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Access routes, devices and guidance methods for intrapericardial delivery in cardiac conditions

Hei Ming Kenneth Ho[1,2], Duncan Q.M Craig[1], Richard M. Day[2*]

[*] r.m.day@ucl.ac.uk, Tel: (+44) 20 3108 2183

[1] University College London School of Pharmacy, 29-39 Brunswick Square, London WC1N 1AX, UK

[2] Centre for Precision Healthcare, UCL Division of Medicine, University College London, 5 University Street, WC1E 6JF, UK

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Declaration of interest

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Abstract

Drug deposition into the intrapericardial space is favourable for achieving localised effects and targeted cardiac delivery owing to its proximity to the myocardium as well as facilitating optimised pharmacokinetic profiles and a reduction in systemic side effects. Access to the pericardium requires invasive procedures but the risks associated with this have been reduced with technological advances, such as combining transatrial and subxiphoid access with different guidance methods. A variety of introducer devices, ranging from needles to loop-catheters, have also been developed and validated in pre-clinical studies investigating intrapericardial delivery of therapeutic agents. Access techniques are generally well-tolerated, self-limiting and safe, although some rare complications associated with certain approaches have been reported. This review covers these access techniques and how they have been applied to the delivery of drugs, cells, and biologicals, demonstrating the potential of intrapericardial delivery for treatments in cardiac arrhythmia, vascular damage, and myocardial infarction.

Introduction

There is increased interest in exploring advanced drug delivery routes to achieve localized or targeted delivery of therapeutic agents that minimise side effects experienced by patients. Localised delivery, by definition, is a form of targeted delivery where the delivered drug resides mainly at a certain site, resulting in reduced movement and absorption into the bloodstream. Two main approaches exist to maintain localised delivery – (i) delivering the drug to a naturally enclosed site, such as pericardium and myocardium in the heart, bladder, synovial space between joints, etc.; (ii) through dosage forms where the drug has limited ability to translocate, such as patches, gels and implants.[1] Localized cardiac delivery is difficult to achieve via conventional delivery routes[1] such as intravenous (IV) and oral delivery, as these result in the drug being introduced into the bloodstream and systemic circulation, hence being subject to typical distribution and plasma protein binding effects which render specific localisation in the heart difficult.

Unmet clinical needs exist for localised and targeted delivery of drugs, cells and genes to the heart, especially for cardiac regeneration post-myocardial infarction and post-operation atrial fibrillation. Common approaches used for localised delivery of drugs to the heart include intramyocardial, intrapericardial and intracoronary routes. Intramyocardial delivery involves direct administration of material into the myocardium, which consists of the thick muscle layer of the heart wall. This approach is suggested to improve the residence time of cells in the myocardium.[1] Thus, it is widely used in cell therapy for delivery of stem cells and derived cells into the heart, but it might precipitate ventricular fibrillation.[2] Meanwhile, intracoronary delivery involves injection or infusion in the coronary artery, which is used

preferably post-MI and with percutaneous cardiac intervention (PCI),[3] but the use is limited due to occlusion of the artery.[4]

Intrapericardial delivery involves the administration of pharmacological agents into the pericardium, a bilaminar sac surrounding the heart. Hence, much larger volumes can be administered via intrapericardial delivery. Drugs or cells that have been delivered into the intrapericardial space have been shown to diffuse across epicardium into the endocardium, penetrate the myocardium spread from the atrium to ventricle[5,6] and achieve localized and targeted action on the heart.[5–8] Moreover, owing to the slow clearance of the pericardial fluid,[9] the pericardial escape of drug is low and thus the pericardium can act as a reservoir for the drug and prolong the half-life in the heart,[10] and reduce peripheral side effects.[11] Furthermore, desired drug concentration in the myocardial tissue can be achieved with a lower dose compared with other routes, such as oral, intravenous or intracoronary delivery.[8,12–14] Thus, intrapericardial delivery offers key benefits over other methods of localised cardiac delivery making it a preferred route for drug delivery to the heart.

The pericardium is subdivided into the parietal and visceral pericardium, as shown in FIG 1. The parietal pericardium is the outer layer, which is made up of a fibrous laminar (fibrosa) and serous laminar (serosa). The two layers in the parietal pericardium are inseparable. The luminal surface of the visceral pericardium is a monolayer of mesothelial cells and exists in continuity with the serous layer of the parietal pericardium.[15] The space contained between the two layers of the serous pericardium is the pericardial space, which contains pericardial fluid to lubricate the membrane and ease the movement of the heart.[15] Volumetric studies of pericardial fluid in adult humans indicate a typical volume of 20 – 60 mL.[16–19] Pericardial fluid is predominately formed by plasma ultrafiltration through

epicardial capillaries, with the addition of a small amount of myocardial interstitial fluid, which has similar characteristics to pleural fluid.[16,17] The fluid is drained through the parietal pericardium lymphatic capillaries.[20] Pericardial fluid contains electrolytes, metabolites, albumin and nutrients including glucose, triglycerides and cholesterol.[17,21]

Since intrapericardial drug delivery remains at a relatively early stage of development, this literature review aims to explore recent advances in access methods and devices, as well as the guidance methods. Drug delivery directly onto the epicardium (also known as the visceral pericardium) is also included in this review. This review will highlight the potential applications of these techniques for the treatment of cardiac conditions not involving the pericardium, such as myocardial infarction, arrhythmias and vascular damage. The choice of route and mode of delivery will also be discussed further in this article.

1. Access routes for intrapericardial delivery

1.1 Thoracotomy

Thoracotomy is a procedure that involves incising the pleural space of the chest. There are two common approaches to thoracotomy adopted in studies for intrapericardial delivery. Medial sternotomy accesses the pleural cavity and heart via an opening of the sternum, which is used in open-heart surgery. Lateral thoracotomy involves an incision on the intercoastal space, with the opening widened by a rib retractor placed between the ribs. Both approaches may be used for not only surgical access but also as a means of facilitating tissue-specific drug delivery.

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

Miyazaki *et al.* first reported intrapericardial drug delivery in dogs via medial sternotomy. The heart was firstly exposed by medial sternotomy and a small incision was made on the anterior surface of the pericardium. Edges of the incision were tied with sutures to produce a square opening (2.5 x 2.5 cm), as illustrated in FIG 2(a). Drug solutions containing prostaglandins, hexamethonium or tetrodotoxin were then instilled into the pericardium.[22–24] After instillation, the drug solution was removed by suction, followed by a washout of the pericardium. This method was adopted mainly in experiments evaluating intrapericardial delivery of anti-arrhythmic drugs in canine models, with the electrodes also placed through the pericardial opening and inserted into the myocardium to trigger ventricular fibrillation. Fei *et al.*[25] and Ayers *et al.*[5] also adopted this method to achieve intrapericardial delivery in dogs but with different sized incisions.

Another device, known as the active hydraulic ventricular support delivery system (ASD) was developed by Yasmeen *et al.*, which allows epicardial drug infusion of lidocaine to suppress ventricular arrhythmias in rats and provides cardiac support.[26] The device is a mesh of flexible and interconnected silicon hollow tubes, with apertures on the side facing the epicardium, as shown in FIG 2(b). Two of the four tubes on the ASD were connected to implantable catheters for drug infusion. To implant the device, the pericardium was first exposed and opened by medial thoracotomy. The device was then inserted over the epicardium to the atrioventricular junction, where its position was fixed with sutures. An implantable catheter was first connected to the device and then tunnelled subcutaneously through the second intercostal space to the anterior chest wall, exiting the thoracic cavity via a 1 cm opening on the skin for drug administration.[26,27]

1.1.2 Catheter system-based delivery approaches for drug instillation and infusion via medial sternotomy

Vereckei *et al.* described a method to infuse anti-fibrillatory drug, ibutilide, into the pericardial space of dogs using a 4.1 Fr fenestrated catheter.[6] The catheter was positioned in the pericardial space via a small incision on the pericardium created after medial sternotomy. The position of the catheter was secured with purse-string sutures and the pericardium was closed with continuous locking sutures. Similarly, Ujhelyi *et al.* utilised a 0.050-inch catheter for procainamide delivery in pigs, where the position of the catheter was also fixed by sutures.[28] However, instead of creating an incision on the pericardium, a 23 G needle was used to perforate the pericardial sac above the anterior basal region following the medial sternotomy.

1.1.3 Epicardial drug-loaded hydrogel spraying via medial sternotomy

Two human clinical trials investigating the use of epicardial amiodarone hydrogel for preventing post-operative atrial fibrillation (POAF) were conducted on patients undergoing coronary artery bypass graft (CABG).[29,30] The pericardium was opened during the procedure for constructing the bypass graft. Before the closure of the pericardium with interrupted sutures, the amiodarone hydrogel was sprayed diffusely using a carbon dioxide driver set over the right atrial lateral wall, left atrial appendage, and transverse sinus area,[29–31] which is shown in FIG 3.

1.1.4 Catheter system-based access approaches via lateral thoracotomy

Lateral thoracotomy rather than medial sternotomy has been the preferred approach in many of the studies conducted during the last decade, as this technique does not require a large incision for entry. This approach has been performed on sheep and goats. Van Brakel *et*

al. created a 3-4 cm incision at the fourth intercostal space in goats and subsequently, a 2 mm opening on the pericardium.[12] A silicon drug delivery catheter was then positioned into the pericardial space to infuse sotalol and flecainide solution intrapericardially to determine the effects on epicardial physiology and AF. Another study adopted a continuous infusion system with drainage to prevent cardiac tamponade.[13] An incision was created in the left fifth intercostal space to reach the pleural space of sheep. A 3 mm opening was then created at the base of the pericardium, with a 10 cm 17 G multi-fenestrated catheter inserted anteriorly to the atrioventricular groove. Another identical catheter was inserted posteriorly. Both catheters were tunnelled through the chest wall and exit near the spine, where they were connected to a self-contained elastomeric autonomous infusion pump for intrapericardial amiodarone infusion. Furthermore, Matthews *et al.* also created the incision at the fifth intercostal space of sheep to expose the heart, followed by insertion of a transparent vinyl catheter, with 1.5 and 2.5 mm internal and external diameters respectively.[32] Eight holes, with 1 mm diameter, were drilled at regular intervals at the end of the catheter. The position was anchored by the sutures and the wound was sealed, before administration of IGF-1 to improve cardiac function in chronic heart failure.

Apart from multi-catheters, several designs of the loop catheter have been reported. McDermott *et al.* used a looped Silastic catheter to access the pericardial space of rats for delivery of bradykinin. The loop, with a diameter of 1 cm and 15-25 holes perforated with a 25 G needle, was secured by heat-shrink tubing.[33] Furthermore, Hermans *et al.* customised a loop catheter device, which comprised of a silicon tube with its end assembled with a polyolefin shrinking sleeve-shaped as a loop.[8] Two separate chambers with two and six holes were present for fluid injection and pericardial fluid withdrawal respectively. Another end of the silicon tube was connected to polyethene tubing, which was guided to the neck of

the rats and externalized through the skin. After 2 days, the osmotic minipumps filled with the drug solutions were implanted. Another group adopted the same method for a 7-day intrapericardial infusion of atenolol and sotalol in rats but used an unspecified catheter.[34]

1.1.5 Needle-based access approaches via lateral thoracotomy

Recently, Garcia *et al.* utilized a blunted 26 G needle to penetrate the pericardium of rats and delivered a cross-linked PEG hydrogel containing amiodarone to treat atrial fibrillation.[11] Thoracotomy was performed on the left thoracic cage of the rats to expose the heart and lung, where the lung was retracted with sterile gauze and the pericardium was hold by burr-free atraumatic forceps before the needle puncture on the pericardium. A blunt needle was used to prevent harm to the heart or other organs during the puncture. Thoracotomy was performed to allow visualisation of the gelation and probably due to the small size of the animals. Therefore, Garcia *et al.* used subxiphoid access in the same study to administer the same hydrogel in larger animals such as pigs, to prevent the disruption of the pericardium caused by the thoracotomy access method.

1.2 Subxiphoid access

Pericardiocentesis is a procedure to aspirate fluid from pericardium in humans, for analysis in cardiac tamponade and pericardial effusion,[35] usually performed in conjunction with imaging. A higher chance for major complications and mortality was associated with blind guidance.[36,37] Similarly, this approach is employed to deliver pharmacological agents. Generally, there are three routes to access the pericardium, namely subxiphoid, para-apical and parasternal approaches. The subxiphoid route is the most common route adopted in the studies, with various designs of introducers, of which epicardial blunt-ended needle or device is inserted between xiphisternum and the left costal margin for 2-3 cm. Then, it is

lowered through the infrasternal angle (15-30^{o} angle with the skin) and directed at a shallow angle to access the pericardium over the anterior aspect of the ventricle while the needle is directed posteriorly toward the left shoulder to reach the pericardium over the inferior aspect of the ventricle.[38]

1.2.1 Device-based access

The PerDUCER® device is used for percutaneous pericardial access and consists of a sheathed needle and a suction tip with a hemispheric cavity to grasp the pericardium, as shown in FIG 4 (a).[39,40] A needle is housed inside a sheath tube, which is connected to a suction syringe on one end and a tapered-ended and half-moon shaped plastic tube with a hemispheric cavity on the other. A side hole in the cavity allows access to the vacuum lumen and the insertion of needles.

Two techniques were used for pericardial delivery with the PerDUCER® device: (1) subxiphoid access to the mediastinal space and (2) pericardial captures, puncture and insertion of guidewire and catheter. The introduction of the PerDUCER® device is usually via a small incision in patients created on the median line below the xiphoid process,[39–41] although one study introduced the device via median sternotomy.[39] A curve blunted cannula, preloaded with a J-tipped guidewire, was advanced into the mediastinal space. The cannula was then replaced with a 19 Fr sheath over the guidewire as the entry for the PerDUCER® device. The device was inserted with the hemispheric cavity on the device placed against the pericardium. The pericardium was sucked into the hemispheric cavity by the vacuum, where pericardium was isolated from the epicardium. The rotating assembly was then unlocked to release the needle. When the vacuum was released, the needle was rotated such that the opening bevel faced down towards the heart to maintain the opening. A

guidewire was inserted through the needle into the pericardial space to direct the insertion of a drug delivery catheter.[39–42]

The AttachLifter device was developed by Rupp *et al.* to overcome difficulties experienced with using the PerDUCER® device.[43] The tented pericardium was punctured with a needle-tipped catheter outside the device after the pericardium was lifted and rotated 90^{o}, preventing the damage to the tissue. A fiberscope was attached to the suction head to identify the location for the access. Furthermore, the suction head contained flexible clamps to grab the tissue more effectively and provided a better seal under vacuum, compared to the metal suction head in PerDUCER®.

A more sophisticated device further advanced from AttachLifter and PerDUCER®, called PeriCardioScope™ (Perifect, Herzliya, Israel), is on the market at the time of writing. A rotatable needle instead of the J-tipped guidewire in PerDUCER® or external needle in AttachLifter was embedded inside the suction head to puncture the pericardium. Therefore, a further step of inserting a guidewire through the needle was required to secure the pericardial entry. Furthermore, it had a camera at the tip of the device, which allows instantaneous visualisation of the pericardium to identify the optimal site of puncture.

1.2.2 Needle-based access

Laham *et al.* reported successful percutaneous subxiphoid access of normal pericardium in pigs using a blunt-tipped epidural introducer needle (Tuohy-17) with fluoroscopic guidance and continuous positive pressure (20-30 mmHg),[44] to push the right ventricle away from the needle's path. Branco *et al.* also utilised the same approach, but without the continuous positive pressure, for delivery of bone marrow mononuclear cells

(BMMC) in swine models.[7] The entry of the needle into pericardial space was both confirmed by injection of diluted contrast media under fluoroscopy. A floppy-tipped guidewire was then inserted into the pericardium, allowing the needle in exchange for a drug infusion catheter.[14,44–46]

1.2.3 Multi-catheter system-based access

Ladage *et al.* reported a subxiphoid intrapericardial injection under fluoroscopy and intravascular ultrasound guidance into myocardial infarcted porcine using a multi-catheter system.[47] An 18 G puncture needle was directed under the sternum toward the pericardium, with the position confirmed by a small bolus injection of contrast dye. A wire was then placed into the pericardium for guiding the introduction of a 5 Fr vascular sheath. A 5 Fr catheter was thereafter inserted for delivery of these agents into the pericardium and subsequently to the myocardium.

Another loop catheter was developed by Garcia *et al,* which is shown in FIG 4(b).[11,48] This was constructed from varying durometers of polyether block amide biocompatible polymeric resin, to deliver hydrogels into the pericardial space of pigs under fluoroscopic guidance. The device comprised a core made of an elastic memory nickel-titanium alloy to facilitate fence development. Two separated internal lumens throughout the device contained the components of the hydrogel. Suction and gel ports were created on the device by precision knifing. The intrapericardial access was performed via the subxiphoid approach in pigs using a 12 cm 21 G micro-puncture needle. A 10 Fr catheter sheath with radiopaque markers, made of a laminated composite shaft and an embedded coil, was placed into the pericardial space. The hydrogel delivery device was then introduced into the pericardium via the sheath and formed a circular fence with a diameter of 5 cm. Its position

was secured by suction. A temporary compartment for gelation was then formed between epicardium, pericardium, and the fence. The delivery device was retracted after gelation, with the help of the shape memory core to avoid disturbing the hydrogel architecture.

1.3 Percutaneous transatrial access

Percutaneous transatrial access involves accessing the pericardial space via an incision created in the heart wall. Uchida *et al.* first reported this approach to access the pericardium of dogs in the mid-1990s.[49] A guiding balloon catheter, with shaft size and balloon size of 9 Fr and 60 Fr respectively, was first advanced through the right femoral vein to the right atrium. The balloon was then inflated with carbon dioxide to push against the heart wall. A 23 G needle-mounted 4 Fr catheter was subsequently introduced by the guide catheter and punctured the pericardium under fluoroscopy.

In the late 1990s, Verrier and Waxman *et al.* reported a multi-catheter system for transatrial access in pigs and dogs.[50] A larger guide catheter was introduced through an introducer sheath that was placed into the femoral or jugular vein and positioned under fluoroscopy guidance into the right atrial appendage. Subsequently, a guide catheter was positioned under fluoroscopic guidance into the right atrial appendage to create support. A custom-designed needle catheter was subsequently advanced through the guidewire and a small perforation on the atrial appendage was created using a hollow radiopaque needle mounted on its tip. Another soft and smaller transatrial guide wire equipped with a second radiopaque marker was then inserted through the needle-catheter and secured the percutaneous pericardial access, with the position in pericardial space confirmed using fluoroscopy. The insertion of the second guidewire allowed the needle-catheter to be withdrawn and exchanged with an application catheter for drug injection or aspiration

catheter for fluid withdrawal on-the-wire.[50,51] Drugs could be infused, instilled or injected into the pericardial space. Waxman *et al.* utilized the combination of an 8 Fr multipurpose guidewire, a customized 21 G needle mounted on a 4 Fr catheter, a soft 0.014-inch angioplasty guidewire and a 4 Fr application catheter with multiple side holes to deliver nitroglycerin into the pericardial space, as displayed in FIG 5 (a-d).[52]

In a further study, Waxman, Verrier and colleagues injected bolus nitroglycerin into the porcine pericardium and conducted pre-clinical trials using an advanced catheter system.[52–55] A stiff-ended 0.014-inch angioplasty guidewire was first inserted into the lumen of a soft open-ended infusion catheter, with a gap of 1 to 2 mm from the end of the infusion catheter. The position of the guidewire was then locked with a stopcock. The complex was subsequently advanced into an 8 Fr multipurpose guide catheter, which was placed in advance into the right atrial appendage via a femoral vein under fluoroscopic guidance. Puncture of the right atrial appendage was achieved using the guidewire tip. The infusion catheter and guidewire were then advanced into the pericardial space as a single unit. The location of the infusion catheter in the heart was confirmed by fluoroscopy before the removal of the guidewire from the infusion catheter.

Apart from drug delivery, epicardial leads and ablation catheters could be placed via the right atrial appendage for therapeutic purpose. Kassab *et al.* conducted a proof-of-concept study placing the epicardial lead for cardiac resynchronisation therapy via transatrial access.[56] The group utilised a bi-lumen catheter to navigate, with one lumen connected the plunger-type tip to vacuum to help fix the position on the right atrial appendage. Another catheter with a distal needle tip was then advanced through another lumen and puncture on the atrium, with the pacing leads implanted in pericardial space. Contrarily, Scanavacca *et al.*

conducted the first study to perform transatrial epicardial mapping and deliver radiofrequency pulses on the atria.[57] The group first placed a long transseptal sheath into the right atrial appendage, where a 7 Fr quadripolar catheter was inserted through the sheath to confirm the position and removed subsequently. A J-tipped guidewire and a dilator were then advanced in the sheath until the end of the dilator were at the atrial wall, where the guidewire was further advanced to perforate the atrial wall and enter the pericardium. An 8mm distal tipped ablation catheter was finally introduced into the pericardium. Mapping and ablation with or without using a closure device were also experimented. In summary, these two studies have laid the foundation for epicardial mapping, ablation and implantation of epicardial leads via transatrial pericardial access.

1.4 Long term safety and complications of intrapericardial access techniques

1.4.1 Thoracotomy

Intrapericardial adhesion, whereby the pericardium sticks to the surface of the heart, is considered an unavoidable consequence of cardiothoracic operations, due to the damage of mesothelial cells during operation. Therefore, post-operative intrapericardial adhesion might occur with procedures involving opening the pericardium, which could prevent and cause technical difficulties in future access reoperation to the pericardium and negatively influence the left ventricular mechanical function.[58] Moreover, intrapericardial delivery might also cause serious complications, especially cardiac tamponade and pericardial effusion, if the delivery system disrupts normal clearance of pericardial fluid. As parietal pericardium is a fibrous membrane and not elastic, a further build-up of pericardial fluid would then create pressure back onto the heart and induce cardiac tamponade. In most procedures involving cardiothoracic surgery, the pericardium is opened to prevent pressure from building up and cardiac tamponade. However, to form a drug reservoir, the pericardium is closed following

the surgery, where reduced cardiac indices, stroke work and increased cardiac tamponade risk have been observed.[59]

1.4.2 Subxiphoid access

The complications of pericardial access include (1) vascular and ventricular injury, (2) injury to other organs and (3) inflammatory reaction to the epicardial access. The insertion of a needle or sheath during epicardial access could potentially puncture the coronary or other major blood vessels, the right ventricle, as well as other organs. Inflammatory responses usually occur after a pericardial puncture, with mild symptomatic pericarditis observed in almost all patients. Severe pericarditis and pericardial inflammatory reaction reportedly occur at a low incident rate.[60] Damage to other organs during epicardial access is unusual, but complications have been reported as the consequences of a hepatic puncture during multiple epicardial punctures attempts.[61] Other complications were summarized in Table 1.

1.4.3 Transatrial access

Pulerwitz *et al.* conducted two preclinical safety studies on the percutaneous transatrial access for intrapericardial drug delivery in Yorkshire pigs. The first study focused mainly on the safety of procedures.[54] Pericardial haematocrit levels, whereby the level of haemoglobin present in the pericardial fluid, evaluated 24 hours after transatrial access to 4.3% from the baseline level of 1.1%. After 2 weeks, the pericardial haematocrit level dropped and returned to the baseline level. The treated pigs were recovered from the procedure uneventfully and did not experience any significant inflammatory response.[54] In both studies, local inflammation and small thrombi formation were observed in the atrial wall and site of puncture, respectively. Therefore, transatrial access into pericardium did not result in significant intrapericardial bleeding even after the pre-treatment of anti-platelet drug

aspirin, which inhibited the coagulation, and in high atrial pressure setting of pulmonary arterial hypertension. The study indicated that the technique appears to be reliable, safe and feasible even under these settings.[55] Moreover, no significant adverse events were observed in animals receiving transatrial access in other studies,[50–53,55] demonstrating that the technique was well-tolerated and safe. Mickelsen *et al.* reported massive pericardial effusion (PE) with hemodynamical significance in half of the pigs during either transvenous or transatrial insertion of epicardial lead for cardiac resynchronization. As the group used a large 8 Fr catheter and did not consistently puncture at the right atrium,[62] the observed complication was not specific to the transatrial approach. Scanavacca *et al.* also observed major pericardial bleeding with hemodynamic collapses in animals undergoing transatrial epicardial ablation and mapping but exited in the right ventricle and tricuspid annulus, which elucidated the importance of appendage at the right atrium instead of other structures.[57] Another review by D'Avila and colleagues further explored the pericardial anatomic variants potentially encountered in transthoracic pericardial approaches.[63]

1.5 Comparison of the intrapericardial delivery techniques

The choice of intrapericardial delivery techniques is determined by whether it is to be used solely for drug delivery or in conjunction with other surgery. Medial and lateral thoracotomy involves open-chest surgery, which is lengthy, invasive, and associated with a higher risk of complications as a larger opening is created on the chest. Therefore, thoracotomies are rarely used as an access method solely for pericardial drug delivery. Instead, pericardial drug delivery is usually performed during CABG or other open-chest surgeries, such as to prevent post-operation arrhythmias. In contrast, transatrial and subxiphoid access are much less invasive than access via thoracotomies. Transatrial access is a quick and simple procedure, which utilizes standard catheters and femoral central venous

access. It typically requires a few minutes for transatrial access after the introduction of a femoral sheath.[52] Similarly, subxiphoid access requires a blunt-ended needle, catheter or delicate pericardial introducer. Moreover, only local anaesthesia is required for these procedures. The size of the opening depends on the device used, ranging from a small incision to allow insertion of a catheter or needle to a larger subxiphoid pericardial window for introducer devices, such as PerDUCER® or PeriCardioScope™.

2. Guidance methods for intrapericardial access

Apart from thoracotomies, which allow direct visualisation of the pericardium, other intrapericardial access techniques require guidance methods to confirm the position and successful entry into the pericardium. Four main types of guidance method have been investigated in clinical trials and experimental studies to assist the pericardial access. Fluoroscopy has been predominantly used in experimental studies whereas echocardiography has been the most common guidance adopted in the clinical setting for pericardiocentesis.[64] Computer tomography (CT) and pericardioscopy are relatively new techniques for assisting pericardial access, which offer advantages over echocardiography, allowing direct visualization of needle advancement. However, limited clinical evidence and experience are available for CT and pericardioscopy guidance.[64] As each guidance is distinctive in terms of working principles and operating procedure, the details of each guidance method are discussed below.

Fluoroscopy was the first imaging technique used with intrapericardial access, usually performed in conjunction with a subxiphoid approach. The technique utilizes a continuous X-ray to allow real-time and dynamic visualization of contrast media or instruments through the body. An epicardial introducer needle containing g contrast medium is inserted and punctures

the pericardium contrast medium is then injected into the pericardial space.[7,65] The access of pericardium is confirmed with tenting at the needle site[38] and a sluggish layering of contrast medium diffusing inferiorly (downwards) observed,[38,65,66] A guidewire is then introduced into the pericardial space in exchange for the introducer needle.[65]

Sosa *et al.* performed pericardial puncture in patients using an epicardial introducer needle (Tuohy-17G) via the subxiphoid route with fluoroscopic guidance.[67] The needle was advanced gently under fluoroscopic guidance until a slight negative pressure was felt. The entry of the needles into the pericardial space was confirmed by injection of diluted contrast media under fluoroscopy. Laham *et al.* also reported a successful percutaneous subxiphoid access in pigs using the same needle and a similar procedure, but with continuous positive pressure (20-30 mmHg) applied during the advancement.[44]

Echo-guided pericardiocentesis was introduced by the Mayo Clinic in 1979,[68] which utilized a 2D phase-arrayed echocardiography to visualize the cardiac anatomy.[69] Callahan *et al.* advocated that the needle is entered from a point where the largest fluid accumulation is the closest to the probe and the needle path is away from any vital organ.[70] The subxiphoid route is a longer route to reach the pericardium compared to the para-apical route and passes through the anterior of the liver capsule. As ultrasound does not penetrate air, the lung is also avoided in echocardiography. Therefore, the apical route instead of the parasternal route is preferred for entry under echocardiography. Two different approaches to echo guidance are available. The first technique is an echo-assisted method, as originally proposed by Tsang *et al.*, the path of the optimal needle trajectory is first determined using echocardiography and memorised by the operator.[68] A polyteflon (Polytef) sheathed needle is then positioned from the predetermined site and advanced to the pericardium via

memorised trajectory without continuous echo-monitoring. Upon entry into the pericardium, the sheathed needle is further advanced for a short distance, where the steel needle core is withdrawn to leave the polyteflon sheath in the pericardium. The position of the sheath is confirmed with the saline echo-contrast medium, where the echo-contrast effect is monitored with 2D-echocardiography. A guidewire and a catheter are subsequently advanced into the sheath to create access. The second technique is an echo-guided method. The echocardiography is used to search for an optimal position and is maintained in that position throughout the procedure. The needle is attached to a multi-angle bracket mounted on the probe, inserted and advanced under a continuous echo-monitoring. When the needle tip is observed on the echocardiography, the syringe is removed and replaced with a guidewire and a catheter.[71,72]

Computer tomography (CT) is a technique using computational combinations of multiple X-ray measurements from different angles to produce cross-sectional tomographic images. In general, several images are taken during the procedure to direct the needle entry. The first image of the whole thoracic cavity is taken to determine the ideal approach and entry point into the pericardium. An introducer needle is then inserted, followed by the acquisition of a new image. The orientation of the needle is then adjusted based on the second image, and the needle is then advanced to the pericardium. Guidewire and catheters are then advanced into the pericardium. The ring advancement of the needle, guidewire and catheter, extra images are acquired when required. After placement of the guidewire and catheter, the final image is obtained to verify the position in the pericardium. Several clinical cases have demonstrated the successful CT-directed pericardiocentesis.[64,73–75]

Pericardioscopy is a tool for microscopic visualization of the epicardium and pericardium, which involves the introduction of an endoscope into the pericardium for taking video and photography. In early studies, two types of endoscopes were designed for pericardial disease diagnosis - a flexible fibreglass endoscope and a rigid 110^{o} angled instrument.[76] However, only the former design was used to assist the pericardial access through PerDUCER® devices. A flexible endoscope was applied into the mediastinal space to identify and select the suitable surface for pericardial access, with no adhesion and fat deposition on the pericardium. The position of the inserted guidewire and subsequently the catheter was also verified via the pericardioscopy.[77] Other devices such as Attachlifter and PeriCardiScope™ are incorporated with fiberscope and pericardiscope respectively on the suction head, which al the continuous visual monitoring throughout the advancement and pericardial access.[43]

3. Applications of intrapericardial drug delivery

3.1 Cardiac arrhythmia

Cardiac arrhythmia refers to conditions that cause the heart to beat irregularly and includes sub-categories such as tachycardia and bradycardia, where atrial fibrillation is one of the most common types of arrhythmia. Intrapericardial delivery of anti-fibrillatory drugs has been investigated for the alleviation of electrical and adrenergic induced atrial fibrillation and prevent postoperative atrial fibrillation (POAF). Most anti-arrhythmic drugs have been delivered in the form of a solution via injections and instillation with drugs dissolved in normal saline or Tyrode's solution, with surfactant if necessary to improve the drug solubility.[5,13] Occasionally, anti-arrhythmic drugs have been delivered in hydrogels or implants to achieve controlled or prolonged release. Implants, with various shapes, have been made from gelatine based Gelfoam[47,78] and delivered via thoracotomy, while hydrogels

have been predominantly composed of polyethene glycol (PEG)[48] and derivative materials such as Co-Seal.[29,30] For catheter-based transatrial or subxiphoid delivery, polymer and crosslinkers have been delivered via separated lumens into the fenced area in the pericardium, where in situ cross-linking occurred.[11] In thoracotomy, polymers were crosslinked and formed hydrogel before application on epicardium via spraying by a carbon dioxide sprayer set.[29,30]

Richardson *et al.* demonstrated that intrapericardial metoprolol effectively lowered the heart rate over a sustained period and minimally altered ventricular contractility or arterial pressure during electrical-induced atrial fibrillation, with undetectable levels of metoprolol in the plasma.[79] Furthermore, Verrier's group injected low and high dose (200 and 4000 μg) nitroglycerin bolus solutions into the porcine pericardium, achieving sustained coronary vasodilation in pigs without experiencing systemic hypotension[52] and exerted potent anti-fibrillatory effects in the close-chest intraluminal obstruction induced ischemic hearts respectively.[53]

Amiodarone is one of the most extensively investigated anti-fibrillatory drugs for intrapericardial delivery. Marcano *et al.* infused amiodarone solution for 3 days, achieving the desired atrial-tissue amiodarone concentration and low systemic concentration.[13] Ayers *et al.* also instilled amiodarone solution into the pericardium of dogs, which produced electrophysiological effects at superficial sites and suppressed electrical induced atrial fibrillation.[5] Moreover, two human clinical trials evaluated the effectiveness of spraying amiodarone onto the epicardium in patients receiving CABG. Although they used the same hydrogel spray system, the experimental design was different between the two studies. Nevertheless, both studies demonstrated that spray delivery of amiodarone to the epicardium

is effective in preventing POAF. A lower incidence of POAF was observed in the group with epicardial amiodarone hydrogel application than in the control group. The epicardial amiodarone application was effective at a low systemic level, well-tolerated, fast-acting, and had a lower risk of ventricular and systematic side-effects.[29,30] In addition to pericardial drug therapy, epicardial pacing leads could also be implanted in the pericardial spaces for cardiac resynchronization therapy in patients with severe heart failures and signs of intraventricular dyssynchrony.[56]

However, not all approaches investigating intrapericardial delivery have been successful. For example, epicardial corticosteroid administration failed to prevent POAF.[29] Vereckei *et al.* also demonstrated that intrapericardial ibutilide infusion failed to achieve a higher termination rate in the dogs with rapid atrial pacing-induced atrial fibrillation, compared to the control group.[6] Another study demonstrated intrapericardial delivery of sotalol and flecainide had a marked effect on atrial epicardial electrophysiology but were ineffective in sustained atrial fibrillation termination.[34]

Tachycardia, whereby the heart rate is abnormally fast, requires emergency treatment in severe cases. Patients with ventricular tachycardia are treated with immediate defibrillation followed by cardioversion involving electrical intervention and/or drugs. Maintenance therapy involves treatments with amiodarone or β-blockers alone or in conjunction with implantation of a cardioverter-defibrillator. However, whilst intravenous β-blockers are effective in alleviating tachycardia, they are associated with unwanted side-effects, including suppression of blood pressure and cardiac contractility.[80] Intrapericardial delivery of β-blockers have exhibited enhanced activity on the baseline heart rate and adrenergic tachycardia, achieving similar anti-tachycardic effects at 10-30 fold lower dose compared to

IV.[34] Intrapericardial β-blockers also suppress tachycardia in haemorrhage and adrenergically induced sinus tachycardia without affecting blood pressure and contractility. The use of intrapericardial delivery of β-blockers could be particularly beneficial to patients with impaired contractility and propensity to hypotension in the surgical setting and during the emergent condition.[80] In addition to drug delivery, epicardial mapping and ablation were also performed via subxiphoid and transatrial accesses to control late and recurrent ventricular tachycardia post-myocardial infarction in swine models.[57]

3.2 Vascular disease

Local delivery to the coronary artery is an attractive and novel approach for focal vascular injury, especially for preventing coronary restenosis after percutaneous cardiac interventions. The unblocked coronary artery is usually fragile, due to the calcification and injury sustained during the intervention. Therefore, intrapericardial delivery provides a good target for localised delivery to the coronary artery due to the proximity. This concept is relatively new and has not been extensively investigated. Stoll *et al.* demonstrated that the content in the pericardial fluid could access the coronary artery, which indicated that drug delivery to the coronary artery via pericardium is feasible.[81] Willerson *et al.* showed intrapericardial administration of sodium nitroprusside, a vasodilator releasing nitric oxide, successfully eliminated platelet aggregation and cyclic flow variation in stenosed and endothelium-injured coronary arteries of dogs.[82]

3.3 Myocardial infarction

Myocardial infarction (MI) is the main cause of death associated with coronary artery disease. Current therapies aim to prevent the spreading of the lesion or reverse heart remodelling but to date have not successfully induced regeneration of damaged cardiac

myocytes. Although cardiomyocytes are thought to renew with a turnover rate of 1% - 0.45% between the age of 25 and 75 respectively,[83] regeneration is slow and is often outpaced by fibrosis, generating fibrous connective tissues and scarring. Therefore, there is an unmet need to develop new therapies for cardiac repair.

A variety of drugs have been delivered into pericardial space to promote cardiac regeneration. For instance, Uchida *et al.* delivered heparin sulphate and fibroblast growth factors (FGF) into the pericardium via a catheter placed transatrially.[49] This study demonstrated angiogenesis from epicardium towards the subepicardial infarcted area as well as myocardial salvage in a canine model of myocardial infarction. In another study, intrapericardial delivery of FGF-2 was found to promote myocardial angiogenesis and improve the myocardial perfusion and function in the ischemic area without significant side effects.[45]

Polizzotti *et al.* have investigated intrapericardial periostin-loaded Gelfoam implants.[78] Periostin is a secreted extracellular matrix protein that has been shown to stimulate cardiomyocyte proliferation and angiogenesis post-MI.[84] Gelfoam is made of gelatine purified from porcine skin, which is non-toxic, non-immunogenic and biodegradable. It triggers the non-fibrotic fibrosis *in-vivo* and forms a fibrin-loaded hydrogel. Gelfoam loaded with a recombinant peptide of periostin stimulated cardiomyocyte mitosis and enhanced angiogenesis in a pig model of myocardial infarction compared to direct injection of recombinant periostin peptide alone.[78] Ladage *et al.* also developed an injectable slurry of Gelfoam loaded with periostin peptide for the treatment of myocardial infarction.[85] However, periostin peptide treatment was associated with myocardial fibrosis at one week and 12 weeks post-treatment, which is likely to limit clinical application.

In addition to drug therapies, intrapericardial cell delivery has also been studied to promote cardiac regeneration. Cells have been delivered in either a suspension, such as Hypothermosol which is a hypothermic preservation media for the preservation of cells and tissues,[86] or in biodegradable polymer scaffolds. Blázquez *et al.* reported an intrapericardial injection of porcine cardiosphere-derived cells (CDC) into a porcine infarct model to modulate the microenvironment for promoting cardiac repair.[86] Changes in immunological parameters were observed, which modulated the inflammatory environment of the infarcted heart and thus promoted cardiac repair indirectly. However, no direct improvement of cardiac function was observed in pigs upon receiving intrapericardial CDC compared to the control group. Nonetheless, Branco *et al.* demonstrated that BMMCs delivered via an intrapericardial infusion were able to diffuse into and penetrate the myocardium, with the BMMCs concentration higher in the infarcted region. This finding suggests that interactions with local factors in the infarcted area may promote cell migration and/ or cell survival of BMMCs.[7]

Conclusions

Pericardial access provides an alternative route for delivering therapeutics to the heart. Encouraging results have been reported when using this route for delivery of cells, drugs and protein for a variety of conditions to induce regeneration of myocardium after acute myocardial infarction, mitigating cardiac arrhythmias, or preventing platelet aggregation and restenosis after reperfusion via the coronary artery. Although current concerns exist regarding invasiveness and associated complications, the intrapericardial delivery offers advantageous pharmacokinetic profiles and provides a new route for drug delivery to achieve a localized therapy to the heart, which could fill the unmet need for targeted cardiac delivery.

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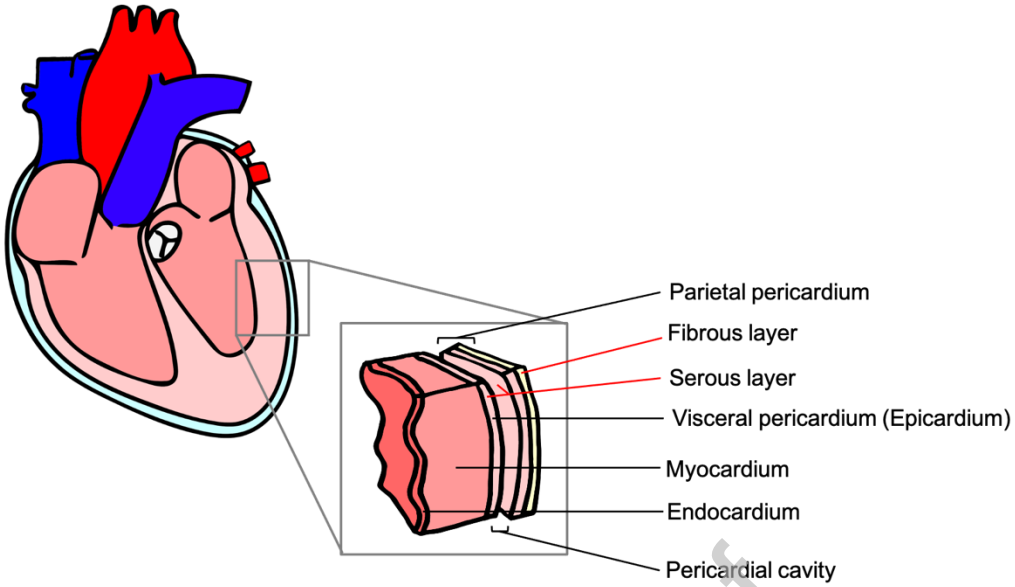

FIG 1. Cross-section of the human heart wall showing the location of the parietal and visceral pericardium.

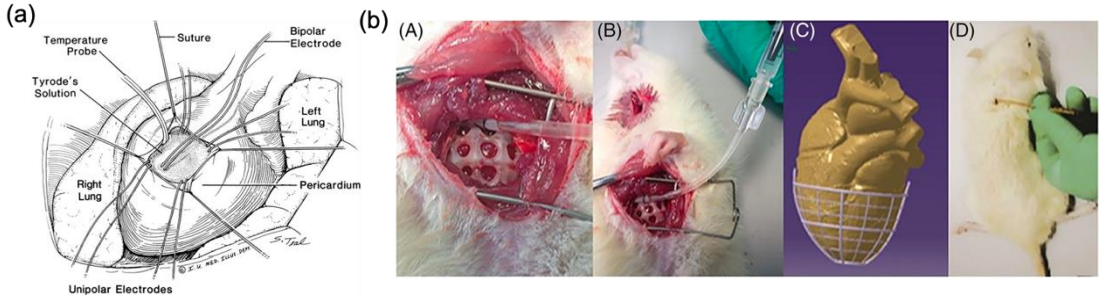

FIG 2. Illustrations of the intrapericardial drug instillation via (a) an incision on the pericardium to form a reservoir[25] and (b) the active hydraulic ventricular support delivery device implanted over the epicardium.[26]

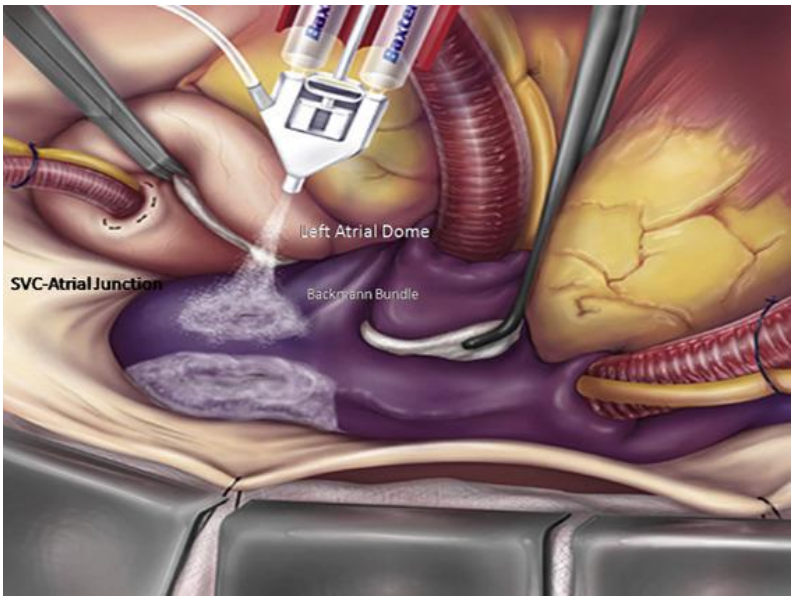

FIG 3. An illustration of epicardial spraying of drug-loaded hydrogel after CABG.[29,30]

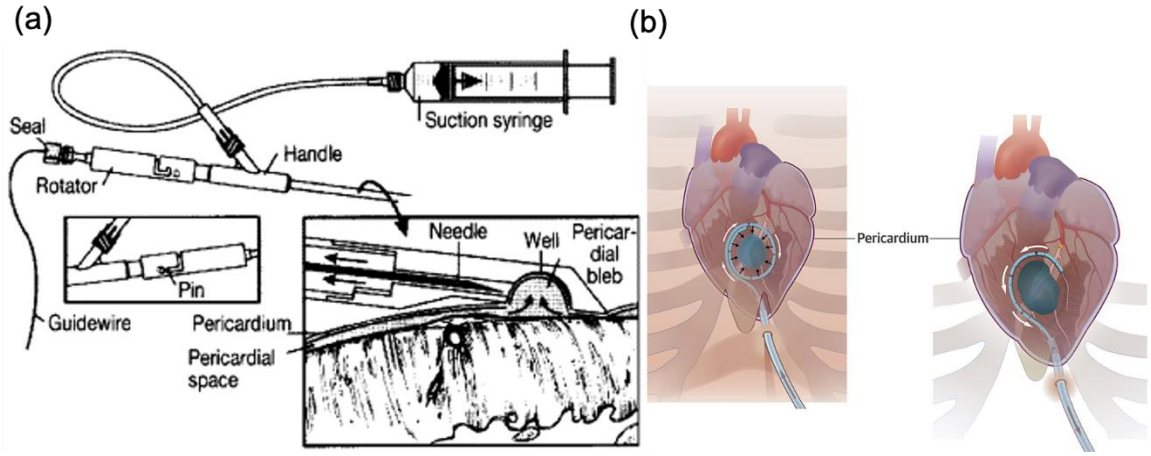

FIG 4. Schematic diagrams of the pericardial introducers (a) PerDUCER® [87] and (b) the loop catheter developed by Garcia *et al.*[48]

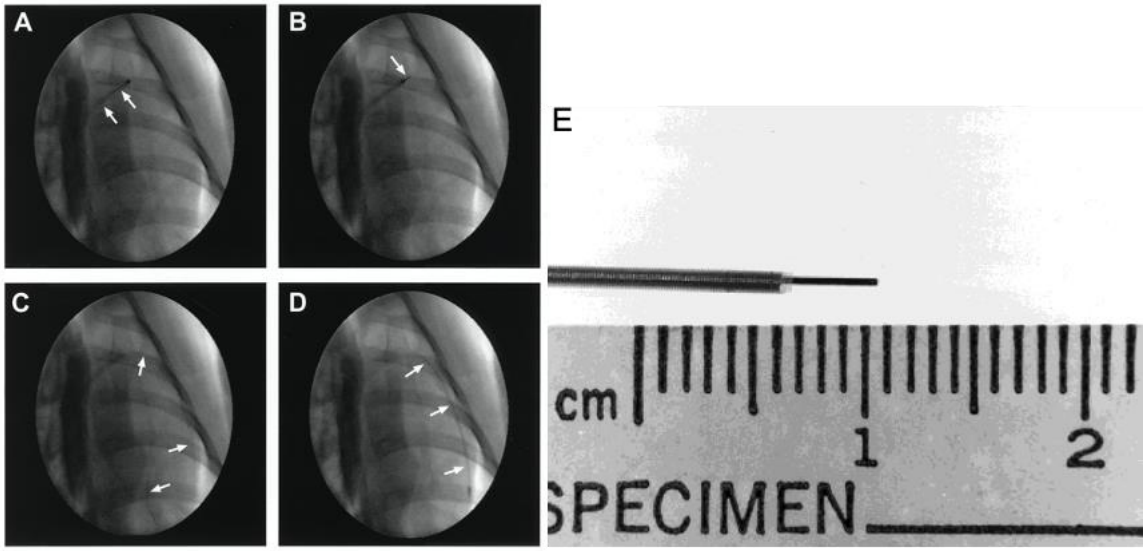

FIG 5. Fluoroscopic images showing (A) Advancement of the 8 Fr catheter into the atrium, (B) Puncture of the pericardium using the needle catheter, (C) Advancement of a guidewire in the pericardial space and (D) advancement of a 4 Fr catheter over the guidewire.[52] (E) An example of a wires system used in transatrial delivery, comprised of a 0.014-inch guidewire mounted inside a 0.038-inch catheter.[55]

Table 1

Summary of the major, minor and rare complications observed during or after the subxiphoid pericardial access (adapted from [59]

	Potential complications	**Incidence rate**	**Description**
Major complications			
Acute	Coronary vessel damage	0.6%[59]	Coronary artery stenosis
Delayed			Myocardial infarction
Acute	Pericardial inflammatory reaction		
	Injury to subdiaphragmatic vessels and abdominal viscera	0.5%[61,65]	
	Pericardial bleeding	10-30%[88]	Mild and self-limiting
		4.5%[59]	Intrapericardial bleeding >80mL
Delayed		0.6%[59]	Delayed tamponade
Acute	Severe pericardial reaction		
Minor complications			
Acute	Chest pain	Almost all patients[59]	
	Pericarditis		Mild symptomatic
	Right ventricular puncture	4.5-17%[59]	Without significant bleeding
Unusual complications			
Acute	Severe pericardial bleeding	Reported in literature[60]	Middle cardiac vein laceration
	Right ventricular pseudoaneurysm		
	Liver puncture		Intra-abdominal bleeding
			Subcapsular hepatic hematoma

Table 2

Summary of various pericardial access methods

Access method	**Thoracotomy**		**Subxiphoid access**	**Transatrial access**
	Medial sternotomy	**Lateral thoracotomy**		
Anaesthesia	General		Local	
Guidance	Not required		1. Pericardioscopy (device-based approach only) 2. Fluoroscopy 3. Echocardiogram 4. Computer tomography	Fluoroscopy
Wound size and scarring	Large	Medium to large	Small to medium size depending on devices	Small puncture on the atrial wall and thigh
Inflammatory response	Pericarditis Bone inflammation Inflammation of the wound	Pericarditis Inflammation of the wound	Pericarditis Inflammation of the wound	Transient inflammation on atrial wall and thigh
Infection risk	High		Low	
Recovery time	Long		Short	
Advantage	Direct visualization of the pericardium	1. Intact chest cage (vs MS) 2. Direct visualization of the pericardium	Various introducer devices available Simplest method	1. Rapid procedure 2. The standard femoral vein catheterization procedure 3. Low complication rate

				4. Standard clinical closure devices available to avoid problems associated to transatrial appendage[65]
Disadvantage	1. Cracked sternum 2. Pericardial adhesion and tamponade 3. Pain and a high chance of complications	1. Pericardial adhesion and tamponade 2.Pain and a high chance of complications	1. Incorrect needle placement (especially under blind insertion) 2. Puncture of other organs	A puncture on the atrium
Suitable use	Should only be used after cardiac-thoracic surgery, or in a small animal like rodents or in AF studies which requires the implantation of the electrodes		Currently used for mapping and ablation,[57,67] but these routes can also be used solely for pericardial drug delivery	

Table 3

Summary of the intrapericardial drug delivery system used to treat arrhythmias in animal studies and human clinical trials

Drug (dosage form)	**Solvent/ carrier**	**Species**	**Outcome**	**Ref**
Experimental studies				
Access method: Thoracotomy				
Amiodarone (injection)	D5W	Sheep	- Prevent POAF with minimal systemic drug distribution and systemic side effects	[13]
Amiodarone (instillation)	D5W with Tween-80	Dog	- Suppressed electrical induced atrial fibrillation superficially	[5]
Amiodarone (implant)	Poly-lysine crosslinked dextran disc	Rabbit	- Higher amiodarone in the right atrium than in the lung - Increased AF threshold and the effective refractory period of the left atrium, and less likely experienced ventricular and systemic side effects	[89]
Amiodarone Sotalol (infusion)	D5W with polysorbate 80, benzyl alcohol and bicarbonate	Goat	- Higher atrial drug concentrations and stronger anti-arhythmic effects at lower drug plasma concentrations	[90]
Atenolol Sotalol (infusion)	Normal saline	Rat	- The β-blocking activity of sotalol and atenolol was greatly enhanced through intrapericardial delivery - Similar anti-tachycardic effects were obtained at a lower dose by 10-30 folds compared to IV	[34]
Ibutilide (infusion)	Normal saline	Dog	- Produced marked atrial physiological effects - Failed to achieve higher termination rate compared to IV	[6]
L-arginine	Tyrode's solution	Dog	- Reduced sympathetic stimulation (SS) induced-	[25]

(instillation)			shortening of the effective refractory period - Reduced the severity of ischemic ventricular arrhythmias promoted during SS	
Lidocaine (instillation)	ASD	Rat	- Reduced recovery time for the first sinus rhythm and reversed myocardial damage post-VF	[26]
Metoprolol (injection)	Normal saline	Pig	- Lower heart rate for sustained periods, with minimal effect on either ventricular contractility or atrial pressure	[79]
Procainamide	Unspecified	Pig	- Prolonged atrial refractoriness and raised AF threshold	[28]
Ranolazine	Unspecified	Pig	- Increased atrial refractoriness and reduced atrial fibrillation inducibility without altering arterial blood pressure	[91]
Sotalol Flecainide (infusion)	Milli-Q water, normal saline	Goat	- Produced a marked effect on atrial epicardial electrophysiology, but intrapericardial delivery was not superior to intravenous delivery for AF termination and AF cycle length prolongation	[12]
Access method: Subxiphoid access				
Amiodarone (hydrogel injection)	Dithiothreitol and bi-cysteine VPM peptide crosslinked 4-arm PEG maleimides hydrogel	Pig Rat	- Reduced the duration of sustained AF and inducibility of AF post-implantation - Lowered off-target drug levels in liver, lung, thyroid and fat compared to intraperitoneal delivery in rats	[48]
Access method: Transatrial access				
Esmolol (injection)	Not reported	Pig	- Reduced haemorrhage and adrenaline-induced tachycardia without affecting blood pressure or ventricular contractility	[80]
Nitroglycerin (injection)	Normal saline	Pig	- Achieved sustained coronary vasodilation without systemic hypotension as a side effect (low dose)	[52] [53]

			- Exerted potent anti-fibrillatory effects in the close-chest intraluminal obstruction induced ischemic hearts (high dose)	
Clinical trials				
Access method: Parasternal and lateral thoracotomy				
Amiodarone (hydrogel spraying)	Co-Seal hydrogel	Human	- Effective in preventing POAF in CABG patients with minimal risk of extracardiac side effects	[29,30]

Table 4

Summary of the intrapericardial drug delivery system used to modulate the infarcted heart or induce cardiac regeneration post-myocardial infarction

Drug or cell (dosage form)	**Solvent/ carrier**	**Species**	**Outcome**	**Ref**
Transatrial access				
CDC (injection)	Hypothermosol	Pig	- Altered the phenotypes of resident lymphocytes and TH1 cytokines in pericardial fluid, modulating the inflammatory environment of the infarcted heart	[86]
Heparin sulphate and bFGF (injection)	Normal saline	Dog	- Reduced percentage weight of the infarct ventricle and increased vascular number, predominantly in the subepicardial area - Neo-angiogenesis from epicardium toward subepicardial infarcted area	[49]
Heparin and FGF-2 (injection)		Pig	- Increased myocardial vascularity, left-to-left angiographic collaterals and left circumflex blood flow post intrapericardial delivery of FGF-2	[45]
Subxiphoid access				
BMMC	Saline	Pig	- Diffused penetrations of BMMC in the myocardium	[7]
Thoracotomy				
Docosahexaenoic acid (DHA)	Normal saline with ethanol	Pig	- Reduced infarct sizes in infarct model - Reduced ventricular fibrillation score during ischemia and related mortality rate	[92]
eGFP vector and	Gelform particles	Pig	- Presence of MSC and expressed eGFP in	[47]

MSC (injectable)			the myocardium	
IGF-1	Saline	Sheep	- Increased ejection fraction post-heart failure	[32]
Nitroglycerine (instillation)	ASD	Rat	- Vasodilation and improved cardiac function - Prevented serum myoglobulin level elevation, decreased ST-elevation post-MI	[27]
Periostin (implants)	Gelform patches	Pig	- Improved survival, cardiac function and left ventricular wall thickness in infarct zone post-MI - Led to substantial fibrosis in the heart	[85]
	Gelfom discs	Mice	- Increased cardiomyocyte cell cycle activity and angiogenesis infarct border zone	[78]