Chapter

Molecular Histopathology and Cytopathology in Cardiovascular Diseases

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Abstract

In this chapter, we describe the most deadly heart diseases, including the fourth parts: Anatomy of the heart, chronic coronary syndrome and acute coronary syndrome and STEMI, Cardiomyopathy, and Pulmonary embolism. The written structure of a component includes Abstract, Pathophysiology, Clinical diagnostic criteria, histopathology, and cytopathology. The content is summarized based on the recommendations of the American Heart Association and the European Society of Cardiology. All images in this chapter are data at our center. In the chapter, we will see the relationship between histopathology and cytopathology and pathophysiology, which will serve as a basis for us to have more studies in the future.

Keywords: anatomy of the heart, coronary artery disease, cardiomyopathy, pulmonary embolism, histopathology and cytopathology

1. Anatomy of the heart

1.1 Orientation of the heart within the thorax

The mirror image of the heart to the anterior chest wall is a quadrilateral bounded by four angles: Upper left (the second intercostal space, 1 cm from the left sternal border), upper right (the second intercostal space, 1 cm from the right sternal border), lower left (the 5th intercostal space with the left midclavicular line corresponding to the apex of the heart), and lower right (the ascending space of the rib to the right border of the sternum).

In describing the orientation of a specific organ, such as the heart, the relationships are as follows:

- Front of the heart: directly related to the sternum, the costal cartilages III-VI, the right and the left lung (**Figure 1a**).

- Diaphragm: The right atrium, right ventricle, and part of the left ventricle are directly related to the diaphragm and located in the epigastrium.

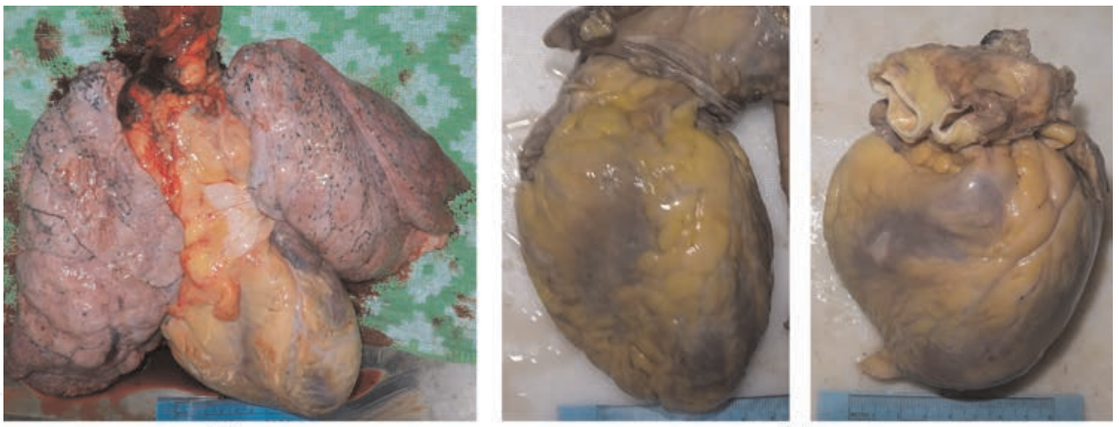

Figure 1.
(a) Heart and lung (b) Cardiac anterior view (left) and posterior view (right).

- Back of the heart: The posterior wall of the left atrium is directly related to the esophagus, so the cardiac image is clearly acquired through transesophageal echocardiography.

1.2 Major veins of the heart

- Superior vena cava: Venous return from the head, neck, and upper extremities into the right atrium through the superior vena cava.

- Inferior vena cava: from the lower abdomen to the right of the spine, this vein has a passage in the parenchyma and posterior to the liver, and receives the superior hepatic vein before into the right atrium through the inferior vena cava.

1.3 Right atrium and septum

The right atrium is directly related to the diaphragm and the substernal area below. The right atrium can be visualized as a hexadecimal volume with several notable structures and associations as follows:

- The upper surface has an orifice of the superior vena cava without the valve.

- The right atrium is shorter and more obtuse than the left atrium.

- The lower surface has the orifice of the inferior vena cava with the Eustachi valve.

- Near the orifice of the inferior vena cava, there is a coronary sinus hole, where the coronary vein drains into the right atrium from the posterior surface of the heart.

1.4 Left atrium and pulmonary veins

The left atrium is located behind and to the left of the right atrium. The left atrium and pulmonary veins are structures located in the deepest layer of the heart.

- The posterior wall of the left atrium is directly related to the esophagus posteriorly, so the intraesophageal probe can easily probe the left atrium and other anterior structures.

- The pulmonary veins (two right and two left) on both sides of the posterior wall of the left atrium. The orifice of pulmonary veins is the deepest and most difficult-to-see structure on transthoracic ultrasound.

- In the anterior wall, outside the left atrium connecting with the left atrium, is a small niche like an ear. In the left atrium, there are some ligaments. The atrium will also be enlarged when there is increased pressure in the left atrium (narrowing, mitral regurgitation...) and is the most likely place to form blood clots, especially in cases of atrial fibrillation. This thrombus may extend from the atrium into the appendage of the left atrium.

1.5 Right ventricle and Interventricular septum

The right ventricle divide structure into two parts, the first extends from the tricuspid valve is the inlet. The inlet component ejected blood to the pulmonary artery through the second part, known as the outflow portion. It is a tubular structure about 1.5 cm long with a funnel shape, the top of which is the orifice of the pulmonary valve.

The interventricular septum is a membrane and muscle that separates the two ventricles. The interventricular septum also has two parts:

- The fragile upper part (2 mm) is called the membranous portion.

- The lower part is the muscular portion (**Figure 2**).

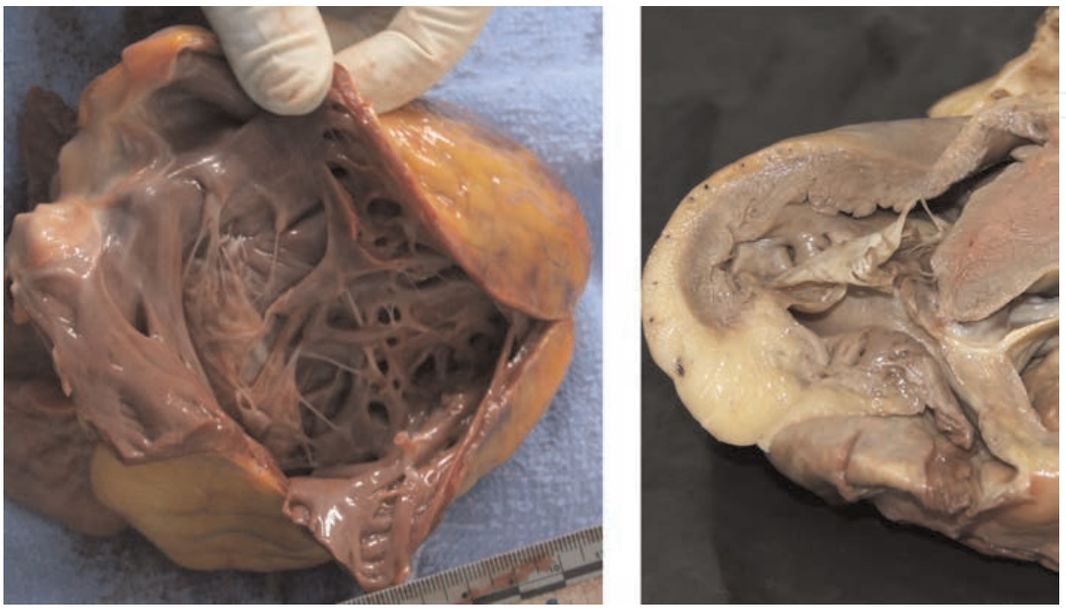

Figure 2
Right ventricle free wall view (left) and septum view (right).

1.6 Left ventricle

The left ventricle is an essential chamber because it ejects blood into the aorta. The left ventricle is located posterior to the right ventricle, an anterior-medial part is covered by the right ventricle, separated by the interventricular septum.

- In the longitudinal view, the left ventricle has an oval shape, with the very small being the apex, the very large (bottom left ventricle) being the mitral valve and the left ventricular (LV) outflow tract.
- The LV muscle layer is much thicker than the right ventricle, on average 1 cm, and the endocardium covers the lumen.
- The LV outflow tract is the route that ejects blood from the left ventricle to the aorta, located between the interventricular septum in front and the anterior mitral leaflet posteriorly, limited from the apex of the anterior mitral valve to the aortic annulus (**Figure 3**).

1.7 Tricuspid valve

Tricuspid valve is a cardiac valve located in the right atrioventricular orifice, whose function is to open during diastole to allow blood to flow from the right atrium to the right ventricle and close during systole to prevent blood backing up into the right atrium.

- Tricuspid valve has three leaflets:
- The anterior tricuspid leaflet is the largest, and most mobile and forms an intracavitary curtain that partially separates the inflow and outflow tracts of the right ventricle.
- The posterior leaflet adheres to the posterior wall of the right ventricle.
- It is especially noticeable that the septal leaflet adheres to the interventricular septum. This leaflet attaches to the membranous portion of the septum 8–10 mm lower than the attachment of the LV mitral valve.

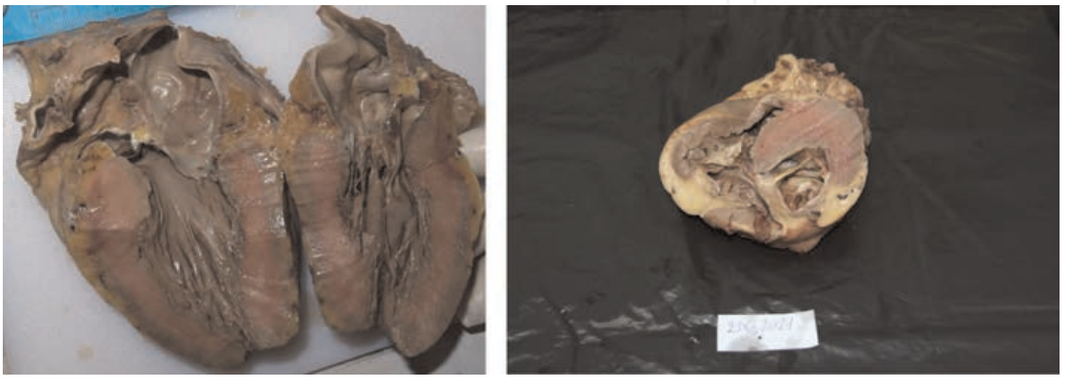

Figure 3.
Left ventricle, long axis (left), and short axis (right).

The tricuspid annulus is a fibrous ring with an average circumference of 105–120 mm. The tricuspid annulus is very often dilated when the right ventricle is dilated (as in pulmonary hypertension) causing tricuspid regurgitation.

1.8 Pulmonary valve

- Pulmonary valve is located at the orifice of the pulmonary artery and has three semicircular leaflets. These leaflets are thin fibrous membranes, two sides covered by endothelium, without ligaments like the atrioventricular valve, but only have one border attached to a fibrous ring called the pulmonary valve ring.

- Pulmonary valve ring average has approximately the circumference of the aortic valve ring from 65 to 70 mm. The size of the annulus is significant to evaluate in the tetralogy of Fallot. The pulmonary artery trunk has an oblique direction to the left shoulder, so to see the pulmonary artery trunk, when ultrasound, it is necessary to tilt the transducer slightly from the left sternal border to the left shoulder.

- The pulmonary artery trunk in regular or congenital malformations all keep anterior to posterior orientation, in contrast to the aorta, which always has an anterior direction. The division of the pulmonary artery is also known as the confluence of the right and left branches.

1.9 Mitral valve

Mitral valve is a simple name for the mitral valve apparatus, which plays an essential role in ensuring the one-way flow of blood from the left atrium to the left ventricle.

The mitral valve apparatus consists of the following components: Annulus, leaflets, subvalvular organization including chordae tendineae and papillary muscle.

- *Annulus:* This is a fibrous ring at the orifice of the mitral valve separating the left atrium and the left ventricle and is the attachment point for the leaflets. The mitral annulus has a standard elliptical shape with an anterior–posterior diameter smaller than the transverse diameter. Mitral regurgitation often leads to annular dilatation and annulus deformity because the anterior–posterior diameter is dilated more than the transverse diameter. These lesions form one of the mechanisms that cause mitral regurgitation.

- *Leaflets:* The two leaflets have a cap shape. The junction of the two leaflets near the annulus creates two valve edges, the anterolateral and posteromedial commissure. The anterior leaflet has more prominent than the posterior leaflet but has a smaller length of attachment to the ring than the attachment of the posterior leaflet. On ultrasound, identify the anterolateral commissure as which edge is closest to the lateral wall of the left ventricle and which posteromedial commissure is located near the interventricular septum.

- *Subvalvular:* The chordae tendineae are fibrous cords that radiate from the top of the papillary muscle to hold the leaflets. There are two papillary muscles arising from the inner surface of the left ventricle near the apex of the heart, the anterolateral and posteromedial papillary muscles.

1.10 Aortic valve

The aortic valve, thicker and stronger than the pulmonary valve, is composed of three components (i.e, annulus, cusps, and commissures), and consists of three leaflets named for their anatomical relationship to the coronary ostium (**Figure 4**):

- Right coronary leaflet: located anterior-right.
- Left coronary leaflet: Anterior-left.
- Non-coronary leaflet: Located posterior-right.

There is no coronary artery in the sinus of Valsalva of the Non-coronary leaflet. Three valve edges are where the three leaflets meet each other at the place of attachment to the valve ring. Valve edges may become fused in rheumatic lesions. The aortic valve ring has a circumference of 65–70 mm in adults.

1.11 Coronary arteries and veins

The right coronary artery from the sinus of Valsalva has an anterior direction in the epicardial layer and enters the right atrioventricular sulcus. The left coronary artery from the left sinus of Valsalva loops posteriorly to the pulmonary artery root, then exits anteriorly. The left main coronary artery bifurcates into the left anterior descending and left circumflex arteries. In a normal person, these arteries are usually only visible for the first 1–2 cm in the left sternal cross-section. Many cardiac veins drain into the right atrium. Most notable because ultrasound can be seen in the coronary sinus, a bulging vein that receives most of the cardiac veins before emptying into the right atrium. This sinus is about 2.5 cm long, enlarged, and located in the coronary sulcus at the back of the heart (**Figure 5**).

1.12 Pericardium

The pericardium is a conical-shaped structure that adheres to and envelops the heart, including the serous and fibrous pericardium. The fibrous pericardium is a resilient sac that surrounds the heart and attaches to the great vessels. The serous

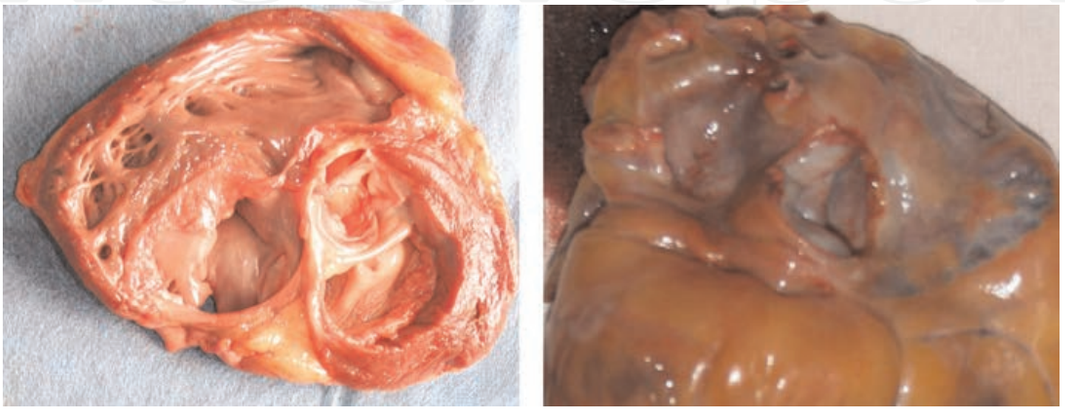

Figure 4.
Aortic valve inferior view (left) and superior view (right).

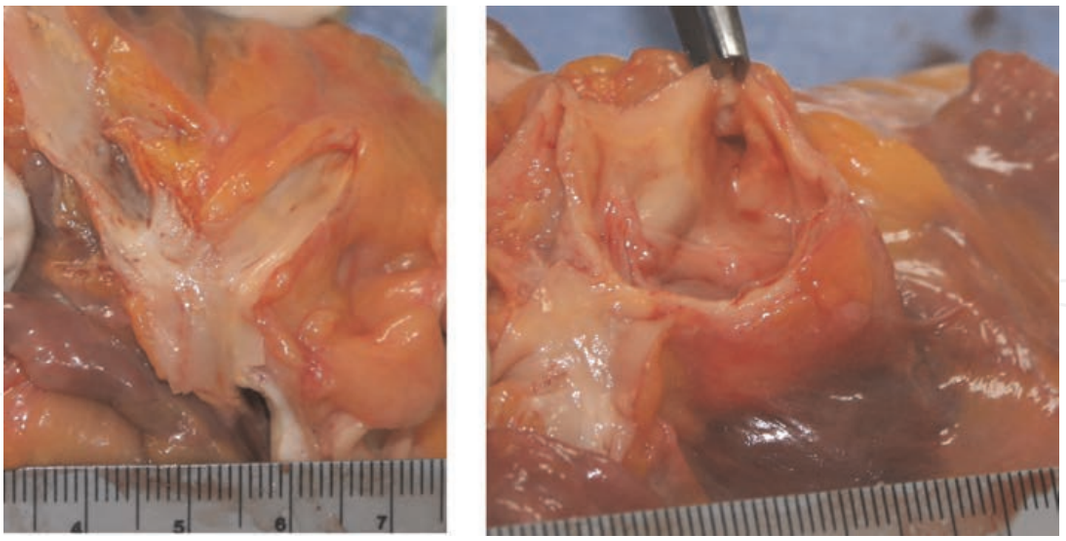

Figure 5.
The left coronary artery: left main, left anterior descending, left circumflex artery (left); ostium (right).

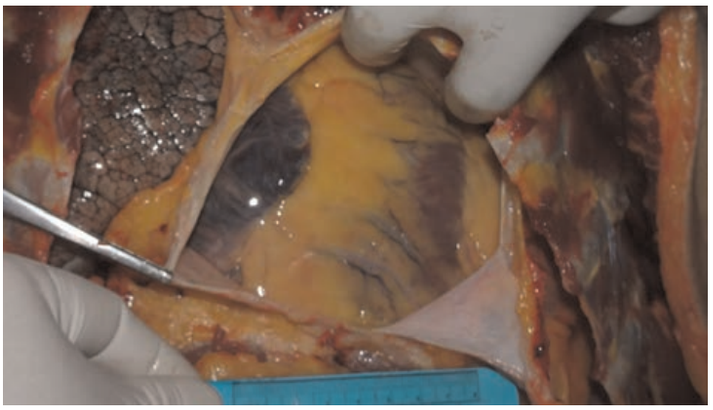

Figure 6.
Pericardium.

pericardium forms the delicate inner lining of the fibrous pericardium and continues onto the surface of the heart and great vessels at the pericardial reflection. Between the layers of the pericardium is a virtual space called the pericardial cavity. Blood and fluid can appear in this space and create a pericardial effusion (**Figure 6**).

2. Coronary artery disease

2.1 Chronic coronary syndrome

2.1.1 Abstract

Coronary artery disease (CAD) is a pathological process characterized by obstructive or non-obstructive atherosclerotic plaque accumulation in the epicardial arteries. The CAD process is dynamic and depends on the stability or instability of atherosclerotic plaques. The acute atherothrombotic event can occur at any time, caused by plaque rupture or erosion, and results in various clinical presentations, categorized as

either acute coronary syndromes (ACS) or chronic coronary syndromes (CCS). The CCS is a new term accepted at the European society of cardiology congress (ESC) 2019, replacing the previous name of stable angina or stable coronary artery disease. According to ESC 2019, CCS has six clinical scenarios: (1) patients with "stable" anginal symptoms and/or dyspnea; (2) patients with newly discovered heart failure or left ventricular dysfunction; (3) patients with stabilized symptoms <1 year after an ACS, or patients with recent revascularization; (4) more than one year after initial diagnosis or revascularization; (5) patients with angina and suspected vasospastic or microvascular disease; (6) CAD is detected at screening without any symptom [1].

2.1.2 Pathophysiology

CCS is a condition involving the relative stability of coronary atherosclerotic plaques, in the absence of an acute atherothrombotic event caused by plaque rupture or erosion. When progressive atherosclerotic plaques cause significant narrowing of the lumen of the coronary arteries (usually above 70% of the lumen diameter), symptoms can be present, most typically angina/shortness of breath during physical exertion and relief at rest [2].

When the lumen of a coronary artery is narrowed, the myocardial perfusion by this vessel is significantly reduced. Especially during physical exertion, the oxygen supply to the heart muscle is impaired while the oxygen demand increases. With this supply–demand imbalance, the heart muscle must depend on anaerobic metabolism to ensure normal function. It is anaerobic metabolic products such as LDH and adenosine that cause chest pain by stimulating the nerve endings of the coronary system. The long-term consequences of this ischemic heart condition are angina attacks during physical exertion, seriously affecting the quality of life as well as the patient's psyche; it may cause impaired LV function and risk of arrhythmias [3]. In addition to the main cause of myocardial hypoxia due to atherosclerosis which causes the narrowing of the coronary vessels, other factors such as vasospasm, especially small blood vessels, anemia, and decreased blood oxygen are also important causes of angina [4]. Factors affecting myocardial oxygen demand are heart rate, myocardial contractility, preload, and afterload. The increase in these factors increases the oxygen demand of the heart muscle and affects myocardial ischemia. Therefore, for the treatment of CCS, increased supply and/or decrease in myocardial oxygen demand along with antiplatelet therapy are core issues [1].

2.1.3 Clinical diagnostic criteria

Angina pectoris: In the diagnosis of CAD, angina is the most important clinical symptom to help with diagnosis, although chest pain has many different causes, so it is necessary to distinguish whether chest pain is caused by coronary heart disease or not. Typical chest pain includes the following characteristics:

- Location: usually behind the sternum and as an area rather than a point, pain can spread to the neck, shoulders, hands, epigastric, or back. Commonly it spreads to the left shoulder or hand.

- Circumstances of appearance: when exerting, having strong emotions, experiencing cold, after a lavish meal, or smoking. Some cases of angina may occur at night, when changing positions, or with tachycardia.

- Character: The pain is like tightening, strangulation, or being weighed down in front of the chest. It may be accompanied by a feeling of shortness of breath, headache, nausea, or sweating. The pain usually lasts about a few minutes (3–5 minutes), it can be longer but usually no more than 20 minutes (when you need to think about acute coronary syndrome). Pains that last less than 1 minute should be caused by another reason rather than the heart [5].

- Investigations such as electrocardiogram, echocardiography, and hs-troponin tests help to rule out acute coronary syndrome as well as other causes of chest pain such as aortic valve stenosis, obstructive hypertrophic cardiomyopathy, aortic dissection … [1, 6].

2.1.4 Histopathology

The most common cause of CCS is atherosclerotic coronary artery obstruction. The microscopic grading of atherosclerosis can be classified according to the Modified American Heart Association criteria [7].

- Pathological intimal thickening: characterized by acellular lipid pools within the intima. No lipid core.

- Fibrous cap atheroma: a lipid core containing extracellular lipid cholesterol crystals and necrotic debris covered by a thick, sometimes multilayered, cap of fibrous tissue. Punctate or patchy calcification. Lymphocytic infiltration may be prominent, especially at the edge of cores.

- Thin fibrous cap atheroma: a thin, occasionally inflamed, fibrous cap covers a lipid core. <65 μm in thickness in the coronary, <200 μm in the carotid arteries. The thin fibrous cap atheroma is a plaque that is considered unstable, with a high risk of rupture, and is also known as "vulnerable plaque".

- Plaque rupture: clear evidence of ruptured fibrous cap and luminal thrombus formation which communicates with the underlying necrotic core.

- Plaque erosion: a fibrous cap atheroma with luminal thrombus as above, but the thrombus formation overly area lacking surface endothelium. Erosion may be seen in early lesions, such as pathological intimal thickening.

- Fibrocalcific lesion: "stable" lesion, a dense collagen plaque containing a large area of calcification and a few scattered smooth muscle cells. This is a consequence of the dystrophic calcification of the lipid core.

- Calcified nodule: heavily calcified lesion, probably one of the last stages of the atherosclerotic process.

- Coronary atheromas may have a focal appearance. The irregular plaques vary both in size and stenosis from place to place, and are often eccentric, resulting in a segmented crescent-shaped lumen artery (**Figures 7** and **8**).

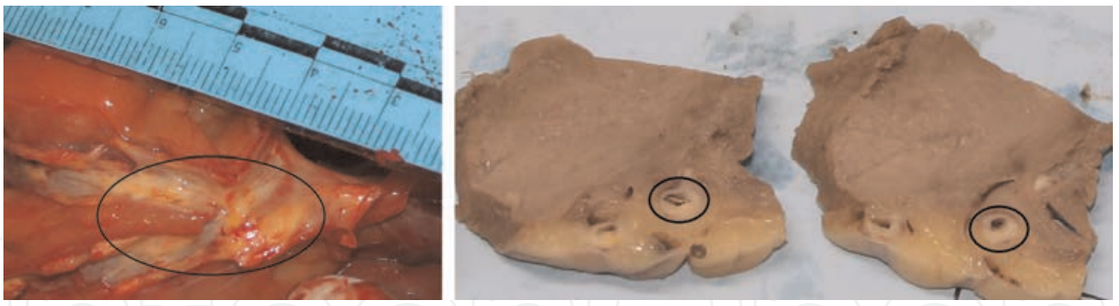

Figure 7.
Histopathology of CCS.

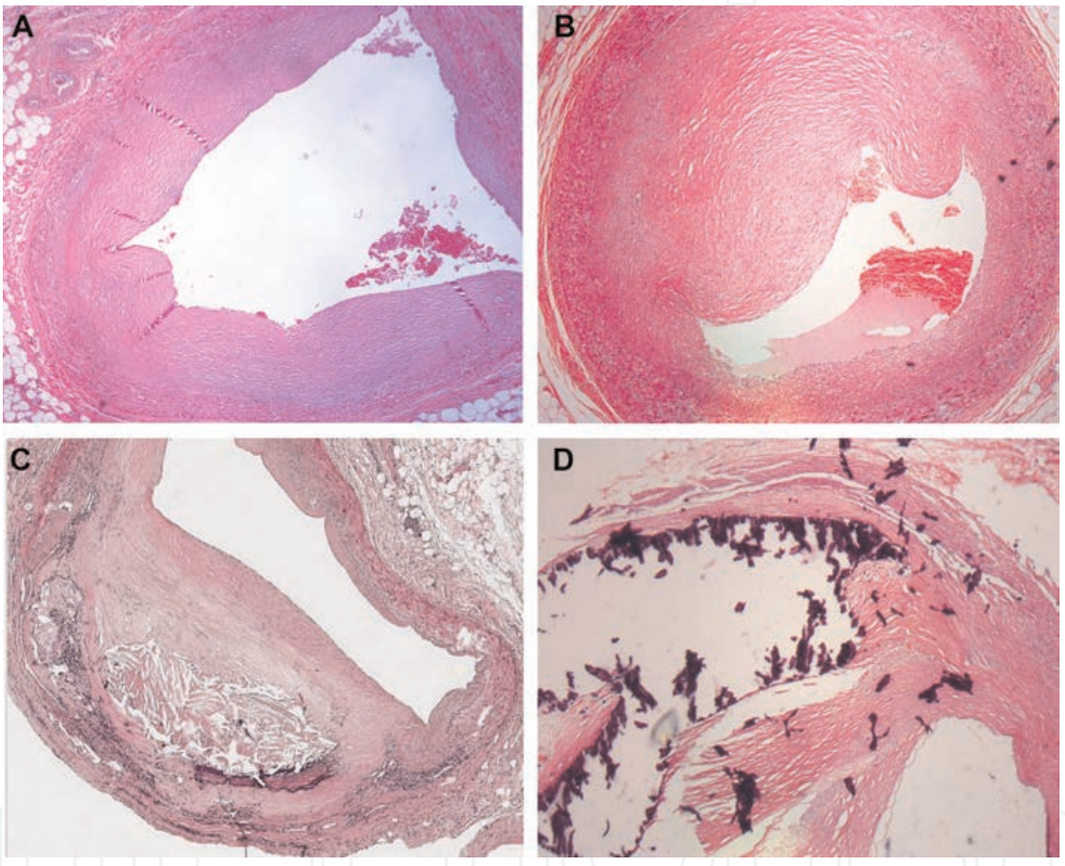

Figure 8.
Micrographs showing the coronary tree. A, the fat tissue in the adventitia (H&E, 100X). B, the severe narrowing lumen by atherosclerotic plaque, with several hemorrhagic necrotic cores and deposition of lipids and infiltration of lipid-laden foam cells in the tunica intima and tunica media (H&E, 100X). C, Panel indicates histological findings features of fibrous cap atheroma with fibrous tissue, necrotic core, and calcification (H&E, 100X). D, intraplaque hemorrhage with the necrotic core with a form of calcification that results in irregular nodules of calcium (H&E, 100X).

2.2 Non-ST elevation acute coronary syndrome

2.2.1 Abstract

Non-ST elevation acute coronary syndrome consists of two clinical scenarios: non-ST elevation myocardial infarction (NSTEMI) and unstable angina. Clinically and in

the electrocardiogram, there is no difference between them, the distinction is in NSTEMI, there is an increase in myocardial biomarkers. The treatment of NSTEMI differs fundamentally from ST-elevation myocardial infarction in approach strategy, time of intervention, and treatment modalities with or without fibrinolysis. An acute coronary syndrome is a severe event of CAD that is the leading cause of cardiovascular death and morbidity. In particular, NSTEMI still accounts for the leading proportion of acute coronary events in developed countries and worldwide. There have been many advances in the effective diagnosis and treatment of acute coronary artery syndrome. However, this is still a severe disease and needs attention [8].

2.2.2 Pathophysiology

The mechanism of ACS is due to the instability of the atherosclerotic plaque and the plaque rupture or erosion. If a large rupture and massive blood clot formation fill the entire lumen of the vessel, it will lead to a transmural myocardial infarction or STEMI. If the rupture is smaller and the clot has not yet led to a complete blockage of a coronary artery, it is unstable angina and NSTEMI. In addition, the mechanisms of the movement of small thrombosis to cause occlusion of microvascular and contraction further aggravate myocardial ischemia. The formation of blood clots occurs due to a cracked atherosclerotic plaque that reveals the subendothelial matrix, which activates the GP IIb/IIIa receptors on the platelet surface when it comes into contact with platelets, causing platelets to aggregate, thereby initiating a blood clotting cascade [9].

The consequence of the above phenomena is a serious and rapid decrease in blood flow to the myocardial area perfused by that coronary artery, clinically manifested as unstable angina pectoris, on the electrocardiogram is an image of acute myocardial ischemia with ST depression or sharp, negative T wave, elevated cardiac enzymes (troponin, CK-MB) [10–12].

2.2.3 Clinical diagnostic criteria

- Clinical: Symptoms of coronary chest pain are the same as in stable angina, although there are differences in the nature of the pain: unstable angina is usually more intense, lasts longer (more than 20 minutes), pain may occur during rest, with no or little response to nitrate [8].

- Electrocardiogram: During the pain, changes in the ST segment can be seen, most commonly ST depression, negative or reversal T wave. Up to 20% of patients do not have immediate changes on the electrocardiogram, so it is recommended to have ECG repeatedly [10].

- Myocardial biomarker: in MI, there is often an increase in hs Troponin I or T, CK, CK-MB [12, 13].

- Echocardiography: helps evaluate regional dyskinesia, LV function, and accompanying heart valve diseases [14].

2.3 Acute ST-elevation myocardial infarction

2.3.1 Abstract

Acute myocardial infarction (MI) is one of the leading causes of death in the US and European countries. It is estimated that in the US every year about 1 million patients are hospitalized and 200,000–300,000 deaths from acute MI. In recent years, advances in diagnosis and treatment have significantly reduced mortality from acute MI. The introduction of the coronary care unit (CCU) in the early 60s, followed by thrombolytic drugs in the 80s, and now percutaneous coronary interventions with advances in drugs therapy has reduced the mortality rate worldwide from about >30% in the past to <7% in the 2000s [15].

2.3.2 Pathophysiology

MI is caused by a complete blockage of one or more coronary artery branches causing sudden myocardial ischemia and necrosis of the myocardial area perfused by that branch of the coronary artery. The main mechanism that causes this phenomenon is the instability and rupture or erosion of the atherosclerotic plaque that causes the formation of thrombosis that fills the entire lumen of the vessels, which abruptly stops the flow of blood to nourish the myocardial area behind that and quickly leads to necrosis [9]. This necrotic process can be rapid or slow depending on whether the patient has previous collateral circulation or not [16]. More than 50% of acute MI occur on previous atherosclerotic lesions that cause only mild stenosis [17]. If the rupture causes the formation of a blood clot that is not large, and has not yet filled the entire lumen of the vessels, then the clinical manifestation is unstable angina. MI is also expanded when there is necrosis of the myocardial area associated with hypoperfusion due to other causes such as acute blood loss and severe hypotension in septic shock (**Figure 9**).

2.3.3 Clinical diagnostic criteria

The definition of myocardial infarction denotes the presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischemia. Diagnostic criteria for MI include an increase or decrease of myocardial biomarker (specifically cardiac troponin) and one of the following conditions:

- Symptoms of acute myocardial ischemia include chest pain, shortness of breath...
- New electrocardiographic transformations associated with myocardial ischemia such as ST elevation, ST depression, and pathological Q waves.
- Images of new regional wall motion abnormality on ultrasound, CMR.
- Identification of a coronary thrombus by angiography or autopsy (**Figure 10**) [18].

2.4 Histopathology and cytopathology of myocardial infarction

Early in an infarct (1–3 hours), myocytes may have a wavy appearance, and there may be interstitial edema (**Figure 11A**). Increased eosinophilic staining of myocytes is

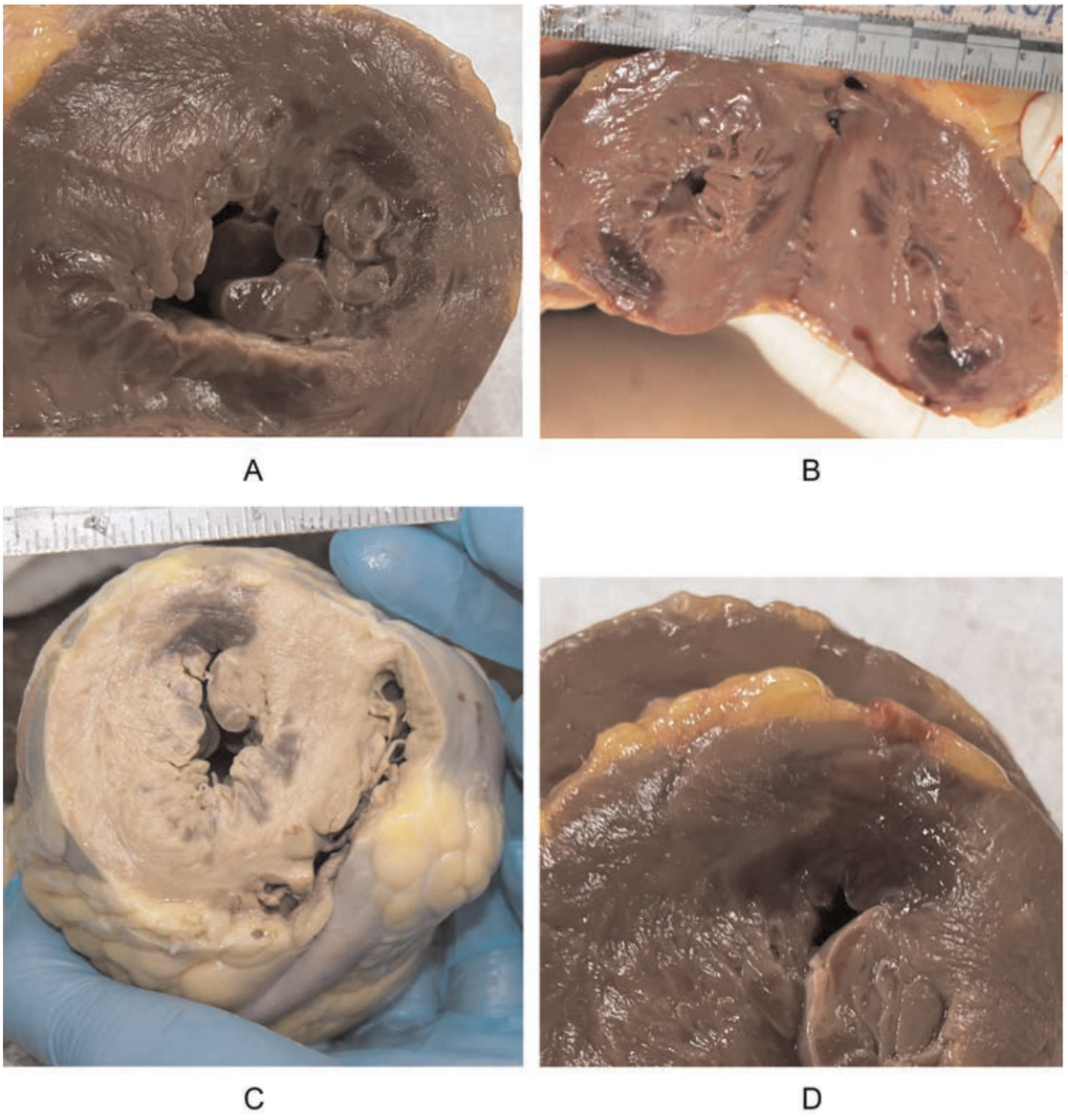

Figure 9.
A regional or focal MI.

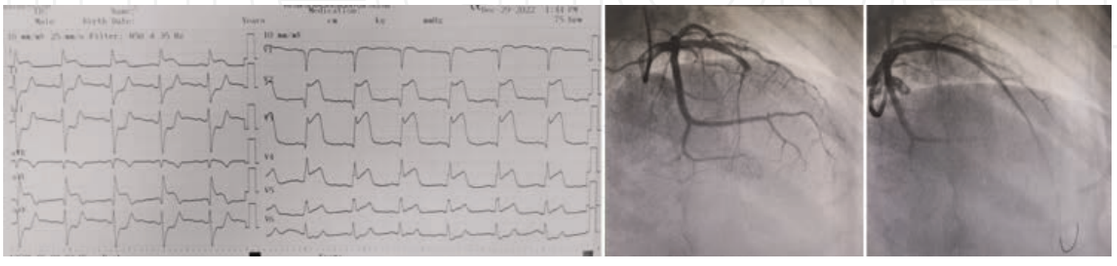

Figure 10.
ECG anterior STEMI (left); coronary thrombus and percutaneous coronary intervention of left anterior descending (right).

usually accompanied by contraction band necrosis and loss of myocyte nuclei (**Figure 11B**). These histologic changes can be appreciated by 4–12 hours, then infiltrated by inflammatory cells. Early ischemia, defined as the first 72 hours, is

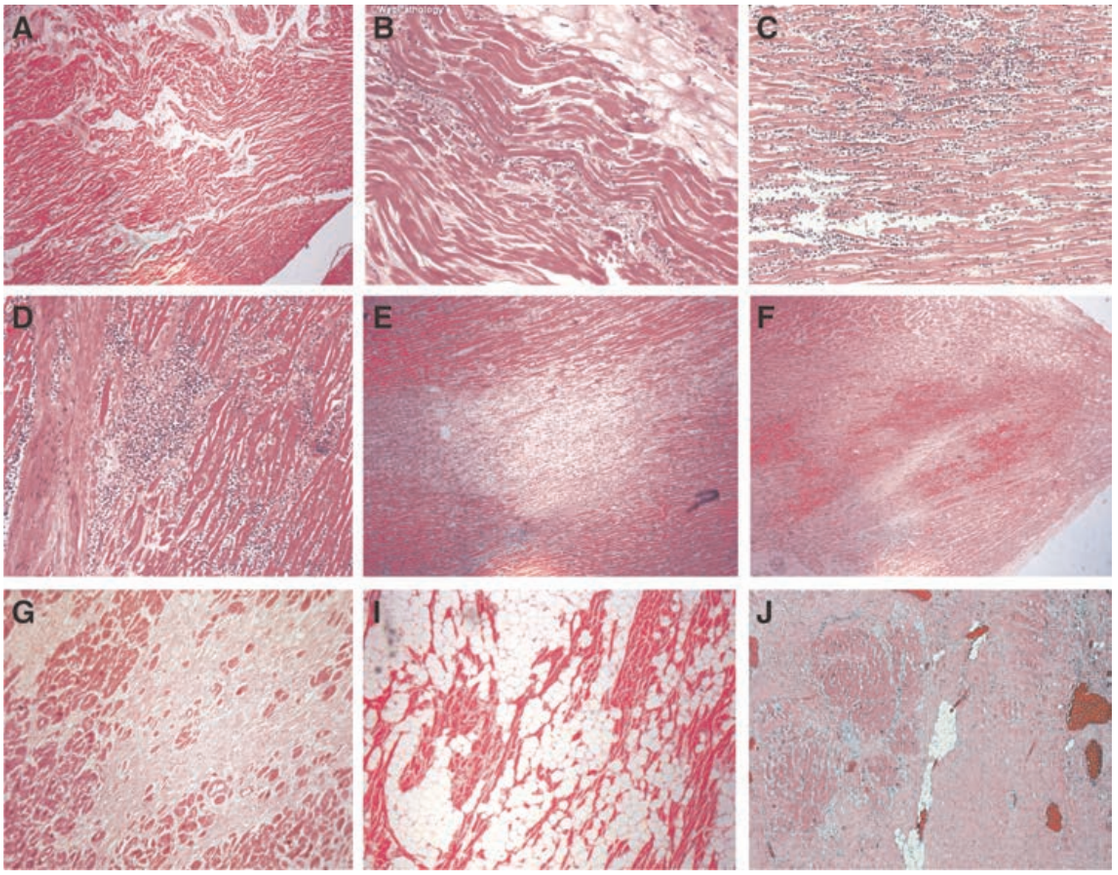

Figure 11.
Histopathology of myocardial infarction.

hallmarked by the first arrival of neutrophils as they marginate through the blood vessels and can be seen in perivascular spaces. Within the first 24–48 hours, neutrophils increase within the interstitium (**Figure 11C**); these interstitial neutrophils mainly stay intact during the first 48 hours. And within 48–72 hours, the degeneration of neutrophils begins. In other words, there is an approximately equal mix of intact and degenerating neutrophils within the first 24–72 hours of early ischemia. When it is closer to 72 hours, degenerating neutrophils and abundant cellular debris start to predominate (**Figure 11D**).

Around the third day (72 hours), there is early removal of myocytes, and the interstitial cells consist of lymphocytes, pigment-laden histiocytes, and myofibroblasts. There has been no appearance of collagen. Over the next stage of five to seven days, interstitial cells continue to proliferate. This is the most cellular stage of the healing process with a large number of interstitial inflammatory cells (**Figure 11E** and **F**). After about two to four weeks, inflammatory cells begin to decrease gradually, and collagen deposition increases (**Figure 11G**). After one to two months, only a few inflammatory cells remain, and collagen is firmly established (**Figure 11H**). After a period of two months, the inflammation ceases, and there is only a dense layer of collagen; the scar is formed. Basically, an infarct does not progress further after two months, although a well-healed scar may undergo additional changes, such as fatty infiltration and neovascularization. However, these are more variable features. There are usually remaining myocytes entrapped within areas of a healed infarct's scar, and this is a potential focus of arrhythmias (**Figure 11I** and **J**).

3. Cardiomyopathy

Cardiomyopathy is a group of structural disorders of the myocardium. Unlike other structural heart disorders such as coronary artery disease, valvular heart disease, and congenital heart disease. Cardiomyopathy is classified into three main types based on pathological features.

3.1 Dilated cardiomyopathy

3.1.1 Abstract

Dilated cardiomyopathy is a myocardial dysfunction causing heart failure in which ventricular dilatation and systolic dysfunction predominate. Symptoms include dyspnea, fatigue, and peripheral edema. Diagnosis is based on clinical findings, quantification of natriuretic peptide (BNP) levels, chest x-ray, echocardiography, and CMR. Treatment of dilated cardiomyopathy is based on etiology. If heart failure is advanced and severe, cardiac resynchronization therapy (CRT), implantable cardioverter defibrillator (ICD), moderate to severe regurgitation repair, LV assist device may be needed in the short-term or long-term and heart transplant [19]. Dilated cardiomyopathy can develop at any age but is more common in adults under age 50. In the United States, men are three times more likely to have the disease than women, and African-Americans are three times more likely to have the disease than whites; about 5 to 8 out of 100,000 people get it each year [20].

3.1.2 Pathophysiology

As primary cardiomyopathy, dilated cardiomyopathy has been identified in the absence of other disorders that can cause dilated cardiomyopathy, malformations such as severe coronary artery disease or hypertension, or valvular heart disease. In some patients, dilated cardiomyopathy is thought to progress from acute myocarditis (often viral etiology in most cases), followed by a latent phase, a stage of disseminated cell death, cardiomyocytes (causing an autoimmune response to virally altered cardiomyocytes), and fibrosis. Regardless of the cause, the myocardium dilates, enlarges, and enlarges to compensate [19, 21]. The disorder affects both the left and right ventricles in most patients but rarely affects only one ventricle. Thrombosis can form due to blood stagnation when time dilates and cardiac dysfunction is significant.

3.1.3 Clinical diagnostic criteria

Diagnosis of dilated cardiomyopathy is based on history, physical examination, and exclusion of other common causes of ventricular dysfunction (eg, hypertension, primary valvular disease, coronary artery disease) by the chest x-ray, electrocardiogram, echocardiography, and cardiac magnetic resonance imaging (CMR). Endocardial biopsies are performed in some cases. In cases of unknown etiology, family members are screened for cardiac dysfunction to detect early-onset heart disease, heart failure, or sudden death (such as echocardiography).

- Serological tests for Toxoplasma, Trigonoscuta cruzi, coxsackievirus, HIV, and echovirus may be performed in appropriate cases.

- Chest X-ray showed an enlarged heart. Pleural effusion, most commonly on the right side, is often associated with pulmonary hypertension and interstitial edema.

- The electrocardiogram usually shows sinus tachycardia and nonspecific ST-segment depression with low voltage or T wave inversion. Occasionally, pathological Q waves appear in the precordial leads, indicating a previous myocardial infarction. Left bundle branch block and atrial fibrillation are common.

- Echocardiography helps to rule out primary valvular disease and shows left ventricular dilation and systolic dysfunction with impaired global contractility or right ventricular dysfunction or functional mitral and tricuspid regurgitation. Echocardiography may also show chamber thrombosis.

- CMR is useful in providing detailed images of myocardial structure and function. CMR with gadolinium contrast agent may show structural abnormalities of the myocardium or scar tissue. CMR can help diagnose active myocarditis, sarcoidosis, muscular dystrophy, or Chagas disease). Positron emission tomography (PET) is highly sensitive for the diagnosis of sarcoidosis.

- Coronary angiography to rule out coronary artery disease. Patients with angina or with certain cardiovascular risk factors and elderly patients are more likely to develop coronary artery disease. Endomyocardial biopsy is indicated if giant cell myocarditis, eosinophilic myocarditis, or sarcoidosis are suspected, as the results will influence the treatment [19, 22].

3.1.4 Histopathology and cytopathology

Dilated cardiomyopathy is a progressive, diffuse process involving cardiomyocytes from the right and left ventricles, resulting in both chambers becoming dilated and dysfunctional. As the myocardium relaxes, it becomes stretchy and thinner. Consequently, the ventricular chamber widens. Since this condition's histologic features are nonspecific, it is a microscopic diagnosis of exclusion. Previous studies have also established such findings, but only in the myocardium of patients with end-stage disease (**Figure 12**).

- Microscopic description: Myocytes have normal architectural distribution but changes in numbers, sizes, and shapes, as well as in the cytoplasm and nucleus. With regards to the size of myocytes, there are significant large variations, as these are a combination of hypertrophic, atrophic, and normal myocardiocytes or are associated with degenerative changes. Due to the atrophy of the myocytes, they have an appearance of long and thin fibers, with a sinuous path and a characteristic appearance of "corrugated fibers" (**Figure 13A**). These fibers are separated from each other by loose spaces, a suggestive aspect of edematous infiltration of the interstitia. The typical atrophy is presented with zonal characters, rarely with extensive or focal elements.

Fibrosis is diffuse or focal in the interstitial or perivascular topography. In interstitia, the fibrillar collagen's presence in intermuscular spaces normally devoid of collagen is noticed. The distribution pattern can vary from a fine peri-myocyte distribution to massive scars. In the case of perivascular fibrosis, collagen has

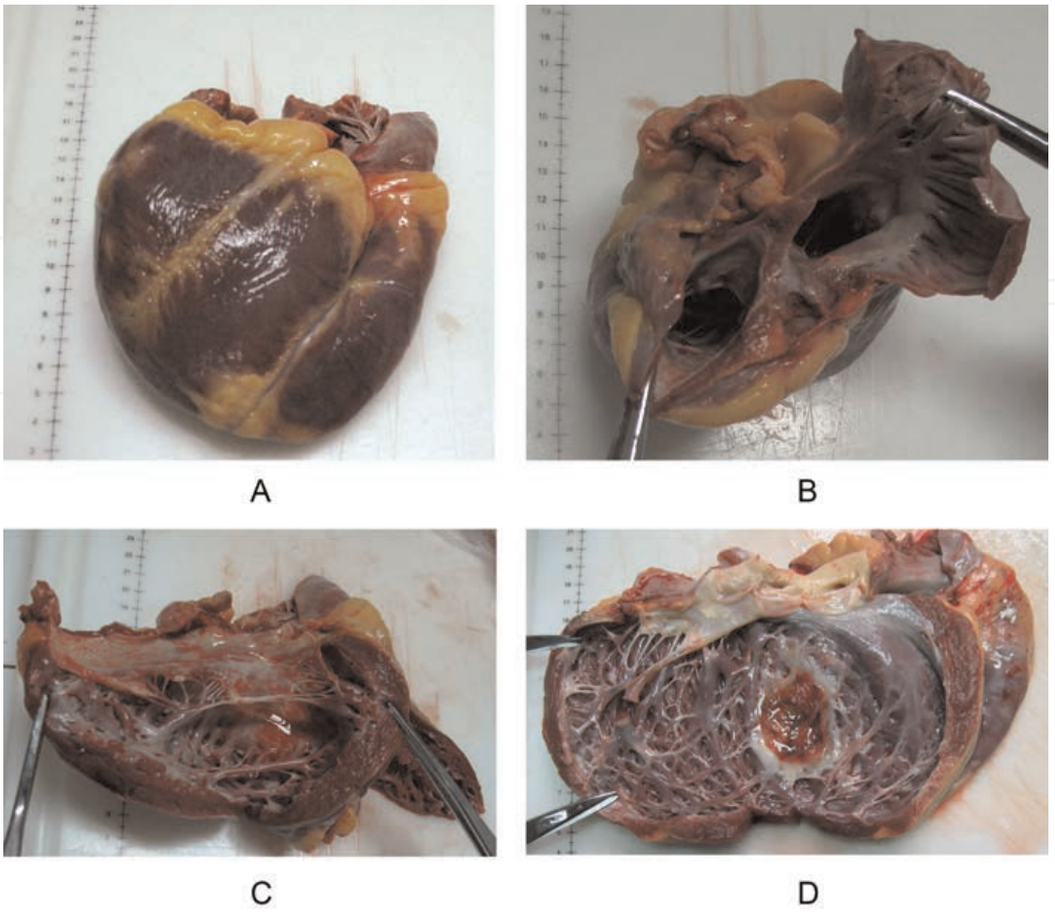

Figure 12.
Dilated cardiomyopathy.

accumulated in the adventitia of intramedullary coronary arteries and arterioles, otherwise remains untouched (**Figure 13B**). The presence of fatty tissue infiltrates (lipomatosis) with focal characters. (**Figure 13C**). Collagen has individually surrounded the myocardial fibers with a "ragged" appearance due to the corrugated cell membrane (**Figure 13D**).

3.2 Hypertrophic cardiomyopathy

3.2.1 Abstract

Hypertrophic cardiomyopathy (HCM) is a congenital or acquired disorder characterized by marked ventricular hypertrophy and diastolic dysfunction but no increased afterload. Symptoms include difficulty breathing, chest pain, fainting, and even sudden death. HCM is diagnosed based on echocardiography and CMR. The initial therapy is beta-blockers, verapamil, disopyramide, alcohol septal ablation, or surgical removal of outlet obstruction [23].

3.2.2 Pathophysiology

Cardiac muscle abnormalities with fibrous tissue and not specific to HCM. The most common is marked hypertrophy and thickening of the anterior septum and the adjacent

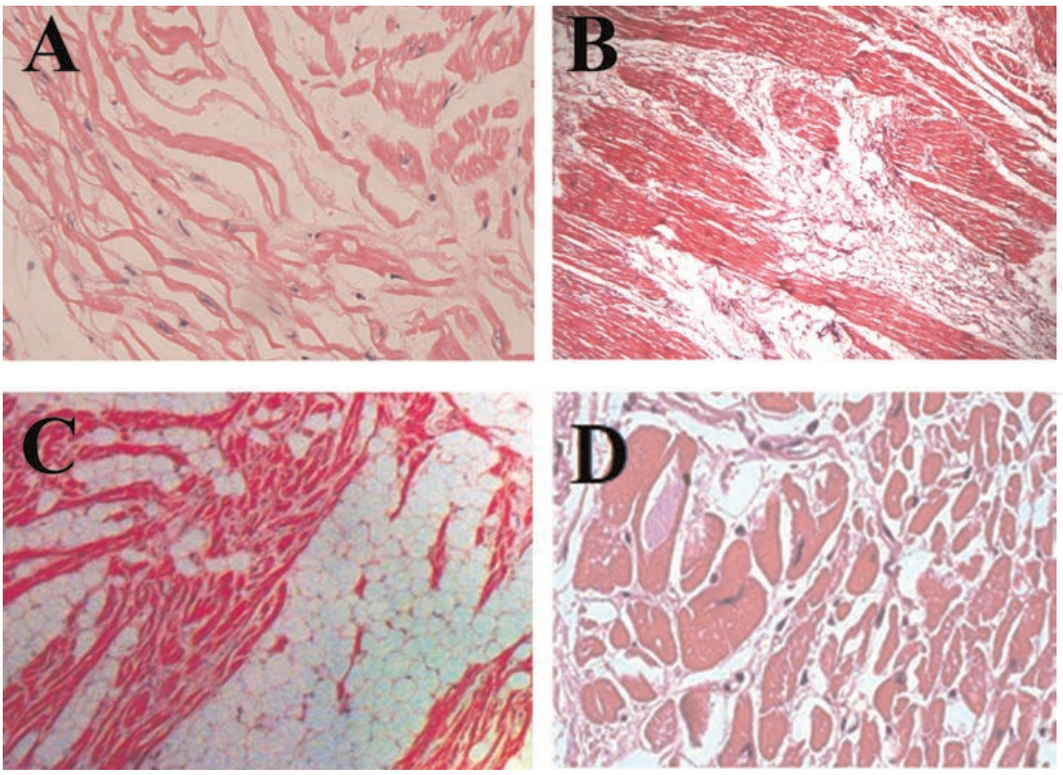

Figure 13.
Microscopic diagnosis dilated cardiomyopathy.

anterior free wall below the aortic valve, with little or no LV posterior wall hypertrophy. Occasionally, isolated apical hypertrophy occurs; most cases are asymmetric hypertrophy, and a few cases of symmetrical hypertrophy have been reported [24].

Two-thirds of patients present with "congestion" at rest or with exercise; obstruction results from mechanical resistance to the LV outflow tract during systole due to the mitral valve's forward motion (SAM). During this period, the mitral valve and valvular structures are drawn into the LV outflow tract due to the Venturi effect of high-velocity blood flow, resulting in flow obstruction and decreased cardiac output. Mitral regurgitation can also occur due to the deformed movement of the leaflets. This blockage and regurgitation cause symptoms associated with heart failure. Less commonly, left midventricular hyperplasia causes elevation of pressure gradient at the site of the papillary muscles [23, 25].

Initially, contractility is completely normal, resulting in a normal ejection fraction (EF). Thereafter, EF increases because the ventricular volume is small and empties almost completely to maintain cardiac output. Hypertrophy leads to a rigid, elastic ventricular chamber that interferes with diastolic filling, increasing end-diastolic pressure and increasing pulmonary venous pressure. As filling resistance and cardiac output decrease, the condition is worsened by any output gradient. Tachycardia allows less time to fill, so symptoms tend to appear mainly with exercise or a rapid heart rate.

Coronary blood flow may be impaired, causing angina, syncope, or arrhythmia in the absence of epicardial coronary artery injury. Impaired flow due to inadequate capillary versus muscle cell density (capillary/muscle imbalance) or narrowing of the lumen of the coronary arteries in the myocardium due to hyperplasia and hypertrophy endothelium and mesothelium. A mismatch between supply and demand can also

arise due to increased oxygen demand, hypertrophy, and adverse loading conditions [23]. In some situations, myocytes die due to ischemia, will be replaced by diffuse fibrosis. Subsequently, the ventricles become enlarged with pre-existing diastolic dysfunction and progressive systolic dysfunction.

3.2.3 Clinical diagnostic criteria

The diagnosis of HCM is suspected based on murmurs and other typical symptoms, especially if the patient has unexplained syncope or a family history of sudden death. HCM must be differentiated from aortic stenosis and coronary artery disease because they have similar clinical symptoms.

- Electrocardiograms in patients with HCM often show LV hypertrophy. Abnormal Q waves in leads I, aVL, V5, and V6 are often present with asymmetrical septal hypertrophy; QRS complexes in V1 and V2, similar to previous septal infarction. Inverted, symmetrical, and deep T waves with ST-segment depression in leads DI, aVL, V5, and V6. P waves are usually broad and notched in leads DII, III, and aVF, with biphasic P waves in leads V1 and V2, indicating left atrial hypertrophy; Bundle branch block is common [26].

- Two-dimensional Doppler echocardiography and CMR help to differentiate other forms of cardiomyopathy and predict the severity of hypertrophy and LV outflow tract obstruction. It also helps to monitor the effectiveness of treatment or surgery. Exercise testing and 24-hour ambulatory ECG outpatient follow-up are recommended during the initial evaluation and every 1 to 2 years to evaluate the risk of sudden cardiac death and guide arrhythmia treatment.

- Cardiac catheterization is usually performed when invasive treatment is considered. Usually, the patient has concomitant coronary artery disease.

- Genetic markers do not affect the treatment or identification of high-risk individuals. However, genetic testing helps screen family members.

3.2.4 Histopathology

Myocyte hypertrophy is correlated with heart size. The disarray of the overall architecture of the hypertrophied myocytes characterizes histopathology in patients with HCM. It notes that whether myocytes may be obviously or barely noticeably enlarged depends on their relative heart size.

The increase in myocytes and interstitial tissue leads to increased myocardial mass. Meanwhile, the heart may or may not increase in overall size due to the hypertrophy of myocytes may or may not be associated with dilation. Dilation is a prominent feature in response to volume overload rather than pressure overload. Regarding pressure overload, the walls may be thick with no dilation, and the chamber volume ratio to wall thickness decreases; this is also known as “concentric hypertrophy”. Although the ventricular wall thickness is measured as a reflection of the degree of hypertrophy, such measurement does not accurately reflect the myocardial mass in hypertrophy with dilation (**Figure 14**).

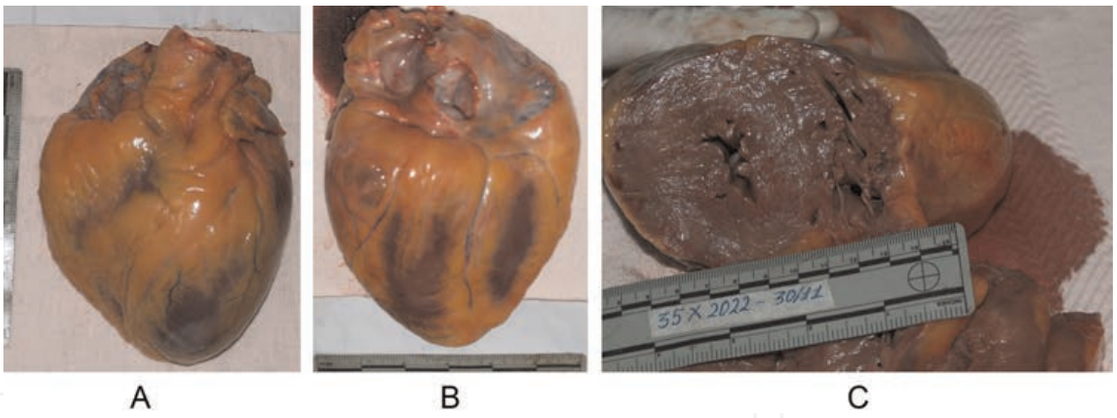

Figure 14.
Very large heart size (18 x 15 cm). Cross section of hypertrophic heart in an adult: The right ventricular free wall thickness is 1,5 cm, the LV is 3,5 cm, and the septum 3 cm.

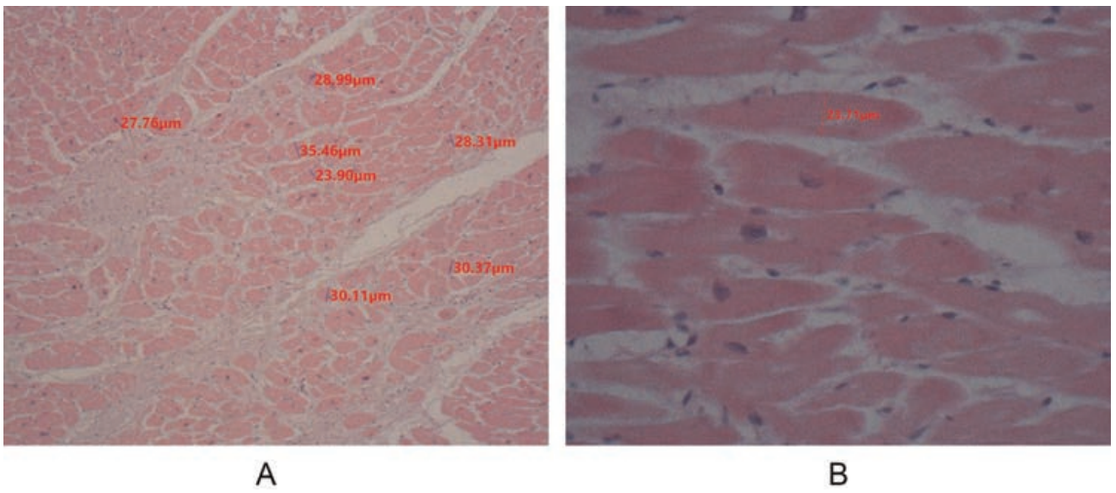

Figure 15.
In Myocardial hypertrophy cardiocyte diameter is up to 25 µm and in severe hypertrophy is usually between 25 and 30 µm.

The diameter of the myocardial cell is also an indicator that predicts different levels of hypertrophy. Under normal conditions, the myocardial cell ranges from 5 to 12 µm in diameter. In cases of mild and moderate hypertrophy, it can go up to 20 µm and 25 µm, respectively. Diameters between 25 and 30 µm usually indicate moderate to severe hypertrophy. And when diameters are greater than 30 µm, severe hypertrophy must be suspected. HCM almost always presents with cell hypertrophy. Hypertrophic myocardial cells show nuclear enlargement, bizarre nuclei, and binucleation (**Figure 15**).

The typical histologic description of hyperchromatic nuclei is like a rectangular shape, or "box-car" nuclei (**Figure 16A**). Myocardial fibrosis can be comprised of three main categories: interstitial, perivascular, and replacement-type fibrosis. In interstitial diffuse fibrosis, bundles of collagen surround the cardiomyocytes individually (**Figure 16B**). Perivascular fibrosis spreads radially around capillary and small arteries. Replacement by adipose tissue is often seen in the terminal stage of fibrosis (**Figure 16C**). Replacement fibrosis is characterized as areas of fibrosis not large enough to be considered an infarct, typically less than 3 mm in size (**Figure 16D**).

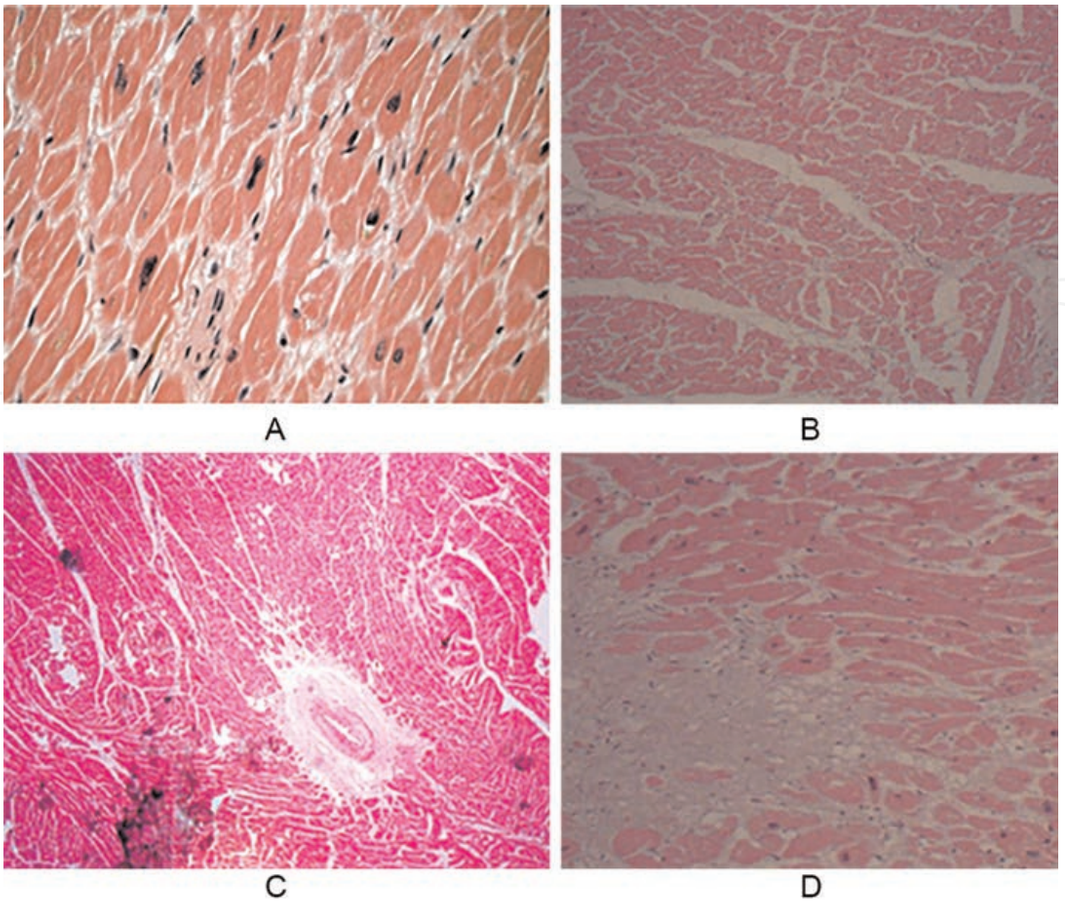

Figure 16.
A: Hyperchromatic nuclei. B: interstitial fibrosis. C: Perivascular fibrosis. D: Replacement fibrosis.

3.3 Restrictive cardiomyopathy

3.3.1 Abstract

Restrictive cardiomyopathy is the least common form of cardiomyopathy. It is characterized by noncompliant ventricular walls that resist diastolic filling; the right or left ventricle or both may be affected. Symptoms include fatigue and shortness of breath, especially with exertion. Restrictive cardiomyopathy is diagnosed based on echocardiography and cardiac catheterization. The medication is often less effective. Surgery is sometimes beneficial [27]. It classifies as non-obstructive (infiltration of the myocardium by an abnormal substance) and fibrosis (fibrosis of the endocardium and subendocardium).

3.3.2 Pathophysiology

Endocardial thickening or myocardial infiltration (with possible myocardial cell death, papillary infiltration, myocardial hypertrophy, and fibrosis) occurs on one side, typically the left or both ventricles. Thus, causing mitral or tricuspid regurgitation. If the nodal and conduction tissues are affected, the sinus node and the atrioventricular node become less functional, sometimes causing varying degrees of SA and AV block. The hemodynamic consequences are diastolic dysfunction with ventricular stiffness, loss of elasticity, impaired diastolic filling capacity, and increased filling pressure,

leading to increased pulmonary venous pressure. The systolic function may worsen. A cardiac chamber thrombus can form, leading to systemic embolism [27].

3.3.3 Clinical diagnostic criteria

Restrictive cardiomyopathy should be suspected in patients with heart failure and preserved ejection fraction, particularly in the presence of systemic disease. An electrocardiogram, chest x-ray, and routine echocardiography are required.

ECG presentation is less specific and may show ST segment and T wave abnormalities and sometimes low voltage. Pathological Q wave, not due to previous myocardial infarction. LV hypertrophy due to compensatory myocardial hypertrophy or both atrioventricular block, and sinoatrial block may be present.

On a chest X-ray, the heart is usually normal in size but may be enlarged in amyloidosis or hemochromatosis. Echocardiography showed a normal LV ejection fraction. Tissue Doppler imaging often shows increased LV filling pressure, and longitudinal decline in contractile function despite normal ejection fraction. In addition, other nonspecific signs such as atrial dilatation and myocardial hypertrophy. In amyloidosis, abnormal echogenic tissue can be observed from the myocardium, and identification of the amyloid type has implications for treatment, genetic counseling, and prognosis [27, 28].

3.4 Some other diseases

In addition to the three common types mentioned above, there may also be other forms such as arrhythmogenic right ventricular cardiomyopathy, Takotsubo cardiomyopathy, peripartum cardiomyopathy, spongiform cardiomyopathy, or secondary cardiomyopathies. Consequences of endocrine, metabolic, neurological, nutritional, autoimmune, toxicological diseases... For each of these diseases, there are separate pathophysiological mechanisms and different diagnostic procedures. Histopathology is diverse, but all have in common that is, leading to cardiovascular mortality or severe cardiac dysfunction.

4. Pulmonary embolism

4.1 Abstract

Pulmonary embolism is caused by the thrombus moving through, most commonly from the large veins of the lower extremities or pelvis. Risk factors for PE are venous stasis, endothelial damage, and disorders associated with hypercoagulability [29]. Symptoms of PE include dyspnea, chest pain, and in more severe cases syncope, respiratory failure, and cardiac arrest. Physical examination may tachypnea, tachycardia, and, in more severe cases, hypotension. Computed tomographic pulmonary angiography is considered the gold standard diagnostic modality for PE with a sensitivity of 83% and specificity of 96%, although ventilation/perfusion is sometimes required. Treatment of PE with anticoagulants and thrombolytics is systemic or directly through the catheter, thrombectomy with mechanical and surgical instruments. When anticoagulation is contraindicated, an inferior vena cava filter should be placed. Preventive measures include

anticoagulation and/or the use of compression stockings and lower extremity decompression devices [30].

4.2 Pathophysiology

As deep vein thrombosis develops, the clots can move through the venous system to the right heart and the pulmonary arteries, where they partially or completely obstruct one or more arterial branches of the pulmonary vessels. The severity depends on the size and amount of the thrombosis, the underlying lung condition, right ventricular function, and the fibrinolytic system's ability to dissolve the clot. The death occurred due to right ventricular failure [29, 30].

Small emboli may have no physiological effects, dissolve immediately, and resolve spontaneously within hours or days. Larger emboli can cause reflex hyperventilation, hypoxia due to inadequate ventilation/perfusion (V/Q), and low venous mixed oxygen due to decreased cardiac output. Low blood pressure, atelectasis due to decreased alveolar CO and surfactant abnormalities, and increased pulmonary vascular resistance due to mechanical obstruction and vasoconstriction lead to tachycardia and hypotension. Endogenous lysis reduces most thrombi, even moderate-sized ones, and physiological changes subside after hours or days. Some emboli are resistant to lysis and can organize and persist, subsequently causing chronic pulmonary hypertension [31, 32]. PE can be classified according to risk:

- High-risk (super-massive): Impaired RV function with hypotension/ severe respiratory failure requiring treatment with vasopressors and high-flow oxygen.

- High risk (massive): Decreased RV function causing hypotension, as defined by systolic blood pressure < 90 mm Hg or decrease in systolic blood pressure 40 mm Hg from baseline over 15 minutes.

- Intermediate risk (submasive): Decreased RV function and/or elevated troponin and/or natriuretic peptide (BNP) levels without hypotension. The European Society of Cardiology defines intermediate-risk PE as patients with a simplified PE severity index (sPESI) > 0.

- Low risk: No RV failure and no hypotension (and according to the European Society of Cardiology, sPESI score = 0) [33].

In 1 to 4% of cases, chronic residual obstruction leads to pulmonary hypertension. This condition can progress and lead to chronic right-sided heart failure [34]. When a large embolus blocks the major pulmonary arteries, or many smaller emboli combine to occlude >50% of the more distal vessels, RV pressure increases, induce in acute RV failure. The risk of death depends on the degree and rate of elevation of RV pressure and the patient's baseline cardiopulmonary status. Patients with pre-existing cardiopulmonary disease are at increased risk of mortality, but young and/or otherwise healthy patients may survive after thrombosis occluding >50% of the pulmonary vascular bed [30, 35].

Pulmonary infarction (ischemia of lung tissue) occurs in <10% of patients with a diagnosis of PE. This low incidence is attributed to the dual blood supply to the lungs

(i.e, bronchi and lungs). In general, pulmonary infarctions are caused by emboli. Smaller occlusions lodge in the more distant pulmonary arteries and are almost completely reversible; pulmonary infarction is detected early by highly sensitive radiographic criteria, often before necrosis occurs.

4.3 Clinical diagnostic criteria

The clinical presentation of PE is nonspecific, which, like many other conditions, makes diagnosis more difficult. Therefore, the current diagnostic method is to assess the risk of PE, thereby recommending appropriate follow-up tests to confirm the diagnosis. According to Ceriani et al., there is currently no best model, although many probabilistic models have been developed to help clinicians easily access the diagnosis of PE. It is recommended to use a scale that is widely used in studies (such as the Wells and Geneva criteria) (**Table 1**) [31].

Wells score		**Revised Geneva score**	
Variable	**Points**	**Variable**	**Points**
Predisposing factors		Predisposing factors	
Previous DVT or PE	+1.5	Age >65	+1
Recent surgery/ immobilization	+1.5	Previous DVT or PE	+3
Cancer	+1	Surgery or fracture Within 1 month	+2
		Active malignancy	+2
Symptoms		Symptoms	
Haemoptysis	+1	Unilateral lower limb pain	+3
		Haemoptysis	+2
Clinical signs		Clinical signs	
Heart rate >100/min	+1.5	Heart rate	+3
		75–94/min	+5
		≥ 95/min	+5
Clinical signs of DVT	+3		
Clinical judgement			
Alternative diagnosis less than PE	+3	Pain can lower limb deep vein at palpation and unilateral oedema	+4
Clinical probability	Total	Clinical probability	Total
Low	0–1	Low	0–3
Intermediate	2–6	Intermediate	4–10
High	≥ 7	High	≥ 11
Clinical probability (2 levels)			
PE unlikely	0–4		
PE likely	0–4		

Table 1.
Clinical prediction scores for PE: the revised Geneva score and the Wells score.

In patients with a shock state, besides PE, other causes that should be considered are acute myocardial infarction, cardiac tamponade, acute aortic syndrome, and acute valvular disease. Therefore, echocardiography should be the first choice for differential diagnosis. For unstable patients who cannot be transported to CT immediately, when echocardiography is suggestive (right ventricular overload), the diagnosis of PE can be accepted. After resuscitation, the patient can be transported for a diagnostic CT scan. In stable patients, diagnosis by Christopher's Algorithm (**Figure 17**) [36].

4.4 Histopathology

Pulmonary thromboembolism can form due to stagnation and inflammation or coagulopathy in the large veins in the legs and pelvis. Observed in the pulmonary artery in the left lung on the cut section is massive pulmonary thromboembolism (**Figure 18A**). The "saddle embolus" (**Figure 18B**) is a bridge from the heart across the pulmonary artery and divides into the right and left main pulmonary arteries. This thromboembolism displays a typical gross appearance, irregular surface, and pale tan to white, admixed with dark red areas. It often causes sudden death.

Thrombus layered is typical of a thrombus that forms in a large vein of the pelvis or lower extremity. It has migrated up the inferior vena cava, through the right heart, and into a pulmonary artery (**Figures 18C–23**).

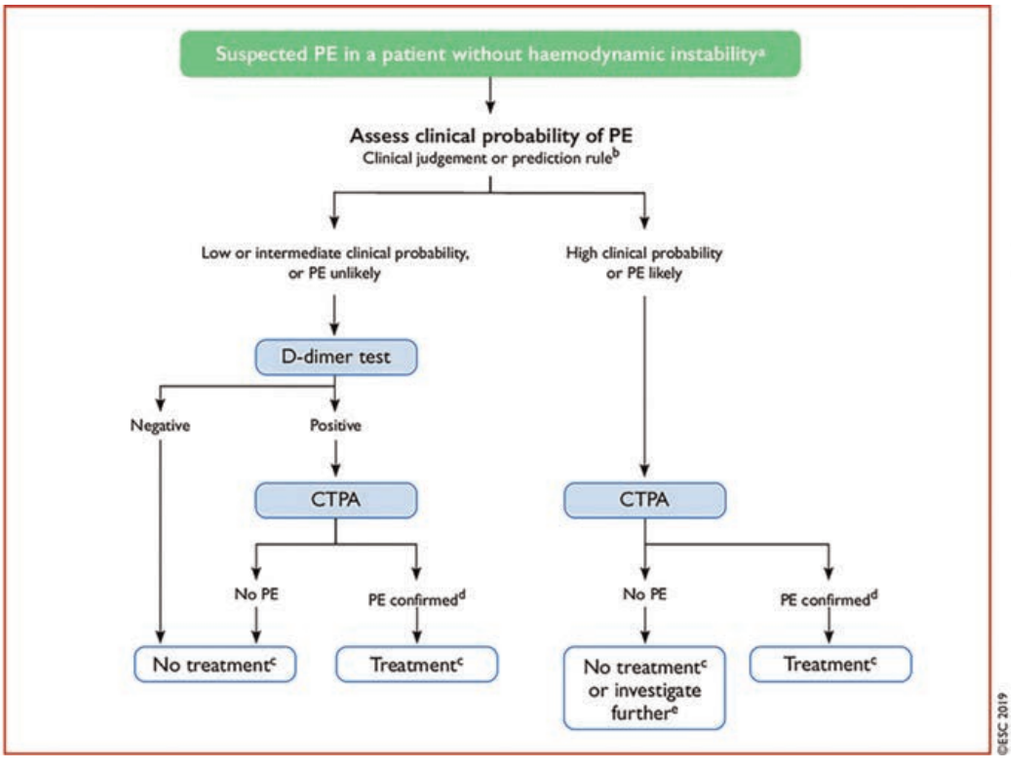

Figure 17.
Christopher's Algorithm.

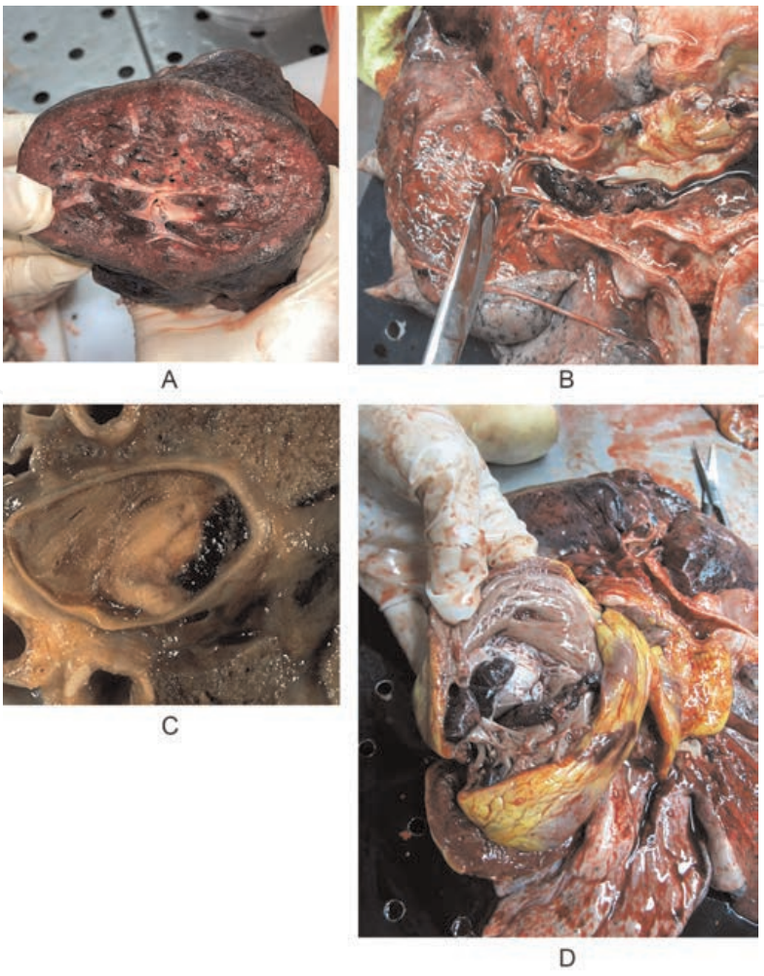

Figure 18.
A: Large pulmonary thromboembolus. B: "Saddle Embolus". C: Thrombus layered. D: PE with right ventricular thrombus.

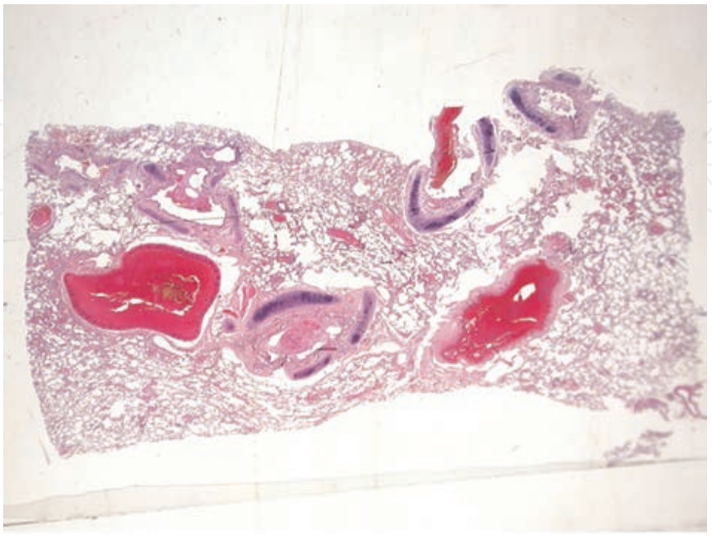

Figure 19.
Thromboembolism is packed into a pulmonary artery.Thromboembolism packs into a pulmonary artery, and thromboembolism forms the organization and dissolution. The interdigitating area of pale pink and red forms the "lines of Zahn" characteristic of a thrombus. These lines represent layers of red cells, platelets, and fibrin laid down in the vessel as the thrombus forms.

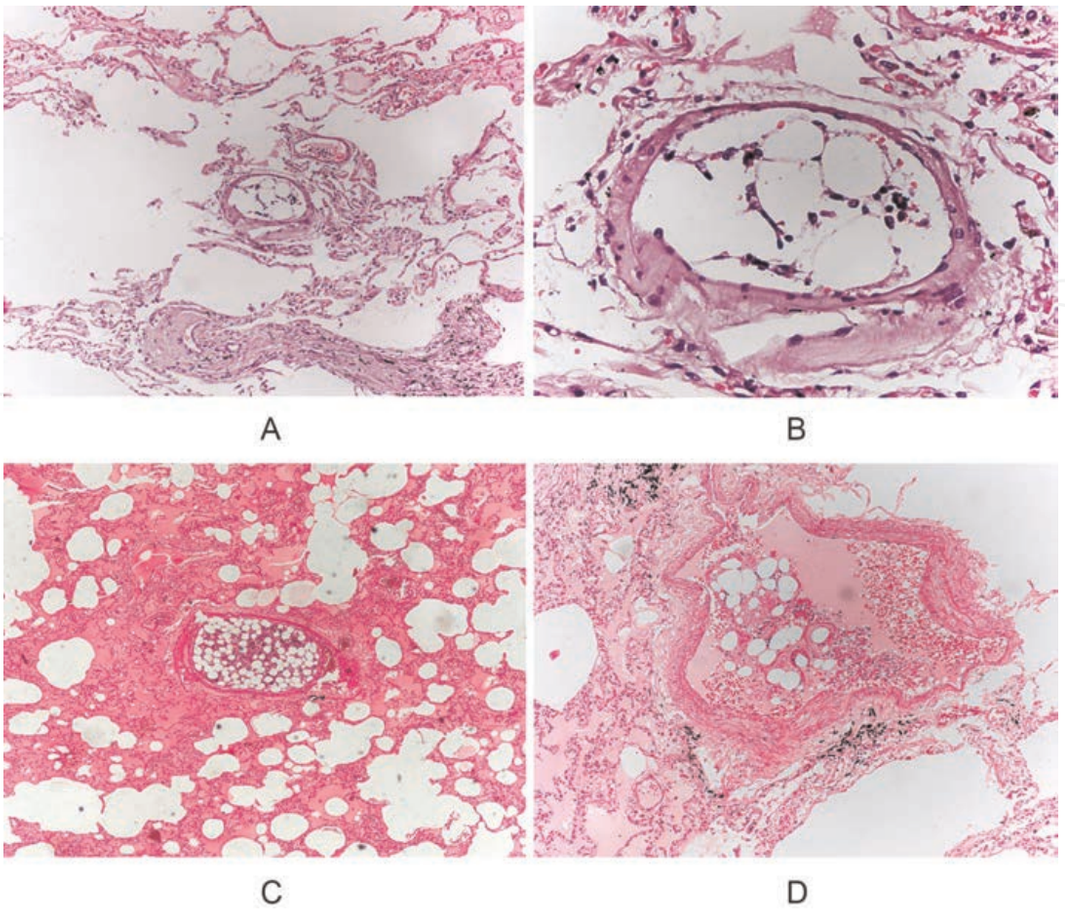

Figure 20.
Fat emboli: The round holes in the vascular spaces of the lung are fat emboli. Fat emboli often occur following trauma with a fracture of long bones. It releases fat globules into the circulation trapped in pulmonary capillaries.

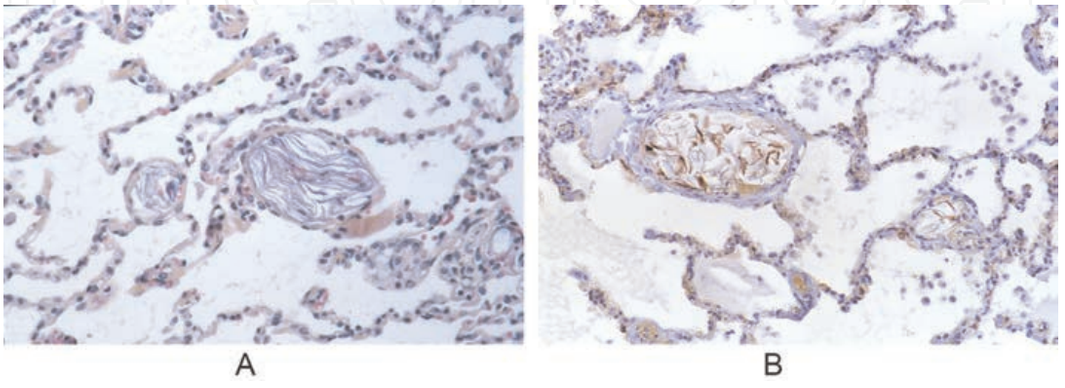

Figure 21.
A: Amniotic fluid embolization (H&E stain). B: Amniotic fluid embolization (Immunohistochemistry CK +) Amniotic fluid embolization: It is an obstetric complication. The pulmonary artery branch is an amniotic fluid embolus with layers of fetal squames, and the outcome is a massive pulmonary embolism.

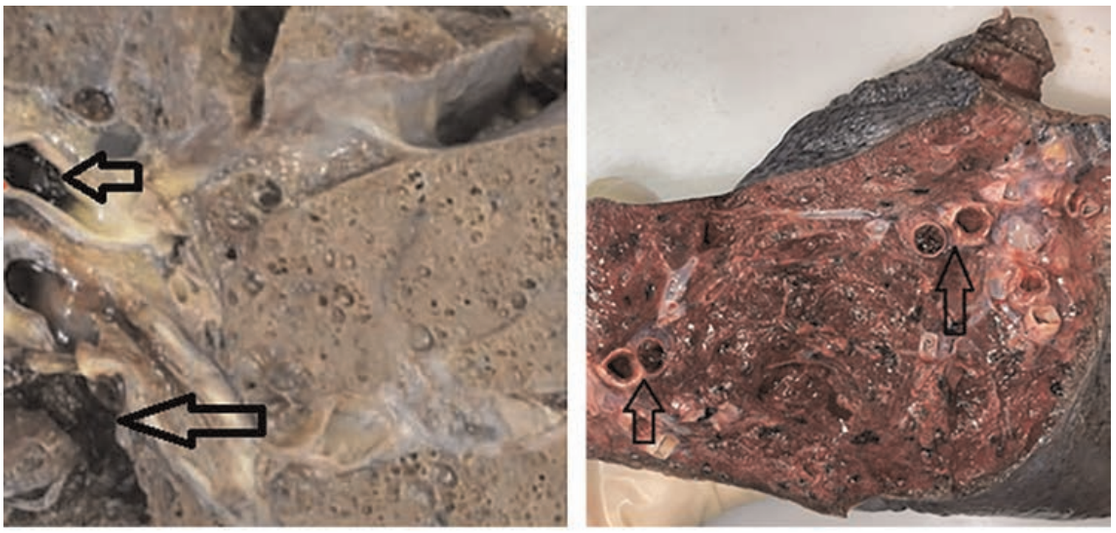

Figure 22.
Pulmonary Arterial Thrombosis due to SARS-CoV-2. Macroscopically: The massive bilateral congestion is grayish-red. The most structural feature is the presence of thrombotic in branches of the pulmonary arteries, varied from focal to extensive in all sizes of the vessels. The bronchial system contains viscous mucus and pleural effusion.

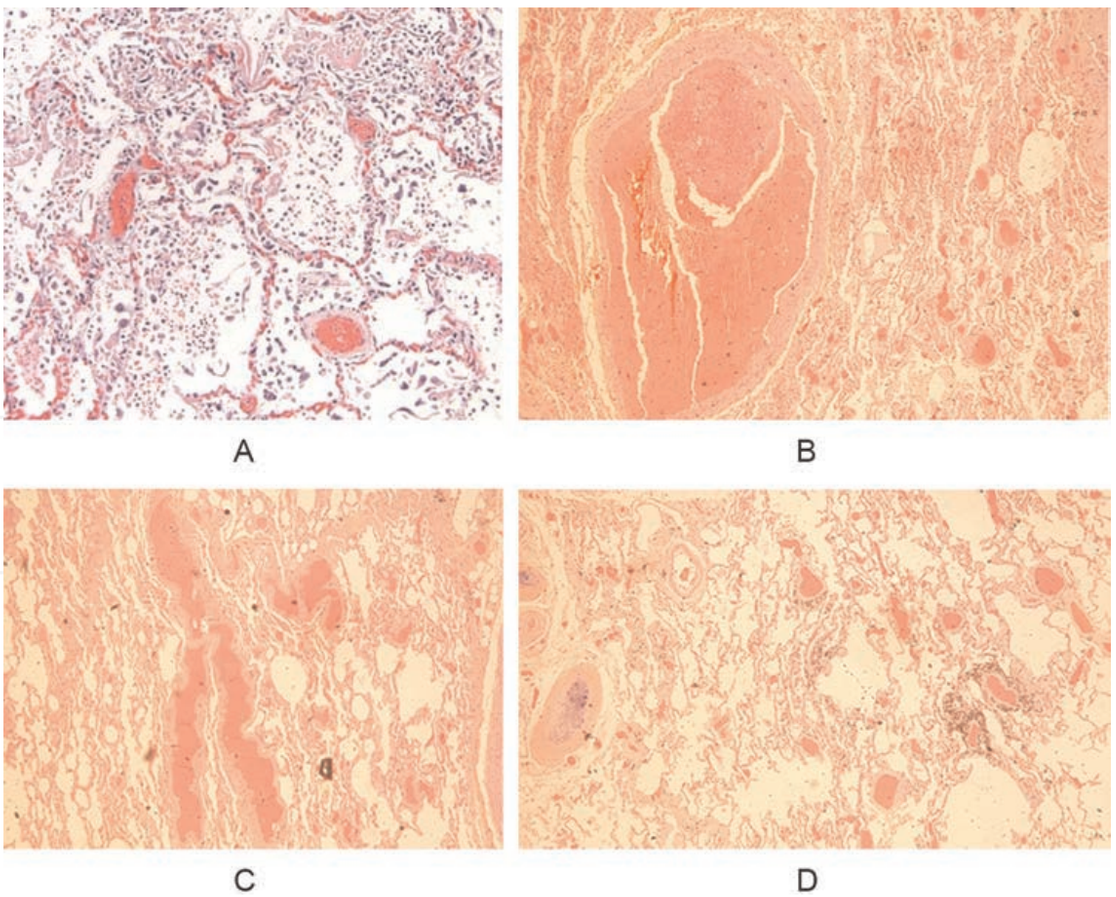

Figure 23.
Pulmonary Arterial Thrombosis due to SARS-CoV-2. Microscopic: Diffuse alveolar damage is a consistent feature of COVID-19, to exudative, proliferative, and fibrotic phases with the alveolar multinucleated giant cells and interstitial and alveolar inflammation. Blood vessels may show fibrinoid necrosis, wall thickening, luminal stenosis, or occlusion. The frequent presence of micro pulmonary thrombosis further supports hypercoagulative status.

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References

[1] Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). European Heart Journal. 2020;**41**(3): 407-477

[2] Pijls NHJ, Sels JWEM. Functional measurement of coronary stenosis. Journal of the American College of Cardiology. 2012;**59**(12): 1045-1057

[3] Canty JM, Suzuki G. Myocardial perfusion and contraction in acute ischemia and chronic ischemic heart disease. Journal of Molecular and Cellular Cardiology. 2012;**52**(4):822-831

[4] Camici PG, d'Amati G, Rimoldi O. Coronary microvascular dysfunction: Mechanisms and functional assessment. Nature Reviews. Cardiology. 2015;**12**(1): 48-62

[5] Reeh J, Therming CB, Heitmann M, Højberg S, Sørum C, Bech J, et al. Prediction of obstructive coronary artery disease and prognosis in patients with suspected stable angina. European Heart Journal. 2019;**40**(18):1426-1435

[6] Madsen DM, Diederichsen ACP, Hosbond SE, Gerke O, Mickley H. Diagnostic and prognostic value of a careful symptom evaluation and high sensitive troponin in patients with suspected stable angina pectoris without prior cardiovascular disease. Atherosclerosis. 2017;**258**:131-137

[7] Virmani R et al. Lessons from sudden coronary death a comprehensive morphological classification scheme for atherosclerotic lesions. Arteriosclerosis, Thrombosis, and Vascular Biology. 2000;**20**:1262-1275

[8] Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). European Heart Journal. 2021;**42**(14):1289-1367

[9] Heusch G, Gersh BJ. The pathophysiology of acute myocardial infarction and strategies of protection beyond reperfusion: A continual challenge. European Heart Journal. 2017; **38**(11):774-784

[10] Diercks DB, Peacock WF, Hiestand BC, Chen AY, Pollack CV, Kirk JD, et al. Frequency and consequences of recording an electrocardiogram >10 minutes after arrival in an emergency room in non–ST-segment elevation acute coronary syndromes (from the CRUSADE initiative). The American Journal of Cardiology. 2006;**97**(4):437-442

[11] Mandelzweig L, Battler A, Boyko V, Bueno H, Danchin N, Filippatos G, et al. The second Euro Heart Survey on acute coronary syndromes: Characteristics, treatment, and outcome of patients with ACS in Europe and the Mediterranean Basin in 2004. European Heart Journal. 2006;**27**(19):2285-2293

[12] Reichlin T, Twerenbold R, Maushart C, Reiter M, Moehring B, Schaub N, et al. Risk stratification in patients with unstable angina using absolute serial

changes of 3 high-sensitive troponin assays. American Heart Journal. 2013; **165**(3):371-378.e3

[13] Kaier TE, Twerenbold R, Puelacher C, Marjot J, Imambaccus N, Boeddinghaus J, et al. Direct comparison of cardiac myosin-binding protein C with cardiac troponins for the early diagnosis of acute myocardial infarction. Circulation. 2017;**136**(16):1495-1508

[14] Lancellotti P, Price S, Edvardsen T, Cosyns B, Neskovic AN, Dulgheru R, et al. The use of echocardiography in acute cardiovascular care: Recommendations of the European Association of Cardiovascular Imaging and the Acute Cardiovascular Care Association. European Heart Journal of Cardiovascular Imaging. 2015;**16**(2):119-146

[15] Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics—2016 update. Circulation. 2016;**133**(4):e38-e360

[16] Seiler C, Stoller M, Pitt B, Meier P. The human coronary collateral circulation: Development and clinical importance. European Heart Journal. 2013;**34**(34):2674-2682

[17] Fishbein MC. The vulnerable and unstable atherosclerotic plaque. Cardiovascular Pathology. 2010;**19**(1): 6-11

[18] Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). European Heart Journal. 2018;**39**(2):119-177

[19] Bozkurt B. Current diagnostic and treatment strategies for specific dilated cardiomyopathies: A scientific statement from the American Heart Association. Circulation. 2016;**134**:e579-e646

[20] F. V. DEC GW. Idiopathic dilated cardiomyopathy. The New England Journal of Medicine. 1994;**331**:1564-1575

[21] Schultheiss H-P. Dilated cardiomyopathy. Nature Reviews Disease Primers: Article number: 5. 2019;**32**

[22] Elliott P. Diagnosis and management of dilated cardiomyopathy. Cardiomyopathy. 2000;**84**:106-106

[23] Ommen SR, Mital S, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy. Circulation. 2020;**142**:e558-e631

[24] Davies MW. Hypertrophic cardiomyopathy-pathology and pathogenesis. Histopathology. 1995;**26**: 493-500

[25] Snir W. Exercise in hypertrophic cardiomyopathy: Restrict or rethink. American Journal of Physiology. 2021; **2021**

[26] Finocchiaro G. The electrocardiogram in the diagnosis and management of patients with hypertrophic cardiomyopathy. Heart Rhythm. 2020;**17**(1):142-151

[27] Muchtar E. Restrictive cardiomyopathy genetics, pathogenesis, clinical manifestations, diagnosis, and therapy. Circulation Research. 2017;**121**: 819-837

[28] B. S. (99m)Tc-pyrophosphate scintigraphy for differentiating light-chain cardiac amyloidosis from the

transthyretin-related familial and senile cardiac amyloidoses. Circulation. Cardiovascular Imaging. 2013;**6**:195-201

[29] Tapson VF. Acute pulmonary embolism. New England Journal of Medicine. 2008;**358**:1037-1052

[30] Tapson VF. Pulmonary Embolism. Fuster and Hurst's The Heart. 2022. p. 15e. ISBN 978-1-264-25756-0

[31] Ceriani E et al. Clinical prediction rules for pulmonary embolism: A systematic review and meta-analysis. Journal of Thrombosis and Haemostasis. 2010;**8**(5):957-970

[32] Manier G. Determinants of hypoxemia during the acute phase of pulmonary embolism in humans. The American Review of Respiratory Disease. 1985;**132**(02):332-338

[33] Konstantinides SV et al. ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). European Respiratory Journal. 2019;**54**:1901647

[34] Olsson OK et al. Chronic thromboembolic pulmonary hypertension. Deutsches Ärzteblatt International. 2014;**111**:856-862

[35] Riedel M. Acute pulmonary embolism: Pathophysiology, clinical presentation, and diagnosis. Heart. 2001; **85**:229-240

[36] Belle V et al. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. JAMA. 2006;**295** (2):172-179