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Liquid reflecting the heart function: Pericardial fluid

Heart mirror: Pericardial fluid

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Abstract

Pericardium is a sac surrounding the heart and big vessels, protecting them against injury and infection and fixing the heart to the mediastinum. As pericardium has an immunologic, paracrine, vasomotor and fibrinolytic activity; it affects myocyte structure, function and gene expression by synthesizing materials such as eicosanoids and prostaglandin. Pericardial fluid (PF) in two-walled pericardial sac surrounding the heart completely, has a potential of reflecting heart function and shows dynamic changes. Since many biomarkers associated with cardiovascular diseases pass to pericardial sac, PF analysis provides to be understood many pathophysiological mechanisms in various pericardial and cardiovascular diseases. The aim of this article is to give actual information about the content of PF that is thought to be passive ultrafiltrate of plasma produced with hydrostatic pressure difference and osmotic concentration gradient for years.

Keywords

Pericardium; Pericardial Fluid; Plasma Ultrafiltrate

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Introduction

Pericard or pericardium is a two walled sac which has a closed fibroserous structure that surrounds heart completely as well as encircles entry-exit roots (proximal ends) of main veins (aorta, vena cava, pulmonary veins, etc.) going to and coming from the heart. Both layers are separated by a slit-like pericardial cavity, which contains 20 to 60 mL of the plasma ultrafiltrate. Pericardial extensions around main veins hold pericardium from the top. Adherence places of pericardium with changing thickness are columna vertebralis, diaphragm, processus xiphoideus and manubrium sterni. Pericard thickness that increases comparatively due to heart and pericardial sac is 1-3.5 mm in humans, 0.32 ± 0.01 mm in sheep and 0.20 ± 0.01 mm in pigs [1].

One of the most important mechanical properties of pericard is limiting the heart sac volumes by keeping this volume at a specific level. This mechanical property of pericard of adjusting heart volumes at a specific volume as a limiter actually resembles tension strength of rubber. Blood transportation to the pericard that has sympathetic and parasympathetic excitation, is done via small branches of the aorta, IMA (Internal mamarian artery) and musculophrenic arteries.

The pericardium is composed of two structures named as fibrous pericardium and serous pericardium. Fibrous pericardium consists of collagen fibers in external whereas serous pericardium consists of mesothelial cells inside. Fibrous pericardium isolates heart from external organs. Serous pericardium is the part between fibrous pericardium and myocardium. Serous pericardium divides into two layers as parietal pericardium and visceral pericardium in itself. Parietal pericardium is a thin layer connecting with fibrous pericardium. It has an acellular structure rich with elastic and collagen fibers. Collagen fibers are structures responsible for rigidity of pericard. In normal and healthy people pericard tension is little and settled in a waveform. In cases of an increase in tension, collagen fibers take a proper form and provide the rigidity of tissue [2].

On the other hand, visceral pericardium as a thin and transparent membrane layer above myocardium formed of a single layer epithelium layer sticking on myocardium firmly. Visceral pericardium becomes even or cubical due to relaxation and contraction movements of the heart. Visceral pericardium consists of collagen tissues involving plenty of elastic fibers. There is another collagen tissue layer associated with conjunctive stroma between epicardium and myocardium. In this layer, there are veins rooted in from the surface of heart, nerves, coronary vessel groove and adipose tissue at the level of coronary vessels.

Many studies done both in the parietal and visceral pericardium (human, dog, pig) showed the same mechanical properties, there showed up only quantitative differences between them. As invitro studies in dog, parietal pericard show the existence of viscoelastic response, this situation substantially shows the existence and organization of elastic and collagen fibers [3]. Parietal pericard is responsible for accession to ventricular volume modulation, intraventricular interaction, and accession to ventricular diastolic pressure/volume proportions. Invitro epicardial studies done on human and pigs proved the existence of elastic properties referred to the orientation and composition of collagen tissues. There are proofs that especially human epicardium contributes to the passive mechanical properties of the myocardium [4]. In this way contribution of epicardium to ventricular end-diastolic volume control is proved.

Pericardial sinuses and nerves

After parietal pericard enwraps starting parts of main vessels, continues in the form of visceral pericard. In fact, visceral pericard provides continuity by forming an inner layer of parietal pericard. In these regions, pericardial sinuses (pockets) are formed. In the anatomy of pericard, there are two sinuses named as oblique sinus and transverse pericardial sinus. Transverse sinus is behind ascending aorta and main pulmonary artery. Transverse sinus is a transition between the venous end (left atrium and upper vena cava) behind the heart and arterial end (aorta and pulmonary truncus) in front of the heart. Since oblique sinus is a blind cavity, it can be seen as the heart is pulled towards the right shoulder. There is inferior vena cavaright side of the oblique sinus. It is believed that visceral pericard is the source of PF.

Among heart chambers only left atrium is an extrapericardial chamber. Pericard that innervates pretty well, also carries mechanoreceptor, chemoreceptor and phrenic nerves. Pericard is nerved by two phrenic nerves and each nerve gives an afferent branch (pericardial branch). These structures play a role in the formation of reflexes that is thought to be generated from pericard irritation and carrying of pain stimulants to pericard.

Development of Pericard

Pericard forming in intrauterine (uterus) period develops from septum transversum that will form a diaphragm and pleuropericardial membrane. Development failures occur in this period causing partial or nonformation of pericard. In development failures of pericard, the case of nonformation of pericard is mostly seen. Anomalies in other organs can also be seen congenital pericardium deficiency [5].

Pericardial cavity, pericardial effusion, and it's content

The gap between the visceral pericardium and parietal pericardium that form serous pericardium is named as the pericardial cavity. In the pericardial cavity, there is physiological serous PF that shows dynamic changes. PF quantity was obtained in different quantities in many sources. Volumetrical studies show that pericardial effusion volume is directly similar to animal dimension. For example in rabbits there is 0.4-1.9 mL, in dogs, there is 0.5-2.5 mL PF it was found approximately 20-60 mL (average 15-35 mL) in human [6, 7]. According to coloration studies regarding PF quantity and content, effusion distribution in the pericardial cavity was found heterogeneous. According to the studies done, it was obtained that the most PF quantity is in atrioventricular and intraventricular sulcus in other words in superior and transversal sinus especially in supine position [8]. Despite the heterogeneous structure of PF, there are also pharmacokinetics studies showing PF is continuously mixed. These studies say that PF combination is the same without considering position [9].

Since it is hard to define PF combination of a normal person, actual data were obtained from cardiothoracic surgery patients or animals. PF, just like pleural fluid, is a fluid having specific properties [10]. Concerning cell population, studies on PF in normal person showed the existence of heterogeneous cell population. In content of PF there are mesothelial cells, lymphocytes (53 %), granulocytes (31 %), macrophages (12 %), eosinophils (1.7 %) and basophils (1.2%). According to this situation in PF "lymphocytosis" has critical importance and when the number of lymphocytes exceeds 60% of all cell population, it is characterized pathologically [11].

Physiology and important functions of Pericard

• Pericard provides soft and serous sac environment for structures around the heart. By forming an environment that the heart can move freely, pericardial effusion that provides lubricity during systole makes the working of heart easily. PF makes this duty by lubricating the epicardial surface with suitable friction.

• Pericard that provides equal distribution of gravity force on heart, plays a protective role on the heart by increasing strength of myocardium. Previous studies showed that myocardium ruptured in a heart without pericard when intracardiac pressure was increased to 1 atmosphere whereas this value was found 1.75 atmosphere in a heart with healthy pericard [12]. So an important proof that pericard increases myocardium strength showed up.

• Connective ligaments in pericard provides heart to remain stable in middle mediastinum, avoid hyperactivity during body position changes by inhibiting tortion and displacement of heart.

• Pericard that has a hemodynamic effect on ventricles, limits distension of heart chambers. During high end-diastolic ventricular pressure, pericard avoids ventriculoatrial blood retrogression [13].

• By isolating heart from adjacent anatomical structures, pericard avoids both cohesion formation and spreading of infection in structures around the heart. For example, an adjacent organ such as lung, mediastinum, esophagus and pleura infections, inflammatory and neoplastic situations cannot reach heart by means of physiological barrier that PF forms [13].

• It prevents over dilatation that is important for thin walled regions such as the right cardiac cavity. In case of overloading of the left ventricle, it decreases right ventricle impulse.

• Pericard that balances the distribution of hydrostatic pressures, eases blood flow to atriums by decreasing intrapericardial pressure during ventricle systole by means of negative pressure.

• Eicosanoids and prostaglandins are oscillated from pericard mesothelium cells. So mesothelium cells affect myocyte structure, function and gene expression [14].

• It causes interaction of ventricles to each other during diastolic filling by providing diastolic coupling between ventricles.

• By means of nerve stimulation response, it helps to regulate cardiac frequency and blood pressure.

• It provides formation of the hydrostatic compensation system that provides end-diastolic pressure staying the same at all hydrostatic levels as well as makes FrankStarling mechanism available for functioning.

• In addition to these functions, pericard has immunologic, vasomotor and fibrinolytic activities.

Changes of pericard during disease

Pericard can show up symptoms in both cardiac and systemic diseases. In cardiac andsystemic disease the response of pericard is acute inflammation and/or increase in PF quantity [15]. In fact, for many years PF was thought to be a passive ultrafiltrate of plasma produced with hydrostatic pressure difference and osmotic concentration gradient [16]. However, the studies done in rabbits and dogs extended this simple opinion by providing analysis of the content and composition of PF [11]. In one of the first far-reaching researches done on humans, detailed information about PF composition of 30 patients having elective open heart surgery, was obtained and found that concentrations (such as urea, uric acid, glucose, and electrolytes) of small molecules are close to each other in both plasma and PF [7].

Production of PF does not only involve filtration processes but also active mechanisms. For example, various biological substances produced by myocardium accumulate as PF. In many previous studies endothelins, adenine nucleosides and angiotensin were determined among accumulated substances in PF. As a result of the comparison of these substances with plasma, it was found that they were in a higher concentration in PF.

As electrolyte content of PF filtered from blood by mesothelium cells involving phospholipid, is close to plasma (pH=7.57, Na=138 mM, Cl=109 mM, K= 4,5 mM), protein content (total protein 3.1 g/dL) is 1/3 of plasma [17]. According to the study done in hounds and rabbits, Ca2 + (1.92 ± 0.04 mmole kg H2O-1), Na + (150.5 ± 0.72 mmole kg H2O-1), Cl- (123.2 ± 0.71 mmole kg H2O-1) and Mg2 + (0.85 ± 0.09 mmole kg H2O-1) were calculated. In the same study K + concentration (3.81 ± 0.07) in PF was found higher compared to plasma. This situation shows that there is K+ leakage from myocardium interstitium towards pericard cavity during systole [18]. Albumin level of PF is however relatively more than plasma, althought protein content of PF is less than plasma. According to another study osmolarity and protein concentration (albumin, globulins, macroglobulins, and fibrinogen) of PF was found lower than plasma [18]. When filtration gradients of substances in PF are taken into consideration, normal PF is found to be transudate [18].

Pericardial hydrodynamic and lymph drainage

In PF formation as well as in pericardial cavity myocardial interstitial fluid and lymph drainage are important sources. PF draining occurs to thoracic ductus via parietal pericardium whereas to right lymphatic ductus through the right pleural gap. The volume of PF is determined with the balance between production and drainage. There are strong proofs that PF is derived from epicardial capillary vessels (probably from parietal pericardium) via ultrafiltration of plasma and as interstitial fluid from myocardium in little quantity [19]. Its drainage to pericardial cavity occurs mainly via parietal pericard lymphatic capillary bed pathway. According to the study done in sheep, it was obtained that the whole of PF drains from the capillary bed pathway once in 5-7 hours [20]. However the hardness of examining PF dynamic under normal procedures and circumstances, the subject could not be clarified exactly. Mainly fluid movement in pericardial layers depends on hydrostatic/osmotic pressure balance between microvascular structure and cavity. In PF as being a physiological fluid showing dynamic change, there are proteins, cytokines, cells, glucose, electrolytes, cholesterol, LDH, natriuretic factors, VEGF, FGF, cell adhesion molecules (ICAM), prostaglandins and phospholipid with lubricating property [21]. Also in PF, there can be found bacterias and viruses entering here in various ways. As PF is permeable for both small and some big molecules, there is an exchange of free fluid electrolyte with the serum that is in dynamic balance form. In some previous studies, during cardiac diseases changing the concentration of substances in PF was reported [22]. In addition to this, PF composition changes in various cardiac diseases and cardiac hypertrophy.

Pericardial pressure

Intrapericardial pressure changes between –5 and +5 mmHg along the respiratory cycle. Intrapericardial pressure that is close to pleural pressure is approximately -6 mmHg at the end

of inspiration whereas approximately -3 mmHg at the end of expiration by showing cyclic changes with respiration. Intrapericardial pressure that is lower than right and left ventricular diastolic pressures, changes due to the volume of fluid accumulated in the pericardial cavity, the speed of fluid accumulation and physical properties of pericard. As central venous pressure is slightly higher than intrapericardial pressure, this situation maintains blood flow from veins to the heart. According to the studies done recently, pericard becomes an application area of new treatment methods. Especially in patients that percutaneous intervention or surgical revascularization cannot be done, intrapericardial ''basic fibroblast growth factor'' applications done to the pericardial cavity to stimulate collateral development in embolies, make pericard new treatment intervention place and method [23].

Examinations done in pericardial effusion

In PF macroscopic and microscopic examinations, cell count, biochemical examinations, cytologic, microbiologic-cultural, inflammatory, pathological, immunologic, malignity and molecular (PCR, proteomics, etc) examinations can be done. By means of pericardiocentesis diagnostic approach in terms of etiologic is presented by examining taken fluid samples. In pericardiocentesis pericardial effusion is provided to be accumulated in front and lower part by bringing the patient to a halfsitting position. In this method between left rib and xiphoid punction with 45 degree angle is done towards shoulder in horizontal, frontal and sagittal plans. The pericardial punction process should be done by fluoroscopy or two dimensional echocardiography. By means of fluoroscopy and echocardiography, both hemodynamic and electrocardiographic control can be provided. During punction with the touch of the needle to ventricle wall, ST segment increase occurs and ventricular premature excretions are observed in echocardiography. If PF is in the front and free cavity of the sac, it is easily extracted. If long term drainage is needed in patients, a catheter named pigtail catheter can be placed in the pericard cavity. After placing the pigtail catheter, if daily drainage decreases under 50cc, the catheter can be taken out. With contrast substance injection done under fluoroscopy, it can be controlled if cardiac cavities were entered or not. If aspiration fluid is hemorrhagic, it can be controlled if its congealed or not.

The future of pericard treatments

In various cardiac diseases concentration of some substances in PF contributes many pathophysiological mechanisms to be understood. For example in a study done on heart insufficiency finding atrial natriuretic and brain natriuretic factors 12 times more in PF, it is thought that these factors play a pathophysiological role as an autocrine or paracrine factor in heart insufficiency [24, 25]. In unstable angina high levels of adhesion molecules such as ICAM-I, VCAM-I, e-selectine and proinflammatory cytokines such as interleukin 6 and 8, supports the relation between coronary artery diseases and inflammation. Again in these patients noradrenaline highness in PF supports the thesis that norepinephrine is responsible for damage in ischemic cardiac muscle and development of arrhythmia. Finding angiotensin-II levels that are thought to be responsible for left ventricle hypertropia and remodeling formation at a low level in PF of these patients, shows that angiotensin-II is not directly responsible for cardiomyocyte hypertrophy. Increasing of pericardial concentrations of various angiogenic factors such as hepatocytic growth factor, vascular endothelial growth factor, acid, and basic fibroblast growth factors that are known to stimulate collateral vessel development in ischemic cardiac patients, make pericard important [24, 25].

Result

For treatment and prevention of cardiovascular diseases, pathogenesis should be understood, new biomarkers should be found and substances preventing disease should be identified and used. Pathological findings of cardiovascular diseases show up in time or remain hidden for a long time, and come up as a sudden heart attack. Before disease shows up itself, there occur changes in various factors such as substance, molecule, protein, etc. within and out of cells, in intercellular space or in body fluid. By means of these changes, many substances can be used as biomarker recently. In follow-up of disease or situation in treatment period effective biomarker is very important. There are some properties in a biomarker that has to be paid attention. A biomarker that is used in cardiac diseases should have high diagnostic and prognostic value, should not be affected from confusing reasons, showing a rapid change in levels according to the condition of the patient and should have single limit value in the evaluation of treatment. Although many biomarkers regarding cardiovascular diseases have been discovered recently, there are question marks due to some absences. For example, obtaining substance expressed in both cardiac and skeletal muscle in the blood causes confusion about if related substance belongs to cardiac tissue or skeletal muscle. In order to annihilate this problem, it is important to make studies on region particular to tissue, on a cell basis, intercellular fluids, and tissue fluids. In previous studies, it was found out that changes of many substances, molecules, proteins, hormone, etc. in PF give clear information about the situation of cardiac tissue.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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