous plug at the site of puncture [78]. While access through the RAA has been successfully demonstrated in several studies [79], one significant challenge that may be hindering its more widespread use is precisely locating the appendage tip under fluoroscopy.

Catheter-based *transvenous access* to the pericardial space has also been demonstrated by Mickelson et al. [80] in a porcine model as a feasible approach to aid in the implantation of chronic medical devices, such as epicardial pacing leads. While all of the animals survived the procedure, the study timeline was relatively short (acute sacrifice and sacrifice after two and six weeks); two of the eight animals exhibited significant over-procedural pericardial effusion; and, finally, the technique would need further development in appropriate heart failure models.

5.6. Devices for pericardial access

The PerDUCER is a pericardial access device whose utility has been examined in swine [81] and humans [12,82] as a safe and effective technique to gain pericardial access in the normal or minimal pericardial space to obtain diagnostic sampling of pericardial fluids, for guidewire placement into the pericardial cavity, or for local intrapericardial delivery. As seen in Fig. 2, it contains a 21-gauge introducer needle located

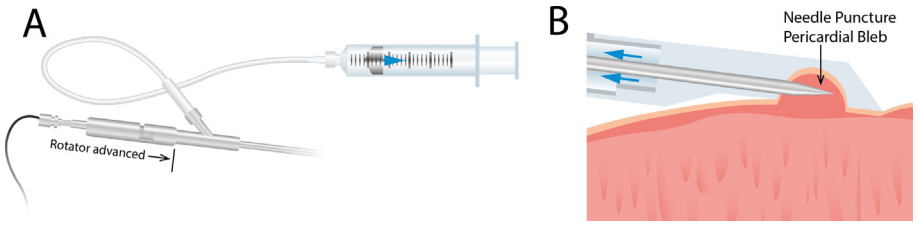

Fig. 2. Device access strategies to the pericardium (PerDUCER). (A) Illustration of the PerDUCER pericardial access device showing its handle and suction syringe and (B) pericardial puncture. Adapted from M. P. Macris, S. R. Igo, Clin. Cardiol. 1999, 22, I36–39 [12].

inside a stainless steel sheath, which ends with a plastic view tube and a hemispheric side hole cavity, where the pericardium is captured by vacuum and then punctured by an introducer needle [83]. The device enables percutaneous pericardial access, even in the absence of pericardial effusion [84], which is significant because intrapericardial therapy and diagnosis was restricted to patients with pericardial effusions [85]. The procedure for PerDUCER insertion has been well-tolerated without significant adverse hemodynamic effects [81]. However, initial clinical application of the PerDUCER has been only partially successful, with higher success of the procedure occurring when pericardioscopy is performed from the anterior mediastinum to enable visualization of portions of the pericardium suitable for puncture, thus avoiding fat deposits, which may compromise pericardial capture [82,84].

Aside from the PerDUCER, other devices have been described in the literature and deployed for pericardial entry. One such example is a prototype of a novel subxiphoid access system that uses pressure-frequency measurements to locate and facilitate access into the pericardial space. Specifically, the pressure-frequency change between pericardial and thoracic space offered a good indicator that pericardial entry was achieved. The system was tested in a pilot series of human clinical studies, where all patients (8) had successful pericardial access and subsequently were able to undergo epicardial ventricular tachycardia ablation [86]. Positive pressure has also been used in another device, described by Laham et al. [72], which when entering the pericardium, pushes the right ventricle away from the needle tip. Pericardial entry was confirmed through a 1 ml diluted contrast injection under fluoroscopy. This method has been tested on 49 Yorkshire pigs where pericardial access was attained without any adverse events or hemodynamic compromise. Histological assessment on a subset of the animals confirmed no cardiac damage after four weeks.

The Cooper Retractor is another device that was traditionally designed for transcervical thymectomy, but in certain situations can be repurposed to aid in performing a subxiphoid pericardiotomy for treating malignant pericardial effusion [87]. Its advantages include greater exposure of the operative field, especially in the case of obese patients, as well as the potential for local as opposed to general anesthesia, and decreased operative time. Further development of these devices to aid in instrumenting the pericardium while maintaining its integrity may help facilitate advancements in pericardial therapeutics and diagnostics.

5.7. Pericardial washout and fluid analysis

Catheters as well as other devices used to access the pericardium allow for both the delivery of agents as well as sampling and analysis of pericardial fluid. This is beneficial, for example, to find the cause of a pericardial effusion or identify organisms that cause infection. Irrigating the pericardial space with a warm saline solution as a postoperative treatment may reduce complications, such as risk of cardiac tamponade, blood loss, and accumulation of blood and clots in the pericardial cavity. Additionally, sampling and analysis of pericardial fluid composition may offer insight into potential patient abnormalities and can be used to aid in diagnosis. For example, post-mortem individuals with severe atherosclerosis of their coronary arteries showed higher levels of Apo B in their pericardial fluid compared to individuals without atherosclerosis. Also, a significant increase of Apo B was found in cases with a positive diagnosis of myocardial infarction [88]. Studies also report that patients with different forms of heart disease have activated lymphocytes and multiple cytokines in their pericardial fluid [89].

High concentrations of immunoreactive endothelin-1 (ET-1) have been measured within the pericardial fluid of humans undergoing cardiac surgery due to heart disease [90,91] as well as in canine [92–95] pericardial fluid. ET-1 is a peptide that has demonstrated the ability to induce vasoconstriction [96]. Further, when administered into the epicardium, it has been linked to cause diminished blood flow, providing evidence that reducing the presence of this immunoreactive protein in the pericardial fluid through saline irrigation may improve coronary circulation in patients [97]. Other agents characterized in the pericardial fluid and associated with poor cardiac outcomes include: atrial natriuretic peptide (ANP) [91,98,99], brain natriuretic peptide (BNP) [100,101], fibroblast growth factor (FGF) [102–105], vascular endothelial growth factor (VEGF) [104,106,107], adenosine [108–110], 8-iso-prostaglandin F2alpha (8-iso-PGF2alpha) [111,112], interleukin (IL)-1beta and IL-6 [113–116], adrenomedullin [117], endostatin [118], and heart-type cytoplasmic fatty acid-binding protein (H-FABP) [119]. However, it should be noted that others have reported nonstatistical significance between patients with ischemic and nonischemic heart disease for some of these cytokines and growth factors [120] as well as dependency on patient treatment variables prior to surgery, such as heparin administration [121]. Alternatively, elevated levels of certain proteins and growth factors, such as ferritin [122] and basic fibroblast growth factor (bFGF) [123], have been shown to provide myocardial protection and mediate collateral development, thereby acting as self-protecting mechanisms against cardiac disease progression. Further, angiogenic growth factors, which can accumulate in the pericardial fluid can contribute to angiogenesis, are self-protecting against myocardial ischemia [124]. Sampling the pericardial fluid and subsequent culture with various cell lines (*i.e.* cardiac myocytes, aortic vascular smooth muscle) can help elucidate cell signaling pathways, which lead to growth or apoptosis [123,125–127]. Taken together, these studies have indicated the complex physiological composition of the pericardial fluid and highlight that its analysis prior to medical intervention holds prognostic value and may aid in assessing a patient's physiological state.

5.8. Biodegradable micro-nanoparticles

Drug delivery through biodegradable micro- or nanoparticles offer another way to target therapeutics to specific tissues and maintain sustained release (Fig. 3). Poly(lactide-co-glycolide) (PLGA) particles have been explored and evaluated as drug delivery systems [128,129], and as opposed to polyurethane matrices, PLGA is biodegradable. Intrapericardial administration of PLGA nanoparticles have been shown to enhance payload myocardial distribution and retention [130]. This strategy allows for prolong drug retention in the pericardium based on physical size, chemical properties, and formulation. Unfortunately, intrapericardial infused PLGA microspheres have shown similar atrial and ventricular drug concentrations [131], indicating that this approach did not allow targeting of one specific myocardial region.

Besides PLGA, poly(cyclohexane-1,4-diyl acetone dimethylene ketal) (PCADK) is another biodegradable polymer formulated to generate drug loaded microspheres. Sy et al. [132] encapsulated the p38-inhibitor SB239063 into microspheres formulated from PCADK and resulted in improved treatment of myocardial infarction (MI) by inhibiting p38 phosphorylation and reducing superoxide and the inflammatory cytokine TNF-α levels. Further, while there is concern that PLGA degradation may increase inflammatory cytokine production [133,134], PCADK offers an alternative biocompatible polymer that may avoid eliciting an inflammatory response. This can be attributed to the stability of polyketals, which degrade into neutral products only in the presence of reactive oxygen species existing in and around inflamed tissue, making them ideal for the treatment of cardiac dysfunction, such as MI. Overall, there is consensus that nanomedicine is poised to have an important impact on the treatment of cardiovascular disease through diagnostic and therapeutic improvements of cardiovascular disorders such as atherosclerosis, restenosis, and myocardial infarction [135].

5.9. Microencapsulated cells

Alginate-poly-L-lysine-alginate has been widely used to microencapsulate a variety of cell types prior to cell transplantation [136]. This

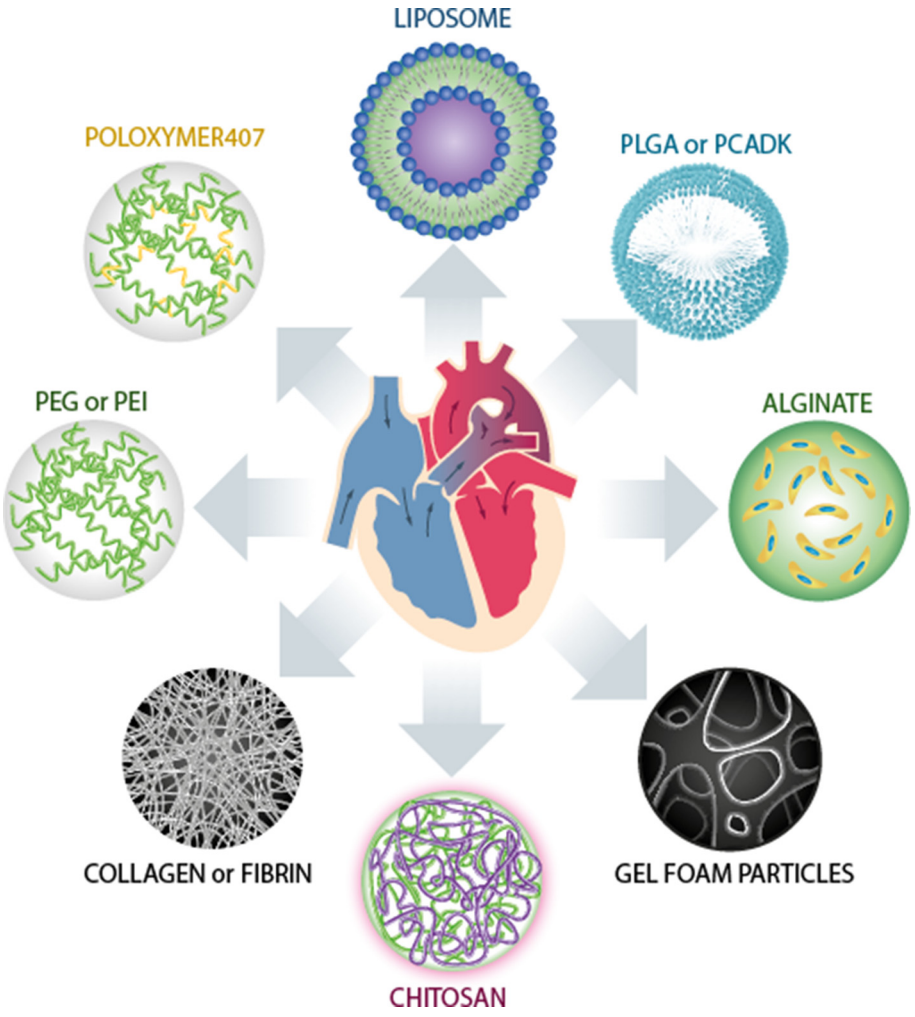

Fig. 3. Micro- and nanoparticles (np) and materials for therapeutic delivery to the heart.

is also the case for human mesenchymal stem cells (MSCs) for pericardial delivery. In one study, alginate was coupled with x-ray and magnetic resonance imaging guidance to monitor and track mesenchymal stem cell retention for the treatment of cardiac disease [28]. Alginate microencapsulation provides additional advantages especially for cell encapsulation as it offers a porous layer while providing immunoprotection for the encapsulated material. Moreover, methods for alginate hydrogel microencapsulation have shown flexibility for use with various cells types, as they can generate microcapsules of different diameters, degradation time, and composition [137]. Yang et al. [138] has shown that bFGF/VEGF embedded in alginate beads sutured to the cryoinjured epicardium increased left ventricular wall thickening and perfusion of the infarcted tissue. Treatment through an encapsulated approach allows for the sustained release of factors, whereby larger microspheres offer greater stability, protection from enzyme degradation, and visibility.

Other hydrogel materials used to encapsulate cells include gelfoam [139,140], chitosan [49,141], fibrin [142], and collagen [143,144], which also act as injectable materials for the delivery of various growth factors [50]. Gelfoam is a Food and Drug Administration (FDA) approved absorbable sponge material that can be intrapericardial injected using a percutaneous approach by safely puncturing the pericardial sac under fluoroscopy and intravascular ultrasound (IVUS) guidance [140]. Gelfoam particles, essentially gelatin sponge, were shown to dissolve in pericardial fluid *in vitro* after about 8.4 days at 38 °C under gentle agitation. Gelfoam can be used to carry biological agents such as mesenchymal stem cells and genes or therapeutic drugs and as a releasing platform. Chitosan nanoparticles coupled with plasmids have demonstrated improved target gene expression when compared with simple transfected genes [145], and since chitosan is temperature responsive, it also offers an injectable scaffold [146,147]. Examples of cell types that have been encapsulated in chitosan include adipose-derived mesenchymal and embryonic stem cells [141,146,147]. Fibrin glue has also been injected with a percutaneous intrapericardial approach for fixation therapy due to left ventricular free wall rupture, offering an alternative to surgical repair [148,149]. It can also be used as a cell delivery vehicle, for example for mesenchymal stromal cells [142], and as a matrix to deliver therapeutic angiogenic agents. Collagen is another injectable biomaterial that provides a matrix for improved retention of stem cells by reducing washout through the vascular system and cell relocation. Dai et al. [150], however, did not see improved cardiac function or remodeling when MSCs in collagen were intramyocardial injected as compared with a saline plus MSC group and hypothesized this was due to collagen interference with the diffusion of oxygen and nutrients through the interstitial space, cell-to-cell communication, or some other unknown toxic effect on the transplanted cells. Ultimately, the authors concluded that collagen may not be an optimal biomaterial to use for a cell-delivery vehicle.

Although not encapsulated, autologous endothelial progenitor cells (EPCs) were delivered IPC by Saltzman et al. [151] in a porcine ischemia model through a percutaneous transatrial approach. The cells were shown to migrate and target an area of need by honing into areas of ischemia and incorporating into the myocardium. This is advantageous as EPCs are associated with neovascularization and preservation of LV

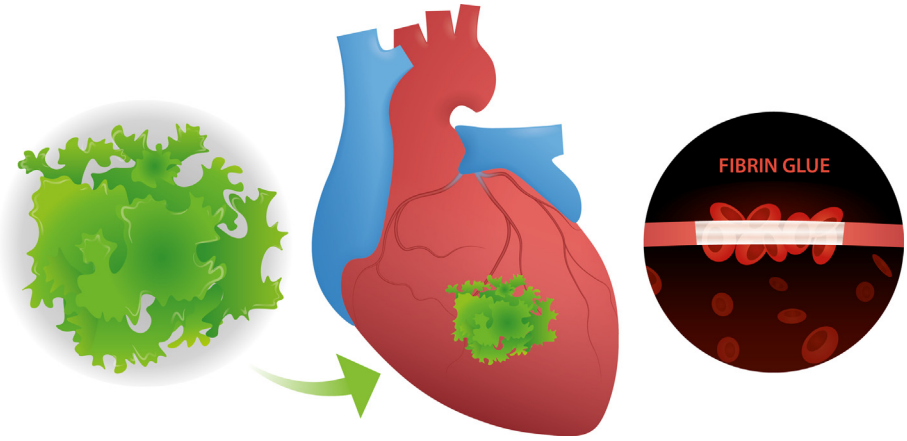

Fig. 4. Drug and cell release matrices.

function. The authors confirm that IPC delivery provides an efficient route of delivery which may overcome the limitations of other administration routes, such as 1) dispersion outside the target tissue to the liver and spleen, 2) access to all areas of ischemia regardless of coronary occlusion, and 3) increased EPC exposure time and concentration to the target tissue, which may allow for a decrease in the number of cells needed for treatment.

5.10. Drug and plasmid releasing matrices

Similarly to the surgical use of fibrin glue as a sealant (Fig. 4), biodegradable poly(ethylene glycol) (PEG) polymers that form a hydrogel comprise the two-component surgical sealant, CoSeal®. When placed on the epicardium, PEG-based biomaterials such as CoSeal® can aid in the prevention of pericardial adhesions after cardiac surgery [152]. When combined with the therapeutic amiodarone and applied to the right atrial epicardium, Bolderman et al. [153] successfully achieved a drug-releasing matrix capable of sustained (>2 weeks) suppression of atrial tachyarrhythmia. Other drug releasing matrices include polyethyleneimine (PEI), a polymer with a high density of positive charges, widely used as a gene carrier, and Poloxamer 407, a triblock copolymer consisting of a central hydrophobic block of polypropylene glycol flanked by two hydrophilic blocks of PEG comprising a thermosensitive gel. Poloxamer 407 has also been used as a formulation for intrapericardial administration of plasmid DNA to improve retention time at the site of injection [69].

Liposome mediated transfer is an additional method for *in vivo* gene delivery into the heart. Liposomes offer an extra advantage as an intravenous gene therapy vector; however, this is not an ideal administration route as it has been found to result in transfection of many organs, particularly the lungs [154]. Specifically, the Hemagglutinating Virus of Japan (HVJ)-liposome complex has been used in the rat myocardium for transfection of a human hepatocyte growth factor (HGF) gene [155,156] as well as a β-galactosidase gene, luciferase reporter gene, and human angiotensin converting enzyme (ACE) gene [157], among others [158,159]. Preparation of the HVJ-liposome complex includes a lipid mixture of phosphatidylserine, phosphatidylcholine, and cholesterol. When a pericardial incubation approach of the HVJ-liposome complex containing vector was compared with direct injection into the apex of the heart with a needle, researchers found a broader area of transfection [157]. Further, the pericardial incubation approach avoids the need of a direct injection into the myocardium, which was noted to recruit neutrophils and cause necrosis at the puncture site [157]. Therefore, a pericardial incubation approach to liposome mediated gene transfer may result in greater transgene expression throughout the heart as well as less inflammation and injury.

5.11. Potential new avenues

Aside from drug eluting particles and matrices, sustained administration of cardioprotectants from an implantable nanochannel drug delivery system (nDS) offers a novel treatment method for long-term sustained release. This can be achieved by exploiting nanoconfinement and molecule-to-surface interactions that dominate diffusive transport at the nanoscale [160], which has been demonstrated for the release of cardiovascular drugs such as atorvastatin and trans-resveratrol [161], as well as atenolol and perindopril [162]. Membranes with nanochannels can be either passively or actively modulated thereby manipulating drug flow to remain within a desired therapeutic window at treatment specific time intervals. In the context of HIV [163], breast cancer [164,165], and metabolic disease [166-168], implants mounted with nanochannel membranes have shown promise in both the prevention and amelioration of these diseases. It is quite logical to expand their application beyond specific tumor or adipose tissue targeting toward the treatment of heart disease, where low cost, effective treatments are urgently needed.

Another area of opportunity for long term therapeutic release into the pericardium would be to couple treatment agents with an already established clinical treatment for patients with advanced heart failure, such as the use of left ventricular assist devices (LVADs). These implants were formally intended to provide circulatory support for patients awaiting heart transplants, but have since evolved and improved survival rates and are now being used as a destination therapy. Early first generation LVADs, such as the HeartMate I® (Thoratec Corp., Pleasanton, CA), Thoratec PVAD™ (Thoratec Corp., Pleasanton, CA), and Novacor N100 (World Heart, Inc., Oakland, CA), were known as volume displacement devices that created pulses to facilitate blood flow, mimicking the physiological action of the heart [169]. Unfortunately, main limitations of these devices were their size and mechanical durability, which led to discomfort and risk of significant complications for long-term support. However, they did ultimately increase survival when compared to medical therapy alone, as demonstrated in the study REMATCH, leading researchers to create second generation LVADs [170]. These improved devices utilized continuous axial flow pumps, which provided constant flow rather than pulsatile. Although initially met with skepticism, the lack of pulsatility did not necessarily correlate with end-organ function [171], eventually leading to acceptability within the scientific and medical communities. Further development led to third generation devices, such as the HeartMate III (Thoratec Corp., Pleasanton, CA). The ingenuity of this device is its bearingless design, which utilizes magnetic and hydrodynamic levitation of an internal impeller to yield advantages including lower rotational speeds, higher efficiency, and enhanced anatomical design [169]. This device is also designed for intrapericardial implantation, thereby better

contouring the heart and not requiring dissection of an upper abdominal pocket [172]. Not only does this design result in shorter implantation times, but also, due to its placement, IPC therapeutic delivery can be easily incorporated, which may aid in improved long-term survival rates.

Other notable treatment avenues include functionalizing particles with targeting moieties, such as E-selectin-targeting to inhibit the formation of atherosclerotic plaques [173] and vascular targeted nanocarriers [174] for treatment of atherosclerosis and other vascular diseases. Dvir et al. [175] used overexpression of the receptor angiotensin II type I (AT1) in the infarcted heart as a target for PEGylated liposomes conjugated with a ligand specific for AT1. The authors first verified *in vitro* in cardiac cells (ventricular myocytes isolated from rats) a 3-fold increase in the expression of the AT1 receptor after exposure to hypoxia when compared with cells grown under normal conditions. The phenomenon was then verified *in vivo* in a mouse model by occluding the left coronary artery with an intramural stitch, resulting in left ventricle MI. Finally, fluorescently labeled AT1 functionalized particles were compared with particles functionalized with the same amino acids in a scrambled order and injected into the right jugular vein after MI, yielding statistically significantly higher levels of AT1 nanoparticles compared to scrambled particles on days 1 ($p = .05$) and 7 ($p = .02$) post infarction. This approach could be further exploited to reduce systemic toxicity and increase local therapeutic effect of a candidate drug. In the context of cancer, active nanoparticle targeting is on the rise, yet its clinical validation is limited and not easily achieved [176]. Such delay in clinical implementation in the field of cancer, one of the most actively studied disease fields, will likely propagate into the field of cardiovascular disease as well. Functionalization combined with diagnostic and therapeutic capacities hold the promise for theranostic approaches related to atherosclerosis, coronary artery disease, and myocardial infarction [177]. Further, scaffolds that contain microneedles, which have been demonstrated for treatment of obesity [178] could be easily adapted to contain cardiovascular drugs with a modified local placement onto the epicardium, similar to other patches used clinically.

6. Conclusions

Intrapericardial delivery of agents has been limited by the lack of proven access methods to the pericardial space that are familiar to clinicians, since the therapeutic potential derived from direct access to this space is yet to be fully realized [179]. An increasing number of studies in the literature indicate that intrapericardial administration is a safe route for therapeutic delivery or cell transplantation and can result in better PK and higher drug efficiencies in conjunction with decreased side effects. While systemic exposure cannot be completely prevented because of lymphatic drainage of the pericardial fluid [180], pericardial delivery has proven advantageous for targeted, sustained delivery to the heart. The low turnover rate of pericardial fluid as well as the coupling of therapeutics with slow degrading polymers offers a means for long-term sustained release to achieve desired therapeutic effect over longer periods of time. Recently developed tools to more safely and effectively enter the pericardial space through use of minimally invasive approaches bring us closer to more widespread clinically feasible application. Further, as researchers continue to identify biomarkers that are regulated in injured or diseased cardiac tissue, more targets will emerge and an increased need to locally deliver therapeutics to reach these targets may be achieved through intrapericardial approaches.

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