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Intrapericardial Drug Delivery: An Updated Review

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Abstract

The pericardium provides a unique site and an enclosed volume for the delivery of drugs to the heart and coronary arteries. In this review emphasis is given on strategies for more localized release and sustained delivery approaches (myocardial patches, cardiac meshes, hydrogels and nanoparticles) to the heart. It covers techniques and devices brought into work to access the pericardial space, as well as therapeutic and cell delivery vehicles that can be used to deliver drugs. Strategies for delivering the drugs to the heart do come short but, various approaches and technologies are emerging as encouraging methods to increase therapeutic myocardial retention, bioactivity, and efficacy, while still having a low incidence of systemic toxic side effects. Finally, multiple encouraging new therapeutic targets in the treatment of heart diseases (myocardial infarction, persistent foetal tachyarrhythmias, cardiac arrhythmias, diabetes atherosclerosis) and its role in cardiac regeneration is also highlighted.

Introduction

The pericardium is a fibro-serous double-layered sac surrounding the majority of the surface of the heart along with the great vessels of the heart. With the development of embryonic heart tube,it invaginates the pericardial sac, which includes the inner serosal layer which adheres to the myocardium and makes the visceral pericardium, which is found to be continuous with the parietal pericardium which is a fibrous-serous layer [1]. The outer fibrous layer is made up of collagen layers along with elastin fibrils, whereas the inner serous layer contains a microvillus surface which is responsible for secreting the pericardial fluid [2]. The thickness of these two layers, the pericardial sac, is 1-2 mm thick and they enclose the pericardial space, which approximately contains 15-35 mL of pericardial fluid [3]. This small amount of fluid present within the potential space serves a function to lubricate the surface between the visceral and parietal layers, thus allowing the heart to beat more smoothly and decrease the friction present between them [4]. The normal pericardium's micro physiology is ideal for eliciting the production of naturally occurring metabolic products, which includes enzymes such as prostacyclin synthase, cyclooxygenase, and lipoxygenase, as well as prostanoids, such as eicosanoids prostacyclin E2, and prostacyclin. Therefore, these substances, especially prostanoids, stimulate myocardial contractility, sympathetic neurotransmission within heart tissue, vasodilation, along with the inhibition of platelet aggregation within the coronary vessels and in the pericardium (Thus these substances promise to cause an affect on reperfusion arrhythmias) [5].

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Over a period of time there has been increased interest in investigating the routes for delivery of drugs to achieve more targeted and localized or targeted therapeutic effects that can minimize the side effects encountered by patients. Localized delivery is a method of targeted delivery in which the delivered drug will be deposited at a certain site, which will result in decreased distribution through movement and absorption into the blood. There are two approaches mainly used to maintain localized delivery, (i) delivery of a drug into a naturally enclosed sac which includes, pericardium of the heart,synovial space found between joints and bladder, etc.; (ii) through dosage forms in which the drug to be injected has a reduced ability to disseminate, such as gels, patches and implants. Localized delivery to the heart is strenuous to achieve through the conventional methods used for the delivery of drugs including oral delivery and intravenous (IV) because these methods will result in introduction of drugs into the bloodstream and eventually into the systemic circulation, hence being more susceptible to distribution seen typically and plasma protein binding effects which reduces the specific localization in the heart tissue [6]. There exists clinical needs for a more targeted and localized delivery of drugs, genes and cells to the pericardium, particularly for the regeneration of heart tissue following a post-myocardial infarction and atrial fibrillation post operatively. Approaches used for localized delivery of drugs to the heart commonly include intrapericardial, intramyocardial, and intracoronary routes. Intramyocardial delivery involves administration of drugs directly into the myocardium, which is made up of the thick muscle layer forming the wall of the heart [7]. Intrapericardial mode of delivery involves the administring of pharmacological agents into the pericardium which is a bilaminar sac surrounding the heart. Therefore, significantly larger volumes of drugs can be administered into this space using intrapericardial mode of delivery. Injection of Drugs or cells that have been injected into the intrapericardial space have been shown to have a diffuse coverage across epicardium into the endocardium, therefore penetrating the myocardium. Thus, it spreads from the atrium to the ventricle and in this way achieves a more targeted and localized action on the heart [8]. When compared to Intracardiac and Intravenous injections, intrapericardial injection can remarkably increase the retention and deposition of the drugs in the myocardium. This method of drug delivery provides multiple advantages in the development and physiological structure of injection technology, and is relatively mature, which also has prominent benefits in cardiac TDD. But Kolettis and his colleagues proposed that insertion of a catheter for intrapericardial injection for drug delivery is more likely to induce an inflammatory response and ultimately cause the formation of fibrosis while harvesting better efficacy. There are specific requirements for intrapericardial injection which includes the physicochemical properties of the pericardial fluid, molecular size of the drug to be delivered, the activity of viruses and cells to be injected into the heart. Intrapericardial injection can be the first TDD method for most of the patients suffering from cardiovascular diseases if the postoperative complications caused by intrapericardial injection can be limited, and appropriate drugs to be delivered can be selected [9]. Sodium nitroprusside's delivery through intrapericardial administration is shown to put an end to the cyclic coronary flow variations in animals like dog at a minimal dose and with a increased success rate, producing a effective and a safer approach than when it is administered intravenously [10]. A drug used for managing supraventricular arrhythmias called Amiodarone was continuously infused through intrapericardial route for a period of 72 hours in a sheep, and the cardiac biopsy specimens showed drug concentration with its active metabolites which includes desethylamiodarone, were found to be equal to, or higher than, those shown in patients taking amiodarone through oral route after chronic use [11]. Which demonstrates the importance of the intrapericardial route over conventional methods of drug delivery.

Thus, there are multiple advantages of intrapericardial delivery as a route of drug administration which include short term dosing that can be used to quickly achieve the levels to cause an therapeutic effect in the heart while decreasing the drug distribution systemically, thereby limiting the risk of complications that can be caused to involvement of systemic circulation as well as decreasing the quantity of drug needed and reducing the exposure to organs such as kidney and liver which are usually the typical sites for drug metabolism.

Anatomy of pericardium

Pericardium is a fibroserous sac enclosing the heart and beginning of great vessels. It is a lubricated container for heart contraction and restricts the movement of heart. It is present in middle mediastinum. It has two layers namely, fibrous pericardium and serous.

Fibrous pericardium is a tough exterior layer and is continuous with the central tendon of the diaphragm. Superiorly it is continuous with the tunica adventitia of the great vessels entering and leaving the heart and with the pretracheal layer of deep cervical fascia. Anteriorly, it is attached to the posterior surface of sternum by stern pericardial ligament. Posteriorly it is bound to the structures in posterior mediastinum by loose connective tissue. Inferiorly it is firmly attached and confluent centrally with the central tendon of diaphragm, and it is referred as pericardiacophrenic ligament. Serous pericardium is mainly composed of mesothelium. It also has two layers. Parietal layer which lines the internal surface of fibrous pericardium. And visceral layer: Forms the epicardium- the outermost layer of the heart wall.

Pericardial cavity

It is the potential space between parietal and visceral layers of serous pericardium. It contains a thin film of fluid which acts as the lubricant to the heart. It is about 20-60 ml in quantity. Phrenic nerve (C3-C5): It is responsible for the somatic innervation of the pericardium, and provides motor and sensory innervation to the diaphragm. The phrenic nerve is a common source of referred pain because it originates in the neck and travels down through the thoracic cavity for example shoulder pain experienced as a result of pericarditis. Arterial supply of pericardium is mainly from the pericardiacophrenic artery, a branch of internal thoracic artery. Whereas the venous drainage is through pericardiacophrenic veins, tributaries of brachiocephalic veins along with tributaries of azygos venous system.

Physiology of pericardium

Pericardium has many functions. These include lubrication as pericardial fluid present between the two layers of serous pericardium reduces the friction generated by heart movements. It also prevents overfilling since he fibrous layer of the pericardium which is relatively inextensible prevents the heart from increasing in size too rapidly, thus placing a physical limit on the potential size of the heart.BIt also plays a role fixing the heart in mediastinum. Protection from infection is also provided by the pericardium which is provided by the fibrous pericardium, from the adjacent organs for example lungs.

Pericardial fluid

Normally the human pericardial cavity contains 20-60 ml of fluid. There is strong evidence that the pericardial fluid is derived by plasma ultrafiltration through the epicardial capillaries (and probably the parietal's pericardium), and small amount of interstitial fluid from the underlying myocardium, during the cardiac cycle and the drainage is mainly through the parietal pericardium lymphatic capillary bed.

The concentrations (in mmole kgr H_2O^{-1}) of Na^+ (150.5 ± 0.72), Cl^- (123.2 ± 0.71), Ca^{2+} (1.92 ± 0.04), and Mg^{2+} (0.85 ± 0.09) were lower in the pericardial fluid than in the plasma. On the contrary, the concentration of K^+ (3.81 ± 0.07) was higher than the plasma, which was accredited to the K + leakage from the myocardial interstitium toward the pericardial cavity, during systole. It also contains different proportions of protein fractions including albumin in highest concentration then globulins, macroglobulins, and fibrinogen in lowest concentrations. So, the pericardial fluid osmolarity was lower than the plasma [12].

Routes to access the pericardial space

Large volumes of drugs can be administered via the intrapericardial route. These drugs have shown to diffuse across epicardium into the endocardium, and the myocardium and then spread from the atrium to ventricle and achieve localized action on the heart. Moreover, the clearance of the pericardial fluid is slow, so it also acts as the reservoir for the drug and prolongs its half-life.

Opened pericardium-based delivery approaches for drug instillation and infusion via medial sternotomy

The heart is exposed by medial sternotomy and a small incision is made on the anterior surface of the pericardium and then drug solutions are instilled into the pericardium [13]. Yasmeen et al. demonstrated in their study a device called Active hydraulic ventricular support Delivery System (ASD) used for drug infusion. First, pericardium was opened through medial thoracotomy and then this device was implanted [14].

Catheter system-based delivery approaches for drug instillation and infusion

In this route, following medial sternotomy, the pericardial sac was perforated with a needle instead of making an incision on the pericardium. Ujhelyi et al. [15] demonstrated this route in their study by fixing catheter by sutures for the drug delivery by this route in experimental animals. Their study showed that pericardial drug delivery did not affect endocardial ventricular electrophysiology.

Epicardial drug-loaded hydrogel spraying

In a study, the patients who were undergoing Coronary Artery Bypass Graft (CABG), were given epicardial amiodarone hydrogel for preventing Post-Operative Atrial Fibrillation (POAF) before closing the pericardium. The amiodarone was sprayed over the right atrial lateral wall, left atrial appendage, and transverse sinus area [16].

Catheter system-based access approaches via lateral thoracotomy:

This is a more preferred approach than medial thoracotomy because it does not require a big incision for entry. Van Brakel et al. [17] made an incision at the fourth intercostal space in experimental animals and reached pericardium. Then he positioned the catheter for drug delivery. He infused sotalol and flecainide solution intrapericardial to observe the effects on epicardial physiology and atrial fibrillation. McDermott et al. [18] also used this route for the delivery of bradykinin in experimental rats.

Needle-based access approaches via lateral thoracotomy

Garcia et al. [19] conducted an experiment on the rats. First thoracotomy was done on the left thoracic cage of rats. He used a blunt needle to prevent damage to the heart and other organs. Then he delivered a cross-linked PEG hydrogel containing amiodarone to treat atrial fibrillation in rats.

Subxiphoid access

The subxiphoid route is used for the delivery of pharmacologic agents to the pericardial fluid. Kyoko Soejima et al. [20] demonstrated in their study the feasibility of using a direct subxiphoid surgical approach to the pericardial space for electrophysiological procedures. The study was done in patients with failed percutaneous epicardial access or patients with prior cardiac surgery. The pericardium was exposed by incision in midline epigastrium and then extended to the left to improve the view of ventricles. This was done under general anesthesia. After the procedure, pericardial drainage was minimal and there was no reaccumulation of fluid. Pericardial adhesions from prior cardiac surgery can make pericardial access difficult via this approach. The complications of this route include vascular injury, ventricular injury, injury to other organs and inflammatory reactions. But they occur with low incidence [16].

Device-based access

The PerDUCER® device is used for device based access. It has a sheathed needle and a suction tip. This device used two techniques: Subxiphoid access to the mediastinal space and the other is pericardial captures, puncture and insertion of guidewire and catheter. A small incision is made usually on the median line below the xiphoid process or via median sternotomy. Then a guidewire is to direct the insertion of a drug delivery catheter [21]. The devices which are available in the market are Attach-Lifter, PerDUCER® or PeriCardioScopeTM. The newer devices had a camera at their tip to allow visualization of pericardium to identify the site of puncture [16].

Needle-based access

It was reported in a study that a blunt-tipped epidural introducer with fluoroscopic guidance with and without continuous positive pressure was used for percutaneous subxiphoid access of normal pericardium. The positive pressure was used to push the right ventricle away so that it does not come in the path of the needle. Then the guidewire was inserted into the pericardium for the delivery of the drug [22].

Multi-catheter system-based access

In this route, a needle is directed under the sternum toward the pericardium under fluoroscopic guidance. It is composed of two separate internal lumens and contains the components of hydrogel. Subxiphoid approach was used [16].

Percutaneous transatrial access

This is nonsurgical, rapid and safe access to the pericardial space. In this approach, the catheter system is used to reach the pericardial space through the right atrial appendage. Verrier and Waxman et al. [23] did a study in the 1990s and demon-

strated the particular application of percutaneous transtrial access to relieve pericardial effusion. The pericardial fluid helps in the early identification of myocardial disease because it reflects myocardial interstitial fluid. Transatrial access to the pericardial space is also used for local cardiac drug delivery, for which it may afford efficient, sustained delivery to perivascular and myocardial tissue while minimizing loss of agent into the circulation.

The transatrial pericardial approach has important intrinsic advantages for administration of pharmacological agents. These include access to perivascular tissue, delivery of drug with minimum loss into the circulation, and perfusion of atrial and ventricular epicardial tissue. The risk of intimal hyperplasia is also reduced in this route because drug is delivered to the adventitial surface rather than the luminal surface. This procedure can be implemented in humans because of the absence of complications and it is easy to perform the procedure. But still the safety of this route needs to be further explored. In summary, this route provides a new opportunity for identification of diagnostic markers in the pericardial fluid; for pericardiocentesis; and to administer therapeutic factors [23]. Pulerwitz et al. [24] conducted a study to see the safety of transatrial access to the normal pericardial space in the settings of aspirin use and pulmonary artery hypertension. He observed some local inflammation and small thrombi formation in the atrial wall and site of puncture, respectively. He showed that this access route into the pericardium did not result in notable intrapericardial bleeding.

Practical carries to deliver drugs to pericardium

Nanoparticles

Nanoparticles (NP) are materials with dimensions under 100 nm. Recently, these materials have emerged as an important resource in current medicine, with uses ranging from in medical imaging to carriers for gene delivery into particular cells. Nanoparticles have a number of qualities that separate them from other available materials due to their size which play a role in reactivity, biological mobility, and energy absorption [25]. Nanoparticles are developed to fill the gap left by other therapeutics methods and also navigate biological barriers that are different in numerous populations and diseases. They can also be optimized to deliver a drug in a more customized way, entering a new era of precision medicine [26].

NP-based drug delivery into pericardial space can provide a way to concentrate treatment to a restricted cardiac compartment that will allow sustained drug delivery to the myocardium. But this method of drug distribution is multifactorial, which is affected by pericardial distribution of fat, abundant in the regions around interventricular and atrioventricular groove, and by apical displacement caused by the motion caused by the beating of the heart [27]. For example therapeutic delivery is attained by injecting into the pericardial space that is Poly D,L-Lactic-Co-Glycolic Acid (PLGA) NPs encapsulated with Remodulin or drug that is unformulated in the case of Myocardial Infarction (MI) which is characterized by occlusion of a blood vessel supplying the, due to development of a clot [28].

Myocardial Patches

Myocardial patches are made of gel, collagen, and other biocompatible materials. One example of a patch material usually used after arteriotomy is bovine pericardium and it has numerous advantages compared with other prosthetic systems, which include superior biocompatibility, easy handling, and less suture line bleeding [29]. Amiodarone-loaded patches when applied, produced considerable increases in right atrial Early Repolarization Pattern (ERP) moreover, increase in conduction times over the time span evaluated in one of the studies. The same study exhibits atrium-specific amiodarone delivery for a much longer time span than observed in studies involving intrapericardial infusion. Significant antiarrhythmic effects of Amiodarone-loaded patches were produced after 28 days of initial application, whereas level of the remained less than 10 ng/ML in plasma, which is 100 times lower than plasma levels required to exhibit therapeutic effect by oral (chronic use) and intravenous delivery of amiodarone Moreover, in extra cardiac tissues, which include fat, skelte muscle, liver, and lung, the peak amiodarone concentrations were up to 2 to 4 orders of magnitude lesser than levels observed during chronic oral administration of amiodarone [30]. Continual improvements and development in biodegradability and Integrity of cardiac patches might attenuate with time, paving a path for more precise applications.

Cardiac meshes

Drug-eluting implants are gaining a lot of attention in recent years due to several advantages over older ways of drug administration and management of diseases. Its most important feature is that it might induce a possibility to control the medication release for extended periods of time without hampering stability of the drug. Surgical meshes have a variety of applications, they need to be tailored according to the disease and the drug used for its management. However, it could still be possible to classify these drugs into antibiotics, antimicrobials and antibacterial molecules [31]. The presence of a permanent mesh inside the body is a problem in itself. It can be overcome by the synthesis of synthetic absorbable polymers. They can be used as coatings, to mitigate the interactivity of implants with the body and give out antibacterial properties, but also can be used as mesh backbone, because they will be degraded eventually, leaving a new and healthy piece of tissue behind [32]. Animal studies involving such meshes exhibited improved drug delivery efficacy as well as enhanced efficiency without sacrificing the integrity of blood vessels after the application of mesh [33]. Meshes can also be customized to particular heart moreover, they can also be altered structurally and electrically helping to deliver electrical impulses to heart that might improve cardiac function in patients with heart failure. They are usually made up of silver nanowires that are embedded in a rubber polymer. An electric mesh was used in rodents that demonstrated to regulate heart beating patterns and also acted as a epicardial defibrillator. This approach provides a more comprehensive coverage to the heart, which provides them an advantage over pacemakers because they deliver electrical stimulation at only particular places in the heart [34].

Hydrogels

Hydrogels maintain a three-dimensional structure that are water-swollen polymeric materials. They are one of the first biomaterials that were designed to be used in the human system. Traditional ways used to synthesize these materials involve multiple steps which include copolymerization,crosslinking via polymer-polymer reaction and crosslinking of reactive polymer precursors [35]. The Polyethylene glycol (PEG)-based hydrogel demonsatrees biodegradability along with prompt tissue adherence, allows improved and localized drug delivery. The same study found that amiodarone-releasing hydrogel used biatrial as an epicardial application was effective in decreasing and preventing the incidence of Postoperative Atrial Fibrillation (POAF).

The treatment was well tolerated, safe and gave higher drug concentrations in the atria for longer periods of time [36]. To evaluate the effectiveness of topical application of hydrogel loaded with amiodarone loaded on a biodegradable disc, a study was done, demonstrating encouraging results [37]. Biatrial epicardial application of drug eluting hydrogel thus, has more advantages over biatrial targeted (localized) drug delivery. Studies show that basic Fibroblast Growth Factor (bFGF)-loaded gel considerably inhibits the apoptosis of cardiac cells instead was shown to promote their proliferation. This increased myocardial angiogenesis and an improved cardiac function was observed with intrapericardial delivery of bFGF hydrogel. In response to the overproduction of Reactive Oxygen Species (ROS) in the pericardial cavity caused by reperfusion injury, Gel-bFGF was also shown to have the capacity for long-term release of bFGF. Given the collaboration between hydrogels and therapeutics used in cardiac repair, it represents an evolution in the field of drug delivery cardiac biomaterials [38].

Intra pericardial drug delivery in cardiac diseases

Persistent tachyarrhythmias

Complicated by hydrops, fetalis carry a poor survival rate. In order to improve the survival as it was seen seven out of eight cases amiodarone was injected into the fetal peritoneal cavity under ultrasound which is a very simple and effective technique [39].

Myocardial infarction

Which is one of the leading complication world-wide.it was found that by administering Hydrogen-rich saline through intraperitoneal injection improves myocardial infarction size of hearts, cardiac function, apoptosis and cytokine release following MI/R [40]. Diabetic Cardiomyopathy (DCM) is an important cause of heart failure in patients with diabetes. LCZ696, a drug for the treatment used for heart failure. It was found out that LCZ696 is more effective for preventing heart failure than valsartan [41]. Another technique is to inject heparin sulphate and fibroblast growth factors into the pericardium by using a catheter. This resulted in angiogenesis from epicardium to the subepicardial infarction area. We can also deliver FGF2 intrapericardial which also promotes myocardial angiogenesis and ultimately enhances myocardial perfusion.

After an episode of myocardial infarction, Periostin is secreted. It is a protein that stimulates cardiomyocyte proliferation and angiogenesis. Gelfoam loaded with recombinant peptide periostin also enhances cardiomyocyte growth and angiogenesis [42].

Cardiac regeneration

Adult mammalian hearts have very low to nil ability to regenerate but by developing a chemical cocktail of Five Small Molecules (5SM) promotes cardiomyocyte proliferation and regeneration.5 Hypothermosol, hypothermic preservation media for the preservation of cells, delivered as intrapericardial injection of porcine Cardiosphere-Derived Cells (CDC) into infarct mode promotes cardiac repair [43].

Vascular diseases

In order to improve the condition of vascular diseases and to enhance the flow we can administer sodium nitroprusside which decreases platelet accumulation and improves the flow especially in injured coronary arteries [42].

Cardiac arrhythmias

Problems in the heart rate are one of the most common conditions worldwide. Most of the antiarrhythmic drugs are administered in the form of solution via injections dissolved in normal saline or Tyrode's Solution with surfactant.Intrapericardial we can administer metoprolol which can lowered the heart rate and does not affect ventricular contractility and arterial pressure.Nitroglycerin bolus solutions into the porcine pericardium,causing coronary vasodilation without hypotension and anti-fibrillatory effects.

Hydrogel spray system, spray delivery of amiodarone to the epicardium is effective in preventing postoperative atrial fibrillation.β-blockers are also injected intrapericardial increases the activity on the baseline heart rate and adrenergic tachycardia, having anti-tachycardic effects [42]. SEO has antioxidant capacity which can improve cardiac rhythm and BP changes as this was done by first injecting DOX in mice which causes various variations including change in creatine phosphokinase, cardiac troponin T, and Lactate Dehydrogenase (LDH), Electrocardiogram (ECG) fluctuations, Heart Rate (HR), and Blood Pressure (BP). These alterations were then treated and hence improved the condition of all the factors mentioned above [44].

Diabetes atherosclerosis

Diabetes mellitus defects of insulin secretion or action. This can lead to metabolic abnormalities and ultimately atherosclerosis due to multiple reasons leading to cardiovascular diseases [45]. Decreased autophagy and activated mitochondria causes this atherosclerosis. Rapamycin (mTOR) and NF-κB signaling pathways were targeted by the active chemical compounds of GBE to attenuate AS as GBE reduced the plaque area plaque lipid deposition plus by inhibiting mTOR can also help to reduce it [46]. Cardiac hypertrophy, an early sign of various heart diseases including coronary heart disease, hypertension, valvular dysfunction and cardiomyopathy. The major cause of this is Cardiomyocyte autophagy and apoptosis. Plantago Asiatica L. Seeds Extract (PASE), a traditional herbal medicine in Asia. PASE attenuated ISO-induced cardiac hypertrophy excessive autophagy and apoptosis in cardiomyocytes ultimately healing cardiac hypertrophy [47].

Conclusion

Pericardial access is an alternative route to deliver therapeutics to the heart. Advanced methods to access the space and deliver the drug have surfaced. Reported results are found to be very encouraging when this route is used to deliver drugs, cells, and multiple proteins used to treat variety of conditions such as regeneration of myocardium following an acute myocardial infarction, improving cardiac arrhythmias, and its positive role in treatment of diabetic atherosclerosis. Therefore, an attractive drug delivery reservoir is provided by the pericardial space that can be used for delivering therapeutic agents to the heart.

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