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Chapter

Acute Pericarditis

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Abstract

Pericardium is a double-layered anatomic structure that surrounds the heart and output sections of the great vessels. Despite numerous functions of this layer, main are the protection of the heart and facilitation of the heart movements. Various diseases were defined related to the pericardium and one of them is acute pericarditis caused by inflammation of the pericardium mostly by infection. In this chapter, it is aimed to give brief information about the mostly seen pericardial diseases and detailed information about the signs, symptoms, diagnosis, and treatment modalities about the acute pericarditis.

Keywords: pericardium, acute pericarditis, infection, inflammation, effusion

1. Introduction

Pericardium is a flask-shaped structure that contains the heart and the proximal parts of the great vessels. Various functions of the pericardium were defined such as stabilization of the heart in its correct anatomic position by maintaining the suitable geometry of the heart and providing the pressure-volume correlation of the cardiac chambers. It also acts as a barrier to protect the heart from spread of infections and neoplasms born of mediastinum. It prevents the abrasion of the surface of the heart due to the movements of the heart by the fluid in pericardial cavity. This fluid contains prostoglandines which is secreted by endothelial and mesothelial cells of the pericardium and regulates the cardiac reflexes, contractile function of the myocardium, and coronary tone of the epicardium [1–3].

Various systemic and cardiac disorders can affect the pericardium. Occasionally, pericardium itself can be locus of isolated disease. Pericardial responses to the detrimental agent are usually acute pericardial inflammation called pericarditis or pericardial effusion whereas both of them often occur together. In addition, if a response of acute pericardial inflammation does not regress, a chronic process includes microscop ic fibroproliferation followed by macroscopic thickening can take place [4].

Acute inflammation of the pericardium, namely acute pericarditis may occur with or without pericardial effusion. It may manifest a systemic disease or an isolated clinical issue. Although multiple causes were defined in the literature underlying factors of acute pericarditis, 90% of the cases are virally originated or idiopathic. Correct and rapid diagnosis may help to prevent undesirable conditions such as recurrent pericarditis and pericardial construction [5].

Acute pericarditis is diagnosed in nearly 0.1% of hospital admissions and 5% of the patients admitted to emergency department with noncardiac chest pain. Bacterial
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causes are rarely detected in the pericarditis cases in developed countries, however especially tuberculosis is widely found to be the cause of the disease in developing countries. Mortality rate of the acute pericarditis for in-hospital patients was found to be 1.1% [6–8].

The purpose of this chapter is to give brief data about the anatomy, histology, and diseases related to pericardium and then broad description about acute pericarditis by reviewing the literature.

2. Anatomy and the histology of the pericardium

The pericardium is a double-layered structure which surrounds the heart and the roots of great vessels. Outer layer consists of connective tissue and called fibrous pericardium and the inner layer consists of serous membrane and called serous pericardium. Serous pericardium has two layers; parietal and visceral layers. Pericardial fluid takes part between these layers [9]. Pericardium itself and its fluid protect the heart against trauma, infection, maintain the stable position of the heart in the mediastinum, and provide lubrication for heart movements [10].

The pericardium also prevents the both overfilling of the heart which can be resulted in low cardiac output and excessive heart dilatation [11]. The pericardiophrenic artery is the main artery of the pericardium and its venous drainage goes into the azygos and internal thoracic veins. Phrenic nerve innervates the pericardium [12].

The amount of the pericardial fluid in adult humans is approximately between 20 and 60 mL (average 15–35 mL) and transudate in nature. Over the half of the cells involved in pericardial fluid are lymphocytes and others are granulocytes, macrophages, eosinophils, basophils, and mesothelial cells [13].

Anterior parietal pericardium is composed of three layers; serosa, fibrosa, and epipericardial connective tissue layer. The serosa includes a surface layer of mesothelial cells, the fibrosa contains collagen and small elastic fibers, and the epicardial connective tissue consists of large bundles of collagen that is the part of pericardiocostal ligament. Electron microscopic examinations showed that mesothelial pericardial cells have unique cilia and covered with microvilli which increases the surface area for transportation of fluid and assumes friction [14]. Mesothelial monolayer generates the visceral pericardium which adheres firmly to the epicardium. Mesothelial cells present in the pericardium are metabolically active and play role in myocardial contractility and modulation of sympathetic neurotransmission by producing endothelin, prostacyclin, eicosanoids, and prostaglandin E2 [15].

3. Diseases of the pericardium

Pericardial diseases can be categorized as acute pericarditis, pericardial effusion, constrictive pericarditis, and cardiac tamponade. Afterward recurrent or chronic pericarditis can be developed in patients. Congenital structural pericardial abnormalities and pericardial cysts are occasionally seen and usually symptom-free [16].

3.1 Congenital structural defects of the pericardium

Congenital defects of the pericardium are uncommon conditions and classified as the size and the location of the defect such as complete or partial absence of the
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DOI: http://dx.doi.org/10.5772/intechopen.109354

pericardium and right or left-sided pericardium. This condition does not change the life expectancy, however in particular cases strangulation and herniation of the cardiac chambers can cause life-threatening situations like sudden cardiac death [17].

Treatment differs from patient's signs and symptoms, and the location and the size of the defect [18].

3.2 Pericardial cysts

Cysts of the pericardium are rarely seen congenital masses located in the mediastinum. Although it is usually asymptomatic it may have severe complications like obstruction of the main bronchi and right ventricle outflow tract, tamponade, and abrupt cardiac death due to size and the location of the lesion. Treatment approaches include follow-up if the patient is asymptomatic and drainage and/or resection if becomes symptomatic [19].

3.3 Pericardial tamponade

Pericardial tamponade is a clinical situation where the intrapericardial fluid accumulation raises the pressure surrounding the heart and compromises cardiac filling. Markedly elevated venous pressures result by compression of the heart cause impaired cardiac output producing cardiogenic shock which can be fatal [5]. The most common causes of the pericardial tamponade are malignancies, idiopathic pericarditis, and uremia [20]. The amount of the fluid that causes the pericardial tamponade differs 100–1000 cc according to the thickening and the stretching features of the pericardium. It may occur with less amount of fluid in patients with recurrent pericarditis due to scar formation [21].

Beck's triad aids in the diagnosis of the cardiac tamponade; decrease in the systemic blood pressure, increase in the systemic venous pressure and diminished heart sounds [22]. However, echocardiography is the gold standard of diagnosis [23].

Treatment of the pericardial tamponade upon the removal of the fluid. This can be performed either by pericardiocentesis or sub-xiphoidal surgery. Resuscitative thoracotomy can be used in emergency department to whom with traumatic arrest [24].

3.4 Pericardial effusion

Pericardial effusion is the accumulation of fluid in the pericardial sac more than it should. Although variety of etiologic factors were defined in the literature lead to pericardial effusion such as infection, inflammation, neoplasms, trauma, cardiac and vascular disorders, many cases of pericardial effusion are idiopathic [25]. Beside, pericardial effusion due to tuberculosis is more common in developing countries while postoperative complications and viral infections that cause pericardial effusion are prevalent in developed countries [26]. Because of the limited elasticity, in acute settings, lesser amount of fluid (100–150 mL) can cause cardiac tamponade. In chronic situations when the accumulation is gradual, the parietal pericardium has enough time to stretch, so pericardial effusion may become over 1 L before it causes tamponade [27]. Tachycardia, increased jugular venous pressure, pulsus paradoxus, orthopnea, and pericardial rub (only in pericarditis) are the main signs and symptoms of the pericardial effusion. Bradycardia and hypotension are usually seen before cardiac arrest [28].

Primary diagnostic tool for pericardial diseases including pericardial effusion remains echocardiography because of its portability, availability, and limited costs. In
addition, computed tomography and cardiac magnetic resonance imaging allow the detection of loculated effusion, pericardial masses, and thickening and associated chest abnormalities by providing larger field of view [25].

Treatment approaches to the pericardial effusion based on underlying disease if it is detectable. If the diagnosis is idiopathic or unclear with elevated inflammatory markers aspirin or non-steroidal anti-inflammatory drugs can be initial therapy which also allows evaluating the response. In the circumstance of recurrent inflammatory situation initial therapy is recommended to be aspirin or non-steroidal anti-inflammatory drugs with colchicine. If accompanying status such as pregnancy or systemic inflammatory disease, corticosteroids at low to moderate doses can be added. Corticosteroids are also be used if there is intolerance or contraindication to aspirin or non-steroidal anti-inflammatory drugs or failure with those drugs. Methotrexate and azathioprine are the other treatment choices [29–32].

3.5 Constrictive pericarditis

Constrictive pericarditis is characterized by fibrosis, scarring, calcification, and loss of elasticity of pericardium which leads to external impedance of heart that inhibits diastolic filling [33]. In the past, tuberculosis played an important role in the etiology of constrictive pericarditis, however today other causes such as thoracic irradiation and previous open heart surgeries are other common causes of the disease. But most cases still seemed to be idiopathic in origin [34].

Various clinical manifestations are related to constrictive pericarditis. These may be associated with volume overload that leads to weight gain or sweating or in association with decreased cardiac output that leads to dyspnea on exertion and fatigue. In addition, congestive hepatomegaly and/or ascites may cause abdominal discomfort. Peripheral edema may also be present. Echocardiography is the best-recommended test for the diagnosis of constrictive pericarditis as in any other pericardial diseases [35].

Exact management of chronic constrictive pericarditis is pericardiectomy with removing as much of pericardium as possible. Myocardial penetration with calcification and fibrosis are the worse prognostic factors. Diuretics can be used to decrease edema. Besides, anti-inflammatory treatment up to 3 months with close follow-up should be started a hemodynamically stable patient with newly diagnosed constrictive pericarditis [36].

4. Acute pericarditis

In general, inflammation of the pericardial sac described as pericarditis. It is the most common pathologic course involving the pericardium. If the duration of pericarditis lasts for less than 4–6 weeks, it is called “acute pericarditis”. Subacute pericarditis is the disease in which the pericarditis lasts for more than 4–6 weeks but less than 3 months. Chronic pericarditis continues more than 3 months. If there is an asymptomatic intervals of 4–6 weeks between episodes then the term “recurrent pericarditis” is used [18].

4.1 Etiology

According to the 2015 European Society of Cardiology guidelines, etiology of the acute pericarditis was divided into two fundamental groups; infectious and...
non-infectious causes. Viral infections are the most common cause of the acute infectious pericarditis. Various types of viral agents were defined that lead to acute pericarditis such as coxsackie A and B viruses, adenoviruses, echoviruses, parvovirus B19, influenza viruses, human immunodeficiency virus, cytomegalovirus, and Epstein-Barr virus [37]. Bacterial microorganisms lead to pericarditis are rarely seen in developed countries however tuberculosis is still considered to be the most common cause of pericarditis in the endemic part of the developing countries. Beside, pneumococcus, *Coxiella burnetii*, meningococcus, streptococcus, and staphylococcus are the other bacterial causes of pericarditis which can appear as purulent tamponade with life-threatening clinical situations [38]. Fungal and parasitic organisms rarely cause acute pericarditis. Histoplasma, Candida, Coccidioides, Blastomyces, Toxoplasmosis, and Echinococcus species can be given as examples of causative agents [39].

Various non-infectious factors that lead to acute pericarditis were described in the literature. The mains are malignancy especially secondary to metastasis, connective tissue disease, and metabolic causes [6].

Blunt-force trauma is supposed to be another cause of acute pericarditis. The clinic becomes apparent days or weeks after initial injury. Pathophysiology of the post-traumatic pericarditis is thought to be autoimmune but exact mechanism still remains unclear [40].

Dressler syndrome is a form of acute pericarditis which happens as a result of injury to pericardium or heart following cardiac surgery or myocardial infarction. It is also called post-myocardial infarction syndrome with delayed inflammatory response usually present greater than 2 weeks after the initial event [41].

Several medications were defined as cause to drug-induced pericarditis. Drugs such as hydralazine, isoniazid, and procainamide cause to lupus-like syndrome which is associated with pericardial involvement and serositis manifesting as pericarditis. Similarly, nivolumab and ipilimumab lead to cardiac toxicity, including pericarditis and myocarditis [42, 43].

In the presence of systemic findings, sarcoidosis and amyloidosis should be kept on mind as the causes of pericarditis [44].

Despite explaining multiple reasons about the source of pericarditis, up to 90% of the cases no clear etiology can be established and diagnosis is made as “acute idiopathic pericarditis”.

### 4.2 Epidemiology

The incidence of acute pericarditis is nearly 27.7/100,000 individuals per year. In developed countries, mortality rate of the disease is 1.1%. Acute pericarditis can be developed in all age groups, however, it is common in patients age between 20 and 50 years. Racial predilection is not defined related to disease. Men are more commonly affected than women. Most of the cases with pericarditis is idiopathic. In developed countries the main reasons of the acute pericarditis are viral infections and malignancies. Tuberculosis and HIV infections are the common causes of pericarditis in developing countries [8, 45–48].

### 4.3 Pathogenesis

Spread of cardiotrophic viruses to the pericardium usually happens via hematogenous way. Thus inflammation and fibrinous changes occur with the infiltration of PMN leukocytes which lead to pericardial effusion. Bacterial pericarditis
result from various ways such as contagious spread of infection within the chest via trauma or surgery, spread from infective endocarditis, hematogenous spread of infection or direct inoculation. Spread of tuberculosis pericarditis happens via lymphatic way or contagious spread from a focus of infection in the lung or pleura [6].

4.4 Clinical presentation and diagnosis

Approximately 95% of the cases with acute pericarditis have sharp, retrosternal, and pleuritic pain that radiates into arms, neck, or jaw like acute myocardial infarction (AMI). However, pain in the acute pericarditis has different manifestations from pain due to AMI. It increases in the supine position with inspiration and coughing. It improves by leaning forward and seated position because of reduced pressure on the parietal pericardium. It also respondless to nitrates in opposite to AMI. Chest pain may radiate to shoulders and trapezius ridges which hardens to make differential diagnosis from other causes of life-threatening diseases like aortic dissection or MI [49]. So differential diagnosis should be performed promptly with the diseases angina pectoris, esophagitis, acute gastritis, gastroesophageal reflux disease, AMI, myocardial ischemia, peptic ulcer disease, pleuritis, pneumonia, esophageal spasm, pulmonary embolism, tension pneumothorax, acute aortic dissection, and esophageal rupture [50].

In the literature, predictors of severe illness in patients with acute pericarditis were defined. Major predictors are; fever greater than 38°C, subacute onset, evidence of cardiac tamponade, large pericardial effusion (an echo-free space greater than 20 mm), and ineffective non-steroidal anti-inflammatory drug treatment after 7 days. Minor predictors are immunocompromised state, acute trauma, history of anti-coagulant therapy, and elevated cardiac troponin levels [51].

If the etiologic factor is bacterial originated patients may present fever, chills, and leukocytosis whereas gastrointestinal or influenza-like symptoms may present in viral etiology [49].

A pericardial friction rub within auscultation is highly pathognomonic and specific for acute pericarditis. It can be detected 35–85% of the cases according to data of different studies. It is characterized by scratchy, rasping triphasic sound related to friction between pericardial layers during atrial and ventricular systole and early ventricular diastole. The intensity of the sound may increase during auscultation in the position of lean forward. Differential diagnosis between pleural and pericardial rub can be performed by asking the patient to hold the breath while auscultation. According to this physical examination if rub is still present it represents the pericardial rub. Because respiration does not affect pericardial friction rub. It should be kept on mind that despite the sensitivity and diagnostic value of frictional rub, its absence does not rule out the diagnosis [52, 53].

Electrocardiographic findings due to pericardial inflammation can be observed nearly 90% of the individuals with acute pericarditis. Four stages of echocardiographic changes were defined: stage 1: diffuse, concave ST segment elevation, stage 2: ST segment normalize, J point returns to baseline, T wave amplitude begins to decrease, PR segment depression begins to appear, stage 3: symmetric, diffuse T wave inversions, stage 4: changes normalize or T wave inversions may become permanent (Figure 1). Beside, Q waves and reciprocal ST segment changes are absent in opposite to AMI [54].

According to European Society of Cardiology 2015 Guidelines, two of four criteria are required to diagnose acute pericarditis [37]. These criteria are;
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DOI: http://dx.doi.org/10.5772/intechopen.109354

1. Pericardial chest pain

2. Pericardial frictional rubs

3. New widespread ST segment elevation or PR segment depression on ECG

4. New or worsening pericardial effusion

In addition to anamnesis, physical examination and electrocardiographic findings supportive findings like chest X-ray, cardiac computed tomography, magnetic resonance imaging, basic metabolic panel, complete blood count, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), troponin I and creatine kinase levels can be used in the evaluation of the disease [55]. Chest radiography is useful to detect the abnormalities related to lungs and mediastinum, especially for pericardial effusion. WBC count, CRP levels, and ESR are usually elevated. Long duration of elevated CRP levels (usually normalizes in 85% of the patients within 2 weeks after treatment) suggests continued inflammation and requires prolonged therapy. Troponin I levels can be elevated up to 50% of patients in association with epicardial inflammation in oppose to myocyte necrosis seen in AMI. This elevation is transient and resolves within 1–2 weeks without adverse prognosis. Elevation of CK-MB can accompany or not [49].

In selected patients viral seromarkers, blood culture and tests for tuberculosis like PPD or quentiferon tuberculosis assay can be performed. If there is a suspicion of opportunistic infection, HIV testing should be obtained because of strong correlation between tuberculosis and fungal infections and immune-suppressed state. Further studies such as anti nuclear antibody or tests toward a systemic disease (systemic lupus erythamosus, sarcoidosis ...) may be done [56].

Despite disadvantages like ionizing radiation and frequent requirement of intravenous contrast material, CT is very useful for evaluating pericardial anatomy, anatomic variants and pericardial abnormalities. On CT scan of patients with acute pericarditis thickening of the pericardium with smooth margins and intense early contrast enhancement with various amounts of effusion can be detected [57].

Figure 1.
ECG changes including nearly diffuse, concave-upwards ST-segment elevation, and PR-segment depressions in acute pericarditis.
Cardiac MRI is another method for the evaluation of the pericardium. It has good spatial and temporal resolution with highly reproducible measurement and does not expose radiation to the patients. Smooth and thickened pericardial images suggest acute or subacute pericarditis whereas irregular and thickened pericardium indicates chronic pericarditis, tumors, metastasis, or fibrosis. It also identifies loculated or localized pericardial effusions with its nature [58].

Two diagnostic imaging methods mentioned above (CT and MRI) should be considered as further imaging modalities in patients with underlying etiologies such as systemic inflammatory diseases, neoplasms, renal diseases, and tuberculosis. Routine trans-thoracic echocardiography is recommended in all patients with acute pericarditis as a first-line diagnostic tool. It can be used to detect the pericardial effusion and its hemodynamic effects on cardiac structures if constrictive pericarditis or cardiac tamponade is suspected (Figure 2). It also gives opportunity to exclude AMI by the evaluation of the abnormalities in wall motion [59].

If there is a suspicion of tuberculosis, neoplastic or purulent pericarditis, or an effusion refractory to treatment leads to cardiac tamponade or hemodynamic compromise, then pericardiocentesis and if possible biopsy of the pericardium are indicated. Symptomatic or large pericardial effusion refractory to treatment also requires pericardiocentesis [50]. In a study designed by Permanyer it is emphasized that rate of pericardial tamponade differs 5–15% of patients with acute idiopathic pericarditis and up to 60% of those with purulent, neoplasm or tuberculosis pericarditis [60].

Two dimensional and M-mode Doppler echocardiography is specific, non-invasive, sensitive, and easily available technique and the gold standard for the diagnosis of pericardial effusion. Small amounts of pericardial fluid may be physiologic and detected during ventricular systole. If it is over 50 mL en echo-free space persists throughout the cardiac cycle. Small effusion was initially detected over the postero-basal left ventricle, as the volume increases it spreads anterior, lateral, and behind parts of the left atrium. “Swinging heart” is a possible sign of pericardial tamponade due to large pericardial effusion [61].

Pericardial effusion analysis can help for the diagnosis of neoplastic and infectious effusions. Tumor markers and cytology should be performed in suspicion of
malignancy. Pericardial fluid culture should be performed at least three times with the blood culture in suspected bacterial infections [62].

Diagnosis and management of pericarditis was summarized in Table 1.

4.5 Treatment

Exercise restriction is recommended therapy for all patients during the symptoms and at least 3 months for athletes. Ibuprofen can be started at 3 × 600 mg/day for 1 or 2 weeks with proton pump inhibitor and dose can be decreased to 400 mg/week when the inflammatory markers become normalized in acute pericarditis [37]. In patients with a history or significant risk factors for coronary artery disease (CAD), aspirin may be used instead of ibuprofen at a dose of 900 mg/day for 1–2 weeks and dose can be decreased to 600 mg/week when the symptoms resolve and inflammation markers normalize. Colchicine treatment requires a careful follow up the patients because of increased risk of incessant or recurrent pericarditis. If appropriately used with pay attention to narrow therapeutic index of the drug, it can be safe. Potential drug interactions and comorbidities of the patients also be kept on mind while prescribing the drug [64]. If underlying autoimmune rheumatic diseases lead to acute pericarditis or there is a contraindication to NSAIDs or colchicines, corticosteroids can be used. Although they are initially effective, they may promote recurrence and attenuate the efficiency of colchicines if used first-line. In the state of idiopathic pericarditis steroids should only be used as adjuvant therapy if there is a recurrence after a trial of NSAIDs and colchicine. Duration of the steroid treatment is 4 weeks if the inflammation markers normalize and symptoms resolve, and doses must be tapered slowly to avoid adrenal insufficiency [31, 65].
For the patients failing first-line therapy with NSAIDs and colchicine or second-line therapy with NSAIDs, steroids, and colchicines, third-line therapeutic approach is possible. This modality includes azathiprine, intravenous immunoglobulin, and an interleukin 1 beta antagonist called anakinra. Surgical pericardiectomy is the last option and rarely required in clinical practice especially to whom has previous cardiac surgery and/or features of constrictive pericarditis [64].

4.6 Miscellaneous facts about acute pericarditis

4.6.1 COVID-19 and acute pericarditis

COVID-19 disease primarily affects respiratory system however, cardiac involvement such as heart failure, myocardial infarction, arrhythmias, endocarditis, myocarditis, and pericarditis were reported nearly 10% of the patients with COVID-19. Although pericarditis was diagnosed in the minority of the cases with COVID-19, accompanied pericardial effusion and cardiac tamponade were observed in some of those patients [66]. Various hypothesis about cardiac involvement due to COVID-19 are mentioned in the literature. One of them emphasized that direct SARS-CoV-2 effects could be the result of cardiac injuries. ACE 2 receptors highly expressed in lung and heart plays a main role in the mechanism of the inflammation [67]. Macrophage-induced inflammation is the other hypothesis for cardiac complication in patients with COVID-19. Activation of macrophages results in release of massive amounts of cytokine which leads to endothelial activation, expression of adhesion molecules for inflammatory cell infiltration and vascular inflammation [68].

Patients with COVID-19 had pericardial effusion up to 27%, although, severity of effusion was mild in the majority of the cases. In addition, pericarditis is associated with high mortality rates and onset of new cardiac complications such as atrial fibrillation and heart failure [69].

4.6.2 Acute pericarditis after chemotherapy

Relationship between high-dose chemotherapy and acute pericarditis was suggested in the literature. Despite unknown mechanism, opportunistic infections, direct toxic or immunological drug-related mechanisms may play a role in this clinical situation [70].

Conflict of interest

The authors declare no conflict of interest.
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Acute Pericarditis
DOI: http://dx.doi.org/10.5772/intechopen.109354


Acute Pericarditis
DOI: http://dx.doi.org/10.5772/intechopen.109354

The American Journal of Cardiology. 1995;75(5):378-382


