The Pericardium

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Abstract

The pericardium is a unique structure that surrounds the heart and serves several important physiological roles. The removal of the pericardium, certain pericardial disorders, or the buildup of fluids within this space will ultimately alter hemodynamic performance. Recent therapeutic approaches have been directed to exploit the space that exists between the pericardium and the epicardial surface of the heart. New devices and techniques are being developed to access this space with minimally invasive approaches. The pharmacokinetics of many drugs may be greatly enhanced if the drug is delivered into the pericardium. As more is learned about the pericardium, it may play a significant role in cardiac therapies.

Keywords

Pericardium • Pericardial fluid • Mechanical effects • Pericardial disorders • Comparative anatomy • Intrapericardial therapeutics

9.1 Introduction

The pericardium is a fibroserous conical sac structure encasing the heart and roots of the great cardiac vessels. In humans, it is located within the mediastinal cavity posterior to the sternum and cartilages of the 3rd through 7th ribs of the left thorax and is separated from the anterior wall of the thorax. It is encompassed from the posterior resting against the bronchi, the esophagus, the descending thoracic aorta, and the posterior regions of the mediastinal surface of each lung. Laterally, the pericardium is covered by the pleurae and lies along the mediastinal surfaces of the lung. It can come into direct contact with the chest wall near the ventricular apical region, but this varies with the dimensions of the long axis of the heart or with various disease states. Under normal circumstances, the pericardium separates and isolates the heart from contact by the surrounding tissues, allowing freedom of cardiac movement within the confines of the pericardial space (Fig. 9.1).

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9.2 Anatomy

In humans, the 1–3 mm thick fibrous pericardium is commonly described as a *flask-shaped bag*. The neck of the pericardium (superior aspect) is closed by its extensions surrounding the great cardiac vessels, while the base is attached to the central tendon and to the muscular fibers of the left side of the diaphragm (Fig. 9.2). Much of the pericar-

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dium's diaphragmatic attachment consists of loose fibrous tissue that can be readily separated and/or isolated, but there is a small area over the central tendon where the diaphragm and the pericardium are completely fused.

Examination of the pericardium reveals that it is composed of two interconnected structures: the serous pericardium and the fibrous pericardium. The serous pericardium is one continuous sac with a large infold that contains the heart (Fig. 9.3). An appropriate analogy would be a fist (representing the heart) pushed into the side of a deflated balloon (representing the serous pericardium), therefore enveloped by two individual layers of material. The interior surface of the pericardium is intimately connected to the surface of the heart and is known as the *visceral pericardium* or the *epicardium*. The exterior surface of the serous pericardium is known as the *parietal pericardium* and is fused with the thick lining of the fibrous pericardium. The pericardial space, where the pericardial fluid resides, is bounded on either side by the parietal and visceral pericardium. To the naked eye, however, the visceral pericardium cannot be distinguished from the surface of the heart, and the parietal pericardium cannot be distinguished from the fibrous pericardium. For this reason, the general use of the term *pericardium* refers to the composite of the parietal and fibrous pericardium, which appears to be a single sac that surrounds the heart. Yet, more accurately, the pericardium should be described as three total layers, with fluid lining between two of them (Fig. 9.3).

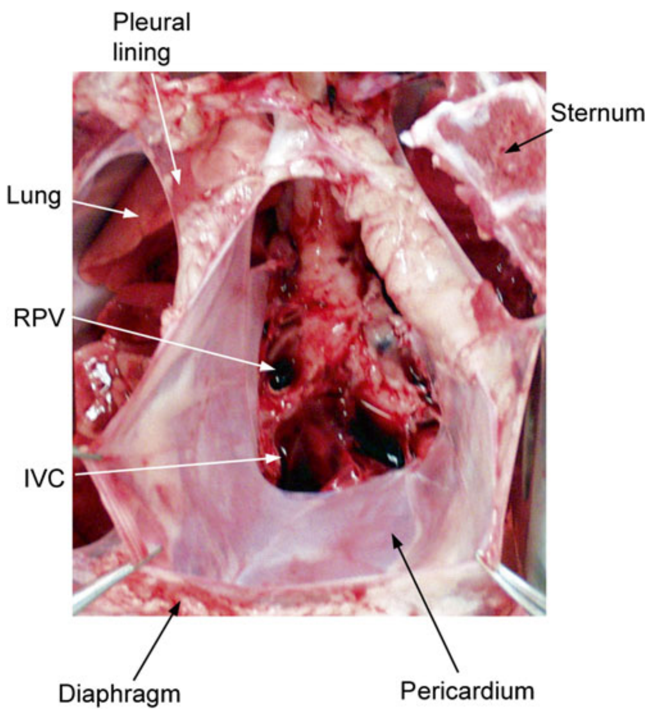
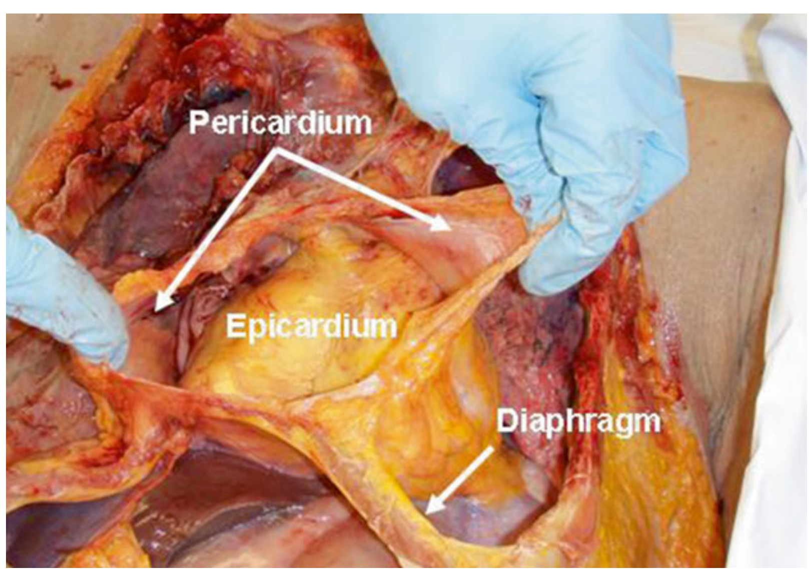


Fig. 9.1 Posterior view of the pericardial sac, with the anterior surface and heart cut away. One can see that the great vessels of the heart penetrate through the pericardium, which extends up these vessels for several centimeters

The inferior vena cava enters the pericardium through the central tendon of the diaphragm where there exists a small area of fusion between the pericardium and the central tendon, but it receives no covering from this fibrous layer. Between the left pulmonary artery and subjacent pulmonary vein is a triangular fold of the serous pericardium known as the *ligament of the left vena cava* (or vestigial fold of Marshall). It is formed by a serous layer over the remnant of the lower part of the left superior vena cava (duct of Cuvier) which regresses during fetal life but remains as a fibrous band stretching from the highest left intercostal vein to the left atrium, where it aligns with a small vein known as the *vein of the left atrium* (or oblique vein of Marshall), eventually opening into the coronary sinus. The pericardium is also attached to the posterior-sternal surface by superior and inferior sternopericardial

Fig. 9.2 The fibrous pericardium of a fresh human cadaver is opened to expose the epicardium of the heart. Note the attachment of the pericardium to the diaphragm



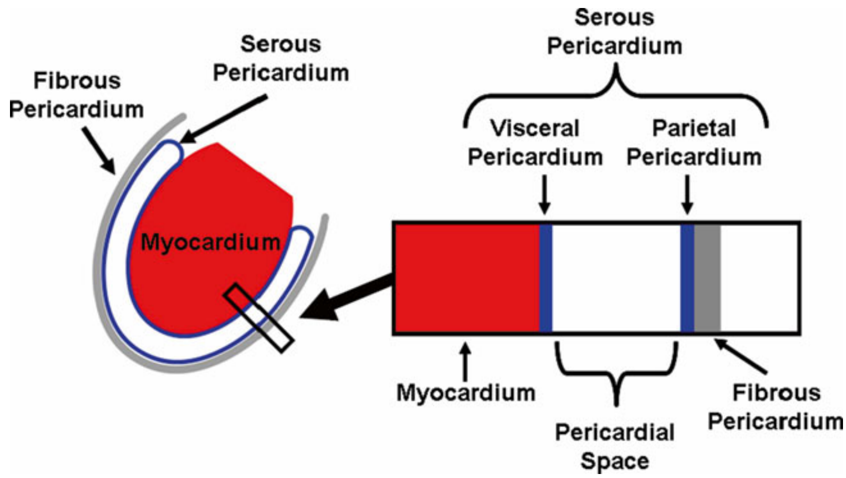


Fig. 9.3 *Left*: A schematic diagram of the serous and fibrous pericardium with respect to the heart. *Right*: An expanded cross-section view shows the attachment of two layers of the serous pericardium (visceral and parietal) to the myocardium and fibrous pericardium, respectively

ligaments that securely anchor the pericardium and also act to maintain the orientation of the heart inside the thorax.

As previously mentioned, the serous pericardium is a closed sac that lines the fibrous pericardium consisting of a visceral and a parietal portion. The visceral portion that covers the heart and great vessels is commonly referred to as the *epicardium* and is continuous with the parietal layer that lines the fibrous pericardium. The parietal portion covering the remaining vessels is arranged in the form of two tubes. The aorta and pulmonary artery are enclosed in one tube (the *arterial mesocardium*), while the superior and inferior venae cavae and the four pulmonary veins are enclosed in the second tube (the *venous mesocardium*) (see JPG 9.1 in the online supplemental material). There is an attachment to the parietal layer between the two branches, behind the left atrium, commonly referred to as the *oblique sinus*. There is also a passage between the venous and arterial mesocardia (i.e., between the aorta and pulmonary artery in front and the atria behind) that is termed the *transverse sinus*. The *superior sinus or superior aortic recess* extends upward along the right side of the ascending aorta to the origination point of the innominate artery. The superior sinus also joins the transverse sinus behind the aorta, and they are both continually fused until they reach the aortic root. For additional text describing this anatomy, also see Chap. 5.

The arteries of the pericardium are derived from the internal mammary and its musculophrenic branch and also from the descending thoracic aorta. The nerves innervating the pericardium are derived from the vagus and phrenic nerves, as well as the sympathetic trunks.

9.3 Physiology of the Normal Pericardium

9.3.1 Pericardial Fluid

In normal hearts, the pericardium should be considered as only a potential space. It contains 20–60 mL of pericardial fluid, most of which resides in the major pericardial sinuses and the atrioventricular grooves [1]. The fluid is an ultrafiltrate of plasma and therefore has many similarities to plasma in its electrolyte composition; pericardial fluid, however, contains about half the total protein concentration, one-third the triglyceride and cholesterol content, and one-fifth the amount of white blood cells [2]. A more complete comparison of plasma and pericardial fluid composition is shown in Table 9.1.

The details of the formation, clearance, and turnover of pericardial fluid have not yet been fully explained. Yet, it is generally agreed that pericardial fluid is derived from plasma leakage from myocardial capillaries [3], and this filtrate is eventually drained by the lymphatic system. During situations of high pericardial fluid pressure, such as in cardiac tamponade, investigators have found that fluid may pass through the pericardium and enter the pleural space [4]. The turnover time of pericardial fluid in humans has not been established, but in sheep it is observed to be every 5.4 h [5].

As mentioned previously, pericardial fluid distribution is not uniform. The majority of the fluid found in the major sinuses and grooves of the heart and makes up the pericardial reserve volume. The fluid is considered to be well mixed due to the motion of the heart, and agents injected into the pericardial space quickly and evenly disperse throughout [5]. Too much pericardial fluid, either due to disease or an intervention, may cause increased pericardial pressure and compromise cardiac performance, a syndrome called *cardiac tamponade*. As shown in Fig. 9.4, the pericardial reserve volume acts as a buffer against increasing pressure; once these groves and sinuses have filled, however, the pressure quickly increases with additional fluid volume.

9.3.2 Mechanical Effects of the Pericardium

The degree to which the pericardium alters heart wall movement(s) varies depending on the ratio of cardiac to pericardial size, loading conditions, and the degree of active and passive filling. Closure of the pericardial sac following open-heart

Table 9.1 Normal plasma composition compared to the pericardial fluid composition of 30 patients undergoing cardiac surgery

	Normal plasma range	Pericardial fluid mean value	Mean fluid/serum ratio
Total protein (g/dL)	6.5–8.2	3.3	0.6
Albumin (g/dL)	3.6–5.5	2.4	0.7
Glucose (mg/dL)	70–110	133	1.0
Urea (mg/dL)	15–45	33	1.0
Calcium (mg/dL)	8.1–10.4	7.3	0.9
LDH (IU/L)	100–260	398	2.4
Creatinine (mg/dL)	0.8–1.2	0.9	0.9
Cholesterol (mg/dL)	130–240	43	0.3
Triglycerides (mg/dL)	50–170	34	0.3
White blood cells (K/μL)	4.0–10.8	1.4	0.2

Data from Ben-Horin [2]

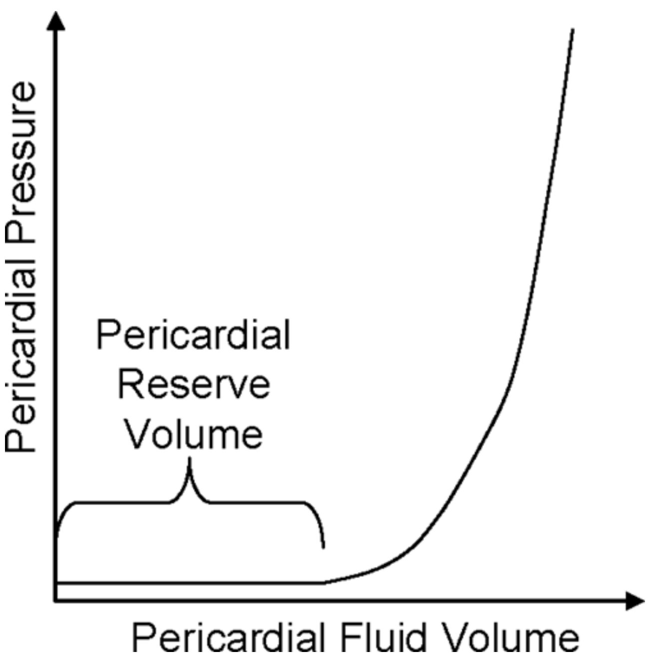


Fig. 9.4 As pericardial fluid volume increases, the pericardial reserve volume is filled. Once the reserve volume is full, pressure within the pericardium rapidly rises and cardiac performance may be compromised. Adapted from Spodick [1]

surgery has been proposed to (1): avoid possible postoperative complications, (2) reduce the frequency of ventricular hypertrophy, and/or (3) facilitate future potential reoperations by reducing fibrosis [6]. Furthermore, reported differences in ventricular performance, dependent on the presence of the pericardium, have been observed following cardiac surgery [7, 8].

In general, the presence of a pericardium physically constrains the heart, often resulting in a depressive hemodynamic influence limiting cardiac output by restraining diastolic ventricular filling [9, 10] (see Video 9.1 in the online supplemental material). The physical constraint by the pericardium is translated into direct external mechanical forces that can also alter patterns in myocardial and systemic blood flow [10, 11]. Direct primary and indirect secondary effects are observed as additional forces through the chamber free walls. Because both the left and right side atria and the left and right side ventricles are bound by a common septum, geometrical changes from chamber interaction(s) are dynamic, depending on the different filling rates and ejection rates of each of the four chambers [12, 13]. Thus, it is important to note that chamber-to-chamber interactions through the interventricular septum and by the pericardium further promote direct mechanical chamber interactions [14–16].

The effects of the pericardium on mechanical measures of cardiac performance are generally not evident until ventricular and atrial filling limitations are reached, changing geometrical and mechanical properties through factors such as maximum chamber volume and elasticity. These effects become more evident as the pericardial limitations become extended [17, 18]. With the known force-length dependence of cardiac muscle, variation of chamber volumes through removal of the pericardium will, in turn, alter isometric tensions and therefore directly impact systolic ejection. On the other hand, in specific cases where the restrictive role of the pericardium greatly increases, such as during cardiac tamponade, an increased intrapericardial fluid volume may result in critical restriction by the pericardium that then reduces cardiac performance (Fig. 9.5) [19, 20].

It should also be noted that increases in intrathoracic pressure will create an additional interaction between the ventricles, as well as between the heart and lungs in a closed chest. Thus, studying cardiac function in situ (with an opened chest) or in vitro allows for the elimination of these influences of intrathoracic pressure and for more direct identification and quantification of pericardial influences on cardiac performance and ejection [21]. Furthermore, such isolation of these pericardial effects from diastolic filling is an important consideration, since normal ventricular output is dependent on diastolic pressure and independent of the presence of the pericardium [22].

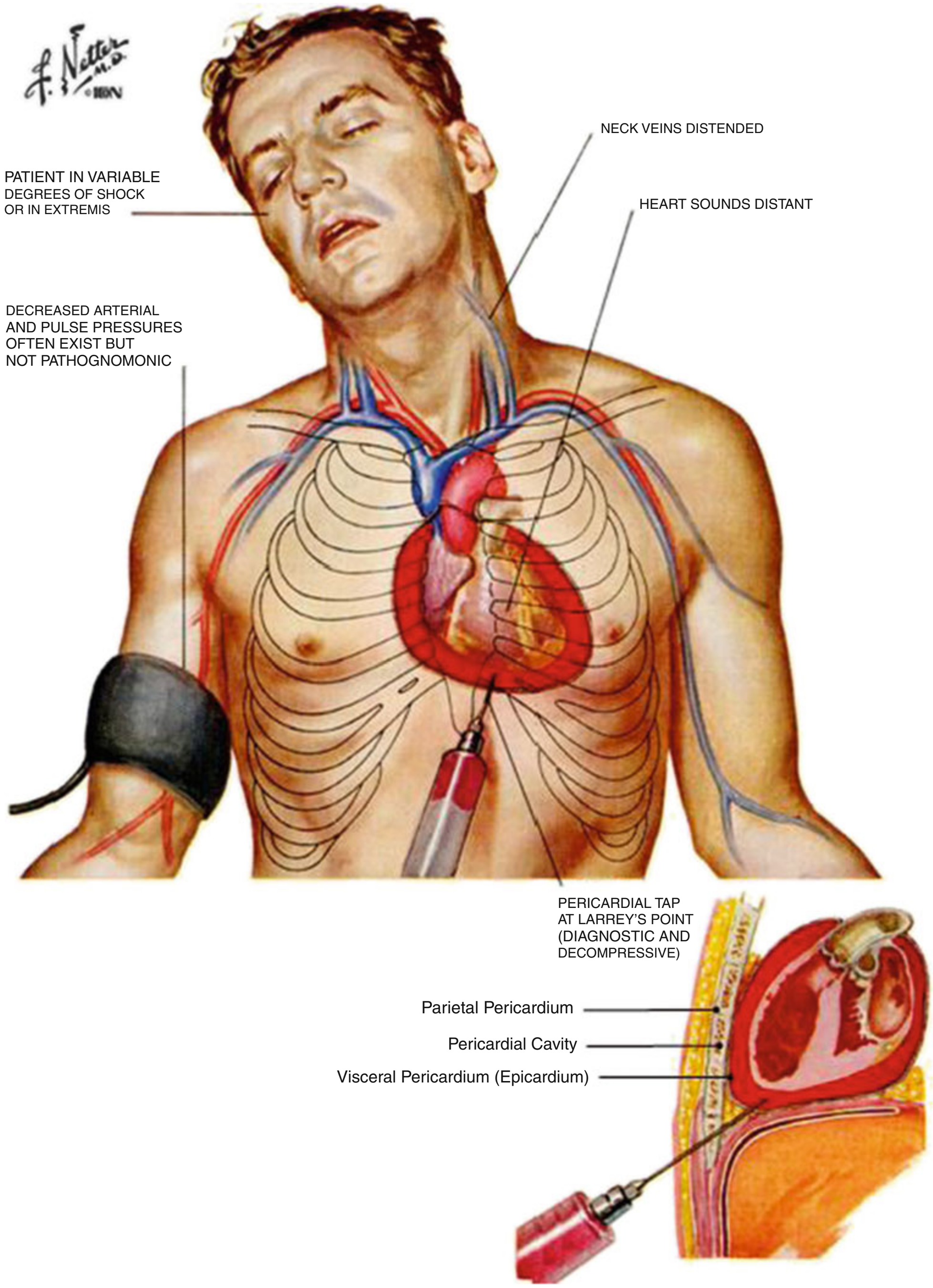


Fig. 9.5 Cardiac tamponade occurs when there is a large accumulation of fluid in the pericardium (*top*). During tamponade, hemodynamics may be seriously compromised. Distended neck veins, decreased blood pressure, various degrees of shock, and distant heart sounds may all be symptoms of tamponade. In most cases, tamponade is treated by pericardiocentesis or drainage of the sac with a long hypodermic needle (*bottom*). ©2006 Elsevier Inc. All rights reserved. www.netterimages.com, Frank Netter

9.4 Pericardial Disorders: Congenital, Pathological, and Iatrogenic

Sir William Osler referred to pericardial disease when he stated that "probably no serious disease is so frequently overlooked by the practitioner" [23]. Many pericardial disorders are asymptomatic and often go unnoticed throughout the patient's life, but some may be fatal (Fig. 9.6). Pericardial disorders may be classified as congenital, pathological, or iatrogenic.

Congenital abnormalities of the pericardium are extremely rare. Partial absence of the pericardium may occur, usually exposing the left side of the heart. Complete absence of the pericardium is even less frequent [23]. Cysts may also form during development in, on, or around the pericardium. These usually are not clinically significant and need to be treated only if they become symptomatic [1]. A list of these major congenital abnormalities is found in Table 9.2.

During disease or injury, the pericardium responds with the production of fluid, fibrin, cells, or a combination of the

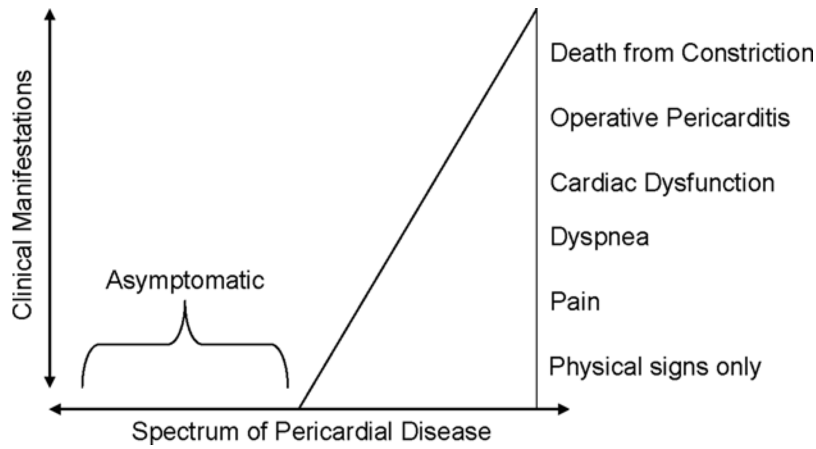


Fig. 9.6 Most pericardial diseases are discovered postmortem, implying that they were asymptomatic throughout the patient's life. Serious pericardial disease, however, may have many clinical manifestations, as shown in the figure. Adapted from Reddy [22]

Table 9.2 Major sources of pericardial disorders (congenital, pathological, or iatrogenic)

Congenital	Pathological	Iatrogenic
Primary	Idiopathic pericarditis	Surgical
Pericardial absence	Due to living agents—infectious, parasitic	Instrument trauma
Cysts	Vasculitis—connective tissue disease	Cardiac resuscitation
Teratoma	Immunopathies/hypersensitivity states	Iatrogenic pneumopericardium
Lymphangioma	Disease of contiguous structures	Drug reactions and complications
Diverticulum	Disorders of metabolism	Radiation
Pericardial bands	Trauma—indirect, direct	
Secondary	Neoplasms—primary, metastatic, multicentric	
Pericarditis due to maternal lupus	Uncertain pathogenesis	
Intrapericardial hernia of abdominal organs		

Adapted from Spodick [1]

three [23]. The amount of each depends upon the type of disease or injury. Numerous forms of pericarditis can initiate an inflammatory response, including fibrinous pericarditis, fibrous pericarditis, infective pericarditis, and cholesterol pericarditis. Diseases unrelated to the pericardium may also trigger a pericardial response, such as a nearby neoplasm or a myocardial infarction. After a transmural myocardial infarction, for example, patients almost always form adhesions between the necrotic area of the myocardium and the fibrous pericardium [23]. Pericardial effusions, or excess fluid in the pericardium, may occur with disease. Large volumes of lymph, chyle, or blood may accumulate in the pericardial sac. If the accumulation of fluid is significant, this may result in impaired cardiac function. This condition, cardiac tamponade, can be fatal if not treated. A list of several major pathologically induced pericardial disorders is also found in Table 9.2.

Finally, iatrogenic disorders often occur during the treatment of unrelated diseases. During cardiac surgery, the pericardium is often removed (partially or entirely) and is rarely repaired. There has been much debate as to whether closing the pericardium after surgery would be beneficial to the patient. Most surgeons believe that closing the pericardium may acutely compromise postoperative hemodynamics and increase the risk of tamponade. More recent research has shown that there are no clinical benefits, but there may be adverse effects resulting from closure of the pericardium after cardiac surgery [24]. Nevertheless, if the pericardium is left open, the exposed epicardium tends to become very fibrous, complicating future interventions. It should be noted that non-cardiac surgical procedures performed near the heart may also induce trauma to the pericardium and cause an inflammatory response. Furthermore, even nonsurgical interventions may damage the pericardium. For example, resuscitation from cardiac arrest (CPR) may cause a fibrous response. In some patients, irradiation may create an effusion and subsequent tamponade [23]. The pericardium may also adversely react to a number of commonly prescribed drugs such as procainamide, penicillin, doxorubicin, anticoagulants, and/or antithrombotics [1]. The reader is again referred to Table 9.2 for a list of major iatrogenic pericardial disorders.

In general, pericardial disorders can be diagnosed using ECG, echocardiography, radiography, and/or auscultation. Pericardial fluid samples and pericardial tissue biopsies may also aid in complicated diagnoses. Typically, once diagnosed, pericardial disorders are often treatable with a number of drugs and/or interventions [25]. In situations of large pericardial effusions, pericardiocentesis is performed by draining the effusion with a hypodermic needle inserted near the xiphoid process (Fig. 9.5). This is usually done under guidance of echocardiography or fluoroscopy to prevent myocardial puncture, but in emergency situations (such as during acute cardiac tamponade), it may be done without guidance ("blindly"). Chronic effusions or other diseases may necessitate a partial or complete pericardiotomy. This is done by creating an opening into the mediastinum (called a pericardial window) to view and remove portions of the pericardium; visualization of the procedure can be enhanced by a laparoscope or thoracoscope. Balloon pericardiotomy is a recently developed minimally invasive technique that uses a balloon to enlarge a small hole in the pericardium [3].

9.5 Comparative Anatomy of the Pericardium

The pericardium is fixed to the great arteries at the base of the heart and is attached to the sternum and diaphragm in all mammals, although the degree of these attachments to the diaphragm varies between and within species [26, 27]. Specifically, the attachment to the central tendinous aponeurosis of the diaphragm is firm and broad in humans and pigs, the phrenopericardial ligament is the only attachment in dogs, and the caudal portion of the pericardium is attached via the strong sternopericardial ligament in sheep [26, 27] (see Video 9.2 in the online supplemental material).

Although the basic structure of the pericardium is the same, differences exist between various species with respect to both geometry and structure [28–30]. Generally, pericardial wall thickness usually increases with increasing heart and cavity size between the various species [28]. Humans are a notable exception to this rule, having a much thicker pericardium than animals with similar heart sizes [28]. Specifically, the pericardium of human hearts varies in thickness between 1 and 3.5 mm [1], while the average pericardial thickness of various animal species is considerably thinner (ovine hearts, 0.32 ± 0.01 mm; porcine hearts, 0.20 ± 0.01 mm; and canine hearts, 0.19 ± 0.01 mm) [29]). Differences in the relative volume of pericardial fluid also exist. Holt [28] reported that most dogs have between 0.5 and 2.5 mL of pericardial fluid (with some dogs having up to 15 mL), compared to 20–60 mL in adult human cadaver hearts. In the Visible Heart® Lab, we have found that 70–80 kg swine have about 7–8 mL of pericardial fluid. When selecting an appropriate animal model for pericardial access procedures or intrapericardial therapeutics, the significant differences of pericardial thickness, pericardial fluid volume, and pericardial attachments between humans and the various animal models must be considered.

9.6 Surgical Uses of the Pericardium

Due to the inherent mechanical properties of the fibrous pericardium, it has been used in various applications during surgery and has also been used in bioprosthetic heart valves. During cardiac surgery, fresh autografts, cryopreserved homografts, or glutaraldehyde-fixed xenografts can be used as patches during reconstructive repairs in both congenital and acquired heart diseases. For example, in congenitally malformed hearts, pericardial patches are used during surgical repairs of the right ventricular outflow tracts and/or during repair of torn aortic leaflets. Pericardial patches have also been used to repair the mitral and aortic valves as well as ventricular walls in acquired diseases [31].

Pericardial tissue has been used in heart valves for many years. The search for an alternative to mechanical valves has led people to investigate many types of bioprosthetic valves. These bioprostheses have consisted of homografts (preserved cadaveric valves), autografts (transplant of a patient's pulmonic valve to the aortic position—the Ross procedure), and xenografts. Xenograft valves have included preserved porcine aortic tissue as well as preserved bovine pericardium. More specifically, glutaraldehyde-fixed bovine or porcine pericardium has been used in the design of aortic and mitral bioprosthetic valves and has realized wide clinical success. Such pericardium is prepared and fixed using specific processes (which typically vary slightly between manufacturers) and then cut to resemble a tri-leaflet semilunar valve and assembled into a stent with a sewing cuff.

With ubiquitous use in heart valves, the biomechanics of glutaraldehyde-fixed pericardium have been carefully studied. Biomechanical properties have been shown to be dependent on species, anatomic orientation, and fixation process. For example, there are significant differences in uniaxial mechanical properties of bovine, porcine, and ostrich pericardium [32]. It has also been shown that collagen fiber orientation, and hence mechanical stiffness, is dependent on the location and orientation of the tissue within the pericardial sac [33]. Finally, uniaxial properties of glutaraldehyde-fixed bovine pericardium can be modulated depending on the stress applied during fixation [34].

9.7 Intrapericardial Therapeutics

9.7.1 Clinical Pericardial Access

Traditionally, pericardial access has been limited to patients with pericardial effusions. The effusion gives physician a buffer between the fibrous pericardium and the epicardium during pericardiocentesis or creating a pericardial window, thus preventing damage to the myocardium and coronary vessels. Recently, there has been an interest in accessing the healthy pericardium for therapeutic procedures and the delivery of therapeutic agents. The challenge of accessing a healthy pericardium is to puncture and catheterize the pericardium with minimal risk to the heart. This is a difficult task considering the almost negligible layer of pericardial fluid in a healthy pericardial sac. The Tuohy needle, a hypodermic needle originally developed for insertion of an epidural catheter, is commonly used for pericardial access. This needle has an anti-coring curve at its tip to prevent puncture of the myocardium.

In an effort to improve the ease of access, several unique biomedical devices or tools have been (or are being) developed with novel catheter designs that allow controlled myocardial penetration during fluoroscopic visualization. For example, the PerDUCER® (Comedicus, Inc., Columbia Heights, MN, USA), which has now become PeriPort® (Cormedics Corp., Houston, TX, USA), uses a sheathed needle with a suction tip designed for grasping the pericardium and accessing the pericardial space while, at the same time, minimizing the risk of myocardial puncture. This device is placed following subxiphoid access into the mediastinum under fluoroscopic guidance from the apparatus positioned onto the anterior outer surface of the pericardial sac (Fig. 9.7). Under manual suction, the sac is retracted and a needle is inserted, allowing for the placement of a guidewire into the space via the needle lumen. The needle is then removed and a standard delivery catheter is placed into position. The Philipp University of Marburg has also developed a similar product called the Marburg Attacher (www.cardiorepair.com/attacher). Other percutaneous subxiphoid techniques have been proposed [35] but are not in current clinical use.

A novel transatrial technique has been developed by Verrier and colleagues [36] which has been successful in animal studies. In this procedure, a guide catheter is introduced into the right atrium from the femoral vein, and a needle catheter is advanced through the guide catheter to pierce the right atrial appendage. A guidewire is then passed through the needle catheter into the pericardial space. A soft delivery catheter can be passed over the guidewire and can reside in pericardial space for long-term drug delivery or for fluid sampling. Studies in swine have shown that catheters left in the pericardial space over long periods of time can remain patent and cause minimal fibrosis and inflammatory response at the epicardium [37, 38].

9.7.2 Intrapericardial Therapies

For quite some time, nonsurgical intrapericardial therapy has been employed in patients with sufficient fluid in the pericardial space allowing a needle to be safely placed within the space [1]. This methodology has been used for patients with clinical indications such as, but not limited to, malignancies, recurrent effusions, uremic pericarditis, and connective tissue disease. As mentioned above, instrumenting the pericardium has been made possible by numerous techniques that allow for the study of intrapericardial therapeutics and diagnostics by clinicians and investigators alike. In addition, with recent advances in minimally invasive cardiac surgical procedures, it is likely that the integrity of the pericardium will be preserved more often during cardiac surgery.

Intrapericardial access has become the foundation of many novel minimally invasive cardiac procedures. This includes epicardial mapping and ablation for both ventricular [39] and atrial [40] arrhythmias in patients where endocardial approaches are challenging or ineffective. Intrapericardial echocardiography, where an intracardiac ultrasound probe is introduced percutaneously into the pericardium, has been shown to aid in complex ablation procedures [41]. Epicardial lead placement can also be performed

Fig. 9.7 The PerDUCER® instrument (Comedicus, Inc., Columbia Heights, MN, USA) uses a sheathed needle with a suction tip designed for grasping the pericardium to access the pericardial space using a transthoracic approach, thus minimizing the risk of myocardial puncture

through minimally invasive access to the pericardium in patients where traditional venous lead implantation has failed [42]. The LARIAT procedure and device (SentreHEART, Redwood City, CA, USA) is a novel approach to percutaneous ligation of the left atrial appendage that relies on both pericardial access and transseptal left atrial access. In this procedure, a device in the pericardium interacts magnetically with a device in the left atrium to position the system and perform the ligation. Initial clinical results of the procedure have shown promising results [43].

Beyond device-based interventions, intrapericardial access has been used to introduce therapeutic agents to treat cardiac disease. Specifically, the endoluminal delivery of various agents has been found to be clinically limited due to short residence time, highly variable deposited agent concentration, inconsistency in delivery concentrations, and relatively rapid washout of agents from the target vessel [44]. A desired example of targeted application includes infusion of concentrated nitric oxide donors, which could present undesirable effects if systemically delivered. Further, one is allowed increased site specificity and the delivery of label-specific therapeutic agents to target cells, receptors, and channels. A great deal of interest has been focused on delivery of angiogenic agents and various growth factors into the intrapericardial space [45–47]. In particular, research has concentrated on administration in patients with ischemic heart disease [48, 49]. Early results indicate several benefits associated with the delivery of angiogenic agents that include increased collateral vessel development, regional myocardial blood flow, myocardial function in the ischemic region, and myocardial vascularity.

In our lab, we have shown that intrapericardial delivery of omega-3 fatty acids can drastically reduce infarct size and lower the occurrence of ventricular arrhythmias. In one study [50], 23 swine were treated with an infusion of either omega-3 fatty acids or saline in the pericardial sac prior to occluding the left anterior descending artery. Prior to, during, and after the occlusion, hemodynamic and electrophysiological data were recorded. Upon sacrificing the animal, the heart was sectioned and stained to determine infarct size. We found that both infarct size and arrhythmia scores were reduced by half in animals treated with omega-3 fatty acids. Furthermore, the treatment had a minimal effect on hemodynamics, which is in contrast to many antiarrhythmic drugs. Current research is underway to determine if this therapy would be feasible in a clinical setting.

9.7.3 Pericardial Pharmacokinetics

As described previously, the pericardium in humans is generally believed to contain 20–60 mL of physiologic fluid (0.25 ± 15 mL/kg) situated within the cavity space [51]. Yet, dye studies suggest that pericardial fluid is not uniformly distributed over the myocardium, with the majority of pericardial fluid residing within the atrioventricular and interventricular grooves as well as the superior-transverse sinuses. Although the pericardial fluid is not uniformly distributed, pharmacokinetic studies suggest that there is complete mixing of the fluid so that pericardial fluid content is spatially uniform [52–54]. Hence, sampling pericardial fluid content should not vary functionally by sampling location [53].

Tissue distribution and drug clearance clearly affect all drug response. Because specific pericardial pharmacokinetic data remain unknown for the majority of compounds, pericardial drug disposition must be gleaned from physical chemical properties based upon a few select studies. Pericardial fluid is cleared via lymphatics and epicardial vasculature, with the former being a very slow process [55]. In addition to these passive clearance mechanisms, the epicardial tissues contain metabolic enzymes that may clear compounds via a biotransformation process. This is likely to occur with certain labile peptides and small molecules such as nitric oxide. Unfortunately, there is very little known today about pericardial drug metabolism. In general, it is considered that whether or not a compound residing in the pericardial space is cleared via lymphatic drainage, passive diffusion or biotransformation will depend on its molecular size, tissue affinity, water solubility, and enzymatic stability. Thus, compounds such as large proteins do not rapidly diffuse into the vascular space and are slowly cleared from the pericardial space perhaps via lymphatics unless, of course, they are biotransformed [53, 56]. Importantly, this yields a pericardial fluid clearance and residence time longer than the corresponding plasma half-life. For example, administering atrial naturetic peptide into the pericardial fluid space had a fivefold longer clearance and residence time within the pericardial fluid space, as compared to plasma clearance of an intravenous dose [56]. Similarly, small water-insoluble compounds may also have very prolonged pericardial fluid residual times.

One case report documented that the pericardial fluid half-life of 5-fluorouracil (sparingly soluble in water) was approximately tenfold longer than plasma half-life (168 versus 16 min); it should be noted that the patient in this investigation had metastatic breast carcinoma with pericardial involvement [52]. The patient had received a relatively large pericardial 5-fluorouracil dose (200 mg) to manage recurrent pericardial effusion. This large dose, however, was associated with nearly undetectable plasma levels, indicating minimal spillover from pericardial fluid into the systemic circulation. While it was expected that 5-fluorouracil would have a longer pericardial residual time because it is water insoluble, it is unknown if these findings would occur in a healthy pericardial fluid space.

On the other hand, small water-soluble compounds have up to five- to eightfold shorter pericardial fluid clearance and residence times as compared to plasma [52]. For example, procainamide is a water-soluble compound that has a pericardial fluid half-life ranging from 30 to 41±2.1 min as compared to the 180-min plasma half-life; it has been reported that the procainamide rapidly diffused out of the pericardial space with a terminal elimination half-life approximately 5–7 times shorter than plasma [57]. However, procainamide spillover from pericardial fluid into plasma was considered not to produce measurable plasma concentrations because of the relatively low pericardial doses (0.5–2 mg/kg). Similarly, it is not surprising that the converse was also true, that intravenously administered procainamide rapidly diffused into the pericardial space, across the plasma to pericardial fluid concentration gradient, such that pericardial fluid procainamide concentrations were similar to plasma approximately 20–30 min following an intravenous injection. The likely explanation for these findings is that the vast ventricular epicardial blood supply served as a clearing system (pericardial administration) or a delivery system (intravenous administration) according to drug concentration diffusion gradient. Importantly, the diffusion of pericardial-administered procainamide into the vascular space will likely prevent drug accumulation in ventricular tissue and a global pharmacologic response.

In addition to pericardial drug residence and clearance times, the determination of distribution volume may be of considerable importance, particularly to achieve desired peak drug concentrations. There is a direct and inverse relationship between peak drug concentrations and drug distribution volumes, such that a low drug distribution volume achieves higher peak concentrations. Perhaps of clinical importance, with the very small pericardial fluid volume, it is likely that pericardial drug doses can be substantially reduced to achieve therapeutic concentrations. This was evident whereby sequential pericardial procainamide doses of 0.5, 1, and 2 mg/kg produced peak pericardial fluid concentrations that ranged from 250 to 900 μg/mL; these concentrations were nearly 1000-fold greater than peak plasma concentrations of procainamide following the administration of a 2 mg/kg intravenous dose. In a follow-up study in which a single procainamide dose was employed, similar findings were documented; it was also reported that a pericardial fluid volume distribution of 1.6±0.16 mL/kg was observed, which is approximately 1000-fold smaller than the plasma procainamide volume distribution of 2000 mL/kg. While pericardial procainamide dosing produced very large pericardial fluid concentrations, procainamide could not be detected in the plasma given the very small doses. With such a powerful diffusion gradient, it is likely that pericardial procainamide delivery can achieve very high atrial tissue concentrations. Indirect evidence of tissue distribution is a procainamide distribution volume that is larger (40–50 mL) than the estimated pericardial fluid volume of 20–30 mL. Since the procainamide pericardial volume of distribution exceeded the expected pericardial volume, there was some tissue distribution. These pharmacodynamic data suggest that tissue distribution mainly occurs in the atrium, likely because the atrium is a very thin structure with a low blood supply. Thus, this tissue architecture is ideal for specialized therapeutic drug diffusion and therefore differs from that of the ventricle(s).

Unfortunately, most pericardial procainamide pharmacokinetic studies performed to date have not directly measured tissue concentrations following infusion. However, in one study which evaluated the pharmacodynamic effects of pericardial amiodarone delivery, the amiodarone tissue distribution was quantified at several myocardial locations [58]. Not surprisingly, it was reported that atrial and epicardial ventricular tissue had the highest amiodarone tissue concentration, while ventricular endocardial amiodarone tissue concentrations were approximately tenfold lower. Importantly, the amiodarone levels were likely still within a therapeutic range. This was supported by the fact that pericardial amiodarone delivery prolonged endocardial ventricular refractory periods by up to 13 %, which was equivalent to epicardial ventricular refractory period measurements and the magnitude of atrial refractory period prolongation. The similar refractory response between epicardial and endocardial measurements, with very large differences in amiodarone tissue concentrations, indicates that amiodarone effects are maximal at low tissue concentrations. Unlike pericardial amiodarone administration, pericardial procainamide had no effect on endocardial ventricular refractory periods [54]. It is likely that such a beneficial ventricular tissue distribution does not occur with more water-soluble compounds such as procainamide. On the other hand, it is not surprising that amiodarone, when administered into the pericardial space, could penetrate ventricular tissue and affect global ventricular electrophysiology because it is highly lipophilic and has a huge tissue distribution including the intracellular space [58]. A more recent study comparing intrapericardial and intravenous administration of amiodarone in goats [59] showed similar results; plasma drug concentrations were significantly lower when amiodarone was administered into the pericardium, yet the drug's antiarrhythmic effects were in many measures improved over intravenous administration. The study also confirmed a high gradient of amiodarone tissue concentration from epicardium to endocardium during intrapericardial administration. We have also shown similar beneficial effects in our lab when comparing intrapericardial and intravenous delivery of metoprolol in swine [60]. Intrapericardial delivery showed lower plasma concentrations, more sustained antitachycardic effects, and less negative effects on contractility and mean arterial pressure when compared with intravenous delivery.

Lastly, perhaps it is possible to modify molecules to achieve an optimal pericardial fluid residence time and thus therapeutic outcomes. More specifically, for some agents, it may be desirable to have a short residence time. For example, pericardial drug delivery to cardiovert atrial fibrillation may require very high drug concentrations for only a brief duration, given the acute nature of the therapy. On the other hand, the ability to manage chronic conditions such as ischemic heart disease or heart failure may necessitate longer pericardial residual times. In this regard, Baek et al. recently showed that a derivatized nitric oxide donor molecule, diazeniumdiolate, with bovine serum albumin resulted in a fivefold increase in pericardial fluid clearance and residence time versus a small molecule nitric oxide donor (diethylenetriamine/NO) [61]. This group went on to show that it may be possible that a single pericardial dose of the nitric oxide donor could inhibit in-stent restenosis. Unlike patients with any type of effusion, the normal pericardium is a very thin layer, bringing it closer to the heart and subsequently increasing the risk of harm to the patient.

The ability to access the pericardial space has created new opportunities to further understand the pharmacokinetics of intrapericardial therapeutics, as well as the role of the pericardium under normal cardiac function and/or following cardiac disease. Despite the growing literature establishing the feasibility of intrapericardial therapeutics and diagnostics, the results of clinical trials employing pericardially delivered agents directed toward arrhythmias, angiogenesis, restenosis, and/or other coronary and myocardial indications are currently lacking.

9.8 Summary

The pericardium is a unique structure that surrounds the heart and serves several important physiological roles. The removal of the pericardium, certain pericardial disorders, or the buildup of fluids within this space will ultimately alter hemodynamic performance. Recent therapeutic approaches have been directed to exploit the space that exists between the pericardium and the epicardial surface of the heart. New devices and techniques are being developed to access this space in a minimally invasive fashion. An important consideration when utilizing animal models to study such devices is that the pericardium in humans is much thicker and there is more pericardial fluid than in commonly employed animal models. The pharmacokinetics of many drugs may be greatly enhanced if the drug is delivered into the pericardium. As more is learned about the pericardium, it may play a significant role in cardiac therapies.

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