The Cardiovascular System and the Coronary Circulation

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Abstract

The cardiovascular system represents the pathway for the delivery and distribution of essential substances to the tissues, as well as for the removal of metabolic waste. Furthermore, it plays an important role in homeostatic mechanisms, such as regulation of body temperature, humoral communication throughout the body and adjustments of oxygen and nutrient supply under different physiologic states. Its main component is the heart, which is composed of two synchronous pumps. A crucial role is played by the coronary arteries, which supply the myocardium and the specialized electrical tissue of the heart with oxygenated blood. Coronary artery disease is the most common cause of morbidity and mortality in developed countries, and is diagnosed using medical imaging techniques and invasive functional assessment procedures. Finally, we also provide insights into aortic pathologies, which comprise a wide spectrum of arterial diseases, with a special focus on coarctation of the aorta.

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2.1 The Cardiovascular System

The invasive evaluation of cardiovascular hemodynamics represents the final frontier when elucidating cardiovascular physiopathology in patients in whom noninvasively obtained data remain inconclusive or require firm confirmation of the clinical aspects.

The circulatory system represents the pathway for delivery and distribution of essential substances to the tissues, removing metabolic waste. The system also plays an important role in homeostatic mechanisms, such as regulation of body temperature, humoral communication throughout the body and adjustments of oxygen and nutrient supply in different physiologic states (Wier and Pappano 2013).

The cardiovascular system provides these functions through a pump (the heart), connected to a series of tubules (large and small arteries), capillaries (an extensive system of thin vessels that confer the capacity for rapid exchanges between different compartments) and veins. The heart consists functionally of two synchronized pumps: the right and the left side of the heart. The right side of the heart consists of right atrium, a chamber receiving deoxygenated blood from the veins (through the superior and inferior vena cava) and the right ventricle, whose function is to pump the blood through the lungs for the rapid exchange of O_2 and CO_2 (also called *pulmonary circulation*) through respiration. The left side of the heart is structured contains the left atrium (receiving oxygenated blood from the lungs) and the left ventricle, whose role is to propel blood and nutrients to the entire body through the aorta—the largest artery in the body (the *systemic circulation*). There are four valves inside the heart (one for each chamber), which ensure unidirectional flow inside and outside of the heart. The pumping role is supported by a muscular tissue (myocardium) which provides electrical and mechanical activation, generating the contractile force necessary for blood distribution to the various organs.

The amount of blood flow propelled by the left ventricle in 1 min is known as the cardiac output (CO). It represents an indicator for the heart's ability to support the needs of the body in a minute. Cardiac output is determined by the product of stroke volume (amount ejected by the heart) and heart rate (beats per minute). In resting conditions, the cardiac output measures approximately 5 L/min, depending on body size, and this value varies largely (being able to increase fivefold during exercise) to meet the body demand (Smith and Fernhall 2011).

Vessels are responsible for delivering oxygen and nutrients throughout the body. Therefore, the circulation systems of most major organs are parallel, but one major exception is the liver, that receives a large amount of blood from the venous circulation of the intestinal tract, which drains into the portal system and to the liver. The parallel arrangement of major vascular beds prevents blood flow changes in one organ from significantly affecting blood flow in other organs (Klabunde 2012).

It is important to note that the large distribution of blood to an organ or a system is controlled by hemodynamic rules. The degree of vasoconstriction or vasodilation in the supplying arterioles of organs is influenced by a series of local factors and not by the output of the heart itself. Therefore, vessels are dynamic structures that permanently vary in diameter to modify the amount of supplied blood in order to meet the demand of oxygen and nutrients (Smith and Fernhall 2011).

Systemic vascular resistance, also called total peripheral resistance represents the resistance to blood flow derived from all the systemic vasculature, except for the pulmonary vasculature. Systemic vascular resistance is determined by changes in vascular diameters and by the blood viscosity. An increase in systemic vascular resistance through vasoconstriction, in response to sympathetic stimulation, depends on the degree of the sympathetic activation, the responsiveness of the vasculature and the number of vascular beds being involved (Klabunde 2012).

During the cardiac cycle the diastolic ventricular filling is augmented by the atrial systole to achieve a certain end-diastolic volume. This is followed by an isovolumic contraction, leading to aortic valve opening (along with pulmonary valve opening in the right heart), followed by stroke volume ejection. Meanwhile, the atrial pressure increases progressively during ventricular systole, as blood continues to fill in the atria and the atrio-ventricular valves are closed. After reaching the point of end-systolic volume of both ventricles, there is a period of isovolumic relaxation, accompanied by the opening of the atrio-ventricular valves (mitral and tricuspid valve) and the passive filling of the heart chambers. In a normal resting state, the diastole occupies approximately two-thirds of the cardiac cycle, whereas both systole and diastole shorten with increased heart rate (Martin and Stephens 2013).

Arterial pressure varies during the cardiac cycle, from a minimum value, called the diastolic pressure, to a maximal one, known as systolic pressure. The difference between the two values is the pulse pressure. It is an important characteristics quantifying the distensibility of large arteries.

To ensure its contractile function, the myocardium requires a proper vascular network. The amount of oxygen used by the working myocardium is influenced by coronary flow and oxygen extraction rate. It is essential that the oxygen supply is continuous in order to ensure the metabolic substrate necessary to convert it to chemical energy (adenosine-triphosphate molecules). Coronary vasculature consists of the two main coronary arteries—right and left coronary arteries; the right coronary artery serves the right atrium and right ventricle; the left coronary artery divides shortly after its origin in the left anterior descending artery and the circumflex artery—ensuring blood supply to the rest of the myocardium. After passing the coronary bed, blood flows towards the coronary sinus through the coronary veins. The myocardial contraction delivers the necessary pressure (equal to the aortic pressure) needed for proper myocardial perfusion.

Coronary flow is influenced by the coronary vascular resistance. Sympathetic activity increases coronary flow, thus increasing rate and force of myocardium contraction. With the increased rate, diastolic filling of coronary arteries is shortened, thus limiting myocardial flow. Consequently, vasoconstriction increases oxygen extraction and thus myocardial metabolism is accelerated.

To function as a pump, the heart has intrinsic electrical activity generated via its excito-conductor tissue, which functions in a sequence that determines the uniform and rhythmical activation of myocardial fibers. This specialized conduction tissue is made of specific cells which have the capacity to generate electrical impulses which are further transmitted to the muscular cells. Under normal conditions, the electrical impulse originates in the sinoatrial node, connected to the atrial myocardium, and is

rapidly distributed through specialized internodal pathways in the atria to the atrioventricular node, in order to further progressively stimulate the ventricles, cell by cell, through the bundle of Hiss and the Purkinje network. This electrical stimulation leads to the contraction of all muscle fibers, arranged so that during systole they will ensure longitudinal, circumferential and radial motion to efficiently pump the blood into the aorta (Smith and Fernhall 2011).

2.2 The Anatomy of the Coronary Arteries

The heart, an ovoid organ, situated between the lungs in an oblique position, is divided into four chambers: two atria (left atrium, the most superior and posterior, and right atrium right antero-inferior) and two ventricles (left ventricle positioned posteriorly, lined by the right ventricle which is the most anterior of the chambers). Each chamber has a different muscular wall and is separated by two valves: mitral valve (separating the left atrium by the left ventricle) and tricuspid valve (which separates right atrium by the right ventricle).

Two important arteries derive from the two ventricles: the pulmonary trunk, from the right ventricle, which transports deoxygenated blood to the lungs, and the aorta, transporting oxygenated blood to the whole body.

From the aorta, at the level of the aortic cusps, arise the coronary arteries, which supply the myocardium and the specialized electrical tissue of the heart with oxygenated blood. In a normal coronary anatomy, the coronary arteries arise perpendicularly from the aorta below the sino-tubular ridge, at the point between the sinuses of Valsalva and the tubular aorta. At this level, usually two coronary ostia are formed, one of the right coronary artery (RCA), originating from the right aortic sinus, and one of the left main coronary artery (LM), which originates from the left aortic sinus. The latter is subdivided in the left anterior descending artery (LAD) and left circumflex artery (LCX) (Fig. 2.1).

Due to the high variability of the coronary anatomy and distribution (Oudkerk and Reiser 2008) that varies in presence, size, shape and length, a general anatomy will be described first (Dewey 2009). Both the RCA and the LCA (along with its branches) decrease in diameter along their lengths (Anderson et al. 2013).

Coronary heart disease (CHD) is the leading cause of death in the world, according to a 2011 report of the World Health Organization (WHO 2011). Even though in some developed countries (Arciero et al. 2004), the CHD mortality decreased, it still remains responsible as the main cause of death for about a third of all deaths in adults (Ford et al. 2007; Lyoyd-Jones et al. 2010). In the past decades great efforts towards population awareness have been made, concentrating on finding, diagnosing and lowering all risk factors for CHD. Primary prevention, defined as lowering risk factors such as smoking, hypertension, high cholesterol, diabetes and a sedentary lifestyle, plays a leading role in lowering the incidence of CHD. Great research, with perhaps the most significant impact in lowering the morbi-mortality in the world after the invention of antibiotics, has been done towards the acute phase treatment and secondary prevention. Besides an extensive array of medication, great progress has been made in the interventional, device-oriented and surgical treatment.

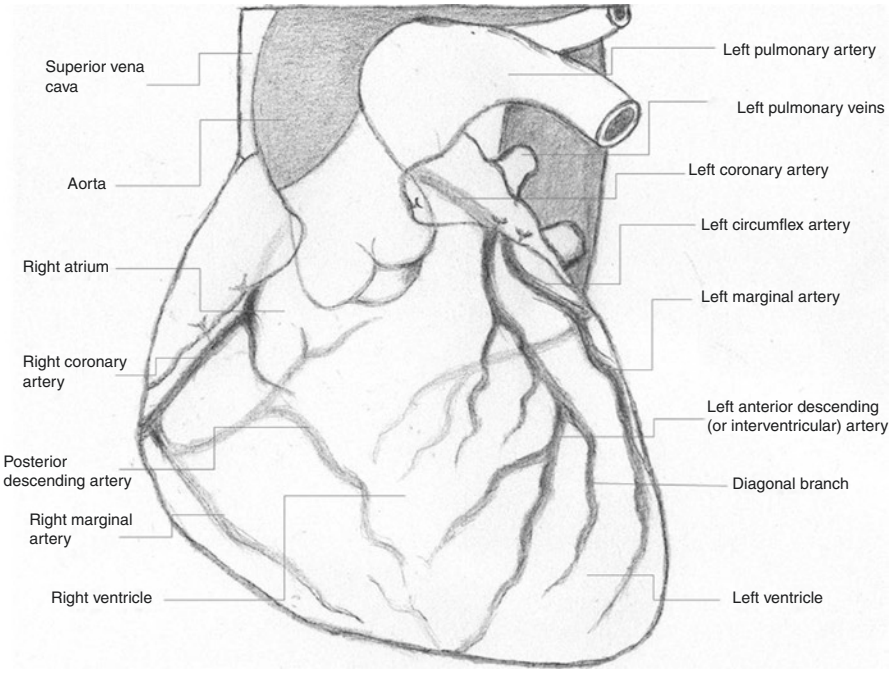

Fig. 2.1 The coronary anatomy

2.2.1 Right Coronary Anatomy

The RCA originates from the right sinus of Valsalva, below the plane of the left coronary artery ostium. It travels between the right atrial appendage and right ventricular outflow tract (RVOT) and continues straight along the right atrioventricular groove. Along its course, the proximal branches of the RCA are the conus artery, the right ventricular branch and the acute marginal branch (AM). The conus branch, often the first branch, supplies the infundibulum. In half of the population, the conus artery arises from the right coronary ostium or from the first millimeters of the RCA. The conus artery describes an anterior and upward route over the RVOT towards the LAD. In patients with LAD occlusion, it may serve as a source of collateral blood supply.

In the other half of the population, the conus artery arises from its own ostium in the right aortic sinus, directly from the aorta, just above the right coronary ostium. Furthermore, in 60% of the cases, RCA provides the sinoatrial node branch.

The RCA supplies branches to the right atrium. Furthermore, the acute marginal branches that arise from the mid-segment of the RCA follow the right ventricle and supply the anterior free wall. They branch off the RCA, detach in an acute angle, vary in size and number and are labeled from proximal to distal: AM1, AM2, AM3 and so forth.

In cases of LAD occlusion, the AM may serve as sources of collateral circulation. The distal portion of the RCA starts just below the origin of the AM branch and continues straight along the diaphragmatic surface of the heart, generating the

posterior descending artery (PDA) in most individuals (85%). The PDA supplies the posterior third of the interventricular septum with septal perforators. After the origin of the PDA, in case of right dominancy (50–60% of cases), the RCA goes beyond crux cordis in the left atrioventricular sulcus and terminates into the postero-lateral artery. The last branch supplies the posterior part of the left ventricle.

When RCA supplies the atrioventricular (AV) nodal branch, it branches off at the crux cordis going upward towards the AV node.

The posteromedial papillary muscle is often supplied only by the PDA, being vulnerable to ischemic dysfunction. A myocardial infarction involving the PDA is more likely to cause mitral regurgitation.

2.2.2 Left Coronary Anatomy

2.2.2.1 Left Main Coronary Artery

The LM originates just above the left sinus of Valsalva and continues behind the pulmonary trunk. Its diameter varies among individuals, between 3 and 6 mm (Oudkerk and Reiser 2008) in diameter and 0–15 mm in length (Dewey 2009).

The LM bifurcates into two large branches: the left anterior descending artery and the left circumflex artery. In one third of the population, the LM ends as a trifurcation generating an intermediate branch (ramus intermedius) that arises between the LAD and the LCX, suppling the myocardium between diagonal and marginal territories (Oudkerk and Reiser 2008). This ramus intermedius can be considered as an obtuse marginal branch or as a diagonal branch, depending on its course along the left ventricle (Dewey 2009). Also, the LM may be absent, in which case the LAD and the LCX then have separate origins (Oudkerk and Reiser 2008).

2.2.2.2 Left Anterior Descending Artery

The LAD courses behind the pulmonary trunk and goes forward between the left atrial appendage and the pulmonary trunk to the anterior interventricular groove (Oudkerk and Reiser 2008). It represents the direct continuation of the left main artery. The LAD and the LM form a curve that resembles a reversed "S" shape (Mukherjee et al. 2010). In its trajectory, it gives rise to diagonal and septal perforating branches.

The first branch that emerges from the LAD is the left conal artery, which supplies the infundibulum. The septal perforating branches arise from the LAD in a 90° angle (Oudkerk and Reiser 2008). In most individuals, the blood supply to the anterior interventricular septum comes from the LAD (Mukherjee et al. 2010). These branches are perforating the interventricular septum displaying a large variation in number, distribution and size; they connect together and with the branches derived from the RCA—posterior descending branch, creating a network of potential collateral channels. All septal branches of the LAD supply 2/3 of the anterior interventricular septum.

Diagonal branches that supply the anterolateral free wall of the left ventricle and the anterolateral papillary muscle also vary widely in number and size. In more than 90% of cases, one to three diagonal branches originate from the LAD and less than

1% have no diagonal branches at all. When diagonal branches are not visible, acquired atherosclerotic occlusion of the diagonal branches is highly probable, especially among patients with echocardiographic movement abnormalities of the anterolateral left ventricle.

Furthermore, LAD goes straight to the apex and terminates along the diaphragmatic aspect of the left ventricle in two thirds of cases. In one third of cases, the distal segment of the LAD ends before reaching the cardiac apex, without reaching the diaphragmatic surface, in which case a dominant RCA is cited, having a posterior descending branch larger and longer than usual which then supplies the apex (Oudkerk and Reiser 2008).

2.2.2.3 The Circumflex Artery

LCX arises from the LM posteriorly, passing by the left atrial appendage and coursing posteriorly to the left AV groove, on the obtuse margin of the heart (Oudkerk and Reiser 2008). It originates from the LM at an approximately right angle, but may have a greater or lesser degree of angulation from the left main at its origin in some patients. As it passes by the atrioventricular groove, it circumscribes the mitral valve annulus, giving rise to the obtuse marginal branches (Mukherjee et al. 2010).

Left atrial branches may arise from the LCX and supply in 40% of the patients the sinoatrial node (Mukherjee et al. 2010). Usually, three obtuse marginal branches are described: the anterolateral branch, the obtuse marginal branch—being the largest of them all—and the posterolateral branch (Oudkerk and Reiser 2008). They supply the posterolateral wall (lateral free wall) of the left ventricle (Dewey 2009). The LCX also generates one or two left atrial circumflex branches that supply the lateral and posterior walls of the left atrium.

In few cases (10%), in left dominancy, the LCX gives rise to the posterior descending artery and the AV nodal arterial branch.

2.2.3 Determination of Dominance

The artery that crosses the crux cordis and gives rise to the PDA, the AV nodal branch and the posterolateral artery is considered to be the dominant coronary artery. A co-dominancy or balanced circulation can be described, when the PDA arises from the RCA and the postero-lateral artery arises from the LCX. Seventy percent of patients are right-dominant, 20% are co-dominant and 10% are left-dominant (Oudkerk and Reiser 2008; Mukherjee et al. 2010). In case of a left-dominant circulation, the RCA is small and does not supply blood to the left ventricular myocardium (Dewey 2009).

2.2.4 Frequent Coronary Artery Variants

Apart from variations of normal anatomy, as those presented above, other variations may be encountered, such as myocardial bridging or variability in the course and origin of the coronary arteries.

Myocardial bridging, which describes the situation when an arterial segment of the coronary artery passes through the myocardium, may be seen in almost 5% of angiography interventions. The most frequent cases of bridging are confined to the LAD or diagonal branches. It is a condition in which, during systole, the muscular bridge running over the artery contracts, leading to the temporary compression of the coronary artery involved; during diastole, the caliber goes back to normal and, in most cases, this anatomic variant does not cause ischemia. In clinical practice, there are cases associated with ischemia (Dewey 2009) secondary to myocardial bridging.

Intracoronary artery continuity or "coronary arcade" describes a rare condition of the coronary circulation in which communications develop between the distal segment of the LCX and the RCA in the posterior atrioventricular sulcus, and between the LAD and the PDA in the interventricular groove. These connections occur in the absence of obstructive coronary disease and they are distinct from coronary collaterals (Mukherjee et al. 2010).

Two most frequent anomalies are an RCA abnormally originating from the LM or the left sinus of Valsalva, or an LCX with an anomalous origin from the RCA or from the right sinus of Valsalva. In the first variant, the course of the RCA is anterior, between the aorta and the pulmonary trunk. This anatomic variant is called "malignant course", because these patients have a high risk for exercise-induced ischemia and sudden death, as at the time of the effort, the arterial segments contain more blood which causes compression and induces ischemia (Dewey 2009). Another anomaly is that of a LM arising from the right sinus of Valsalva which then courses between the aorta and the pulmonary trunk, this being the most dangerous variety of an anatomic anomaly (Mukherjee et al. 2010; Anderson et al. 2013). On the other hand, an LCX originating from the RCA or right sinus of Valsalva, coursing posteriorly to the aorta and entering in its proper location, in the left atrioventricular groove, is actually a benign condition which never causes ischemia (Dewey 2009).

2.2.5 Angiography of the Coronary Vessels

The most frequent indication for a coronary evaluation is diagnosing coronary atherosclerosis, based on which the clinician can decide upon the most appropriate treatment strategy (bypass surgery, angioplasty or medical therapy). The indications for angiography are well established and should be based on clinical guidelines. Coronary angiography is to be performed in symptomatic patients with noninvasive evidence of myocardial ischemia.

In patients with unstable angina, coronary angiography will be performed after initiation of intensive drug therapy with the aim of stabilizing the atherosclerotic plaque. The intervention will usually be performed within the first 6 weeks from the acute episode.

Acute myocardial infarction patients currently undergo primary angioplasty. It is currently unclear whether asymptomatic patients benefit from coronary angiography post-myocardial infarction.

Other indications for a coronary angiography are atypical chest pain syndromes in patients with cardiovascular risk factors, ventricular arrhythmias, heart failure of unclear etiology (Moscucci 2014).

2.3 Coronary Artery Disease

2.3.1 Pathophysiology of Coronary Artery Disease

Coronary artery disease (CAD) is the most common cause of morbidity and mortality in developed countries. It represents the final common pathway after combining genetic predisposition with lifestyle factors. This concept includes diseases that result from atherosclerotic changes of the coronary vessels, generating a whole spectrum of coronary plaques, from stable plaques (lipid-poor, thick fibrous cap) to unstable ones (lipid-rich, thin fibrous cap) (Ashley and Niuebauer 2004).

The atherosclerotic process develops early in life, but it presents large variations among individuals, with an unpredictable speed of progression (Theroux 2011). The severity of events correlates with the type of coronary plaques: the more unstable, the more likely to rupture, generate pro-thrombotic events, release vasoconstrictive factors and lead to partial or complete occlusion of the affected coronary artery (Ashley and Niuebauer 2004). Temporary occlusion leads to (possibly reversible) ischemia (insufficient blood supply to the affected tissue), but permanent occlusion is associated with transmural myocardial infarction (irreversible ischemia followed by death of affected tissue).

The atherosclerotic process often develops in multiple vascular beds (coronary arteries but also cerebral, carotid and peripheral arteries). Patients affected by atherosclerosis therefore manifest symptoms characteristic of systemic atherosclerotic disease. The REACH Registry included 68,000 patients from 44 countries across six major regions; the study enrolled patients aged over 45 with at least three atherosclerotic risk factors or documented coronary artery disease, cerebrovascular disease or peripheral artery disease. This research had found that as much as 30% of coronary artery disease patients had systemic atherosclerotic disease (disease in more than one arterial bed) (Ohman et al. 2006).

The most important risk factors for developing and enhancing atherosclerosis are dyslipidemia, smoking, arterial hypertension, diabetes mellitus, obesity, immune mechanisms or hemodynamic factors, all of them generating injury and consequently dysfunctionality of the endothelium—the interior lining of the arteries.

2.3.1.1 Atherosclerotic Risk Factors

Dyslipidemia is a condition characterized by an abnormally high level of circulating lipids and represents a major risk factor for developing atherosclerosis. Many studies have found that in countries with a high consumption of saturated fat and a high prevalence of hypercholesterolemia, there is a strong association with coronary heart disease, as opposed to populations whose diet is based on low saturated fat intake and have low serum cholesterol levels (Mediterranean areas) (Estruch et al. 2013).

Data from the Framingham Study and other cohorts have shown that the risk of coronary heart disease increases with higher total serum cholesterol levels. Particularly, elevated levels of LDL-cholesterol (low density lipoprotein-cholesterol, commonly known "bad cholesterol") are associated with an increased incidence of atherosclerosis and subsequent complications. In opposition, HDL-cholesterol (high-density lipoprotein) particles seem to protect against this process, due to their ability to transport cholesterol away from the peripheral tissues back to the liver, having antioxidant and anti-inflammatory properties (Lilly 2011).

High levels of cholesterol and its fractions (LDL-C and similar) are usually the consequence of a high fat intake diet. However, they may be secondary to an abnormal lipid metabolism, as in the case of genetic anomalies of the genes encoding LDL-receptors. These conditions are known as familial hypercholesterolemias, characterized by high plasma LDL levels from very early ages, leading to premature atherosclerosis during the first decades of life and eventually major cardiac events (myocardial infarction, stroke) in subjects as young as 30 years old.

Strategies that improve plasma lipid levels can limit the effects of atherosclerosis. Lifestyle changes have shown positive effects on the reduction of LDL levels, slowing the progression of atherosclerotic plaque (Barry et al. 2014). The current European guidelines on Cardiovascular Prevention recommend an optimal LDL cholesterol level as low as <100 mg/dL for those with high cardiovascular risk, or an even lower goal of <70 mg/dL for those at higher risk of future cardiovascular events (established cardiovascular disease, diabetes mellitus type 2 with target organ damage, moderate to severe chronic kidney disease) or other associating risk factors (Reiner et al. 2011). Diet and physical exercise comprise two important tools in the overall risk reduction.

When lifestyle modifications fail to achieve target values, pharmacologic agents should be used to improve abnormal lipid levels. The main categories of lipid-altering agents are: HMG-CoA (3-hydroxy-3-methyl-glutaryl-coenzyme A) reductase, also known as statins, niacin, fibric acid derivatives, cholesterol intestinal absorbtion inhibitors, bile acid-binding agents and, the more recently approved PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors. The currently most effective and widely used LDL lowering therapy is statin therapy (Lilly 2011).

Smoking increases the risk of atherosclerotic disease and promotes ischemic events. The heaviest smokers carry on the highest risk for cardiovascular events. The act of smoking enhances oxidative modification of LDL-cholesterol particles, decreases the circulating level of HDL-cholesterol, promoting endothelial dysfunction and tissue hypoxia and increases platelets adhesiveness (Lilly 2011). In a recent multiethnic study, current smoking and cumulative exposure remain important modifiable determinants of cardiovascular disease (McEvoy et al. 2015). Smoking cessation can reverse or slow some of the adverse outcomes.

Arterial hypertension is a condition characterized by high blood pressure values (>140/90 mmHg) which acts as a risk factor both for the development and the progression and acceleration of atherosclerosis, coronary heart disease and major cardiovascular events. The risk increases progressively with higher pressure values (especially systolic). Hypertension may produce acceleration of the atherosclerotic

process by increasing the permeability of the vessel wall to lipoproteins, augmenting hemodynamic stress and enhancing the development of foam cells (fat-laden immune cells indicative of atherosclerotic deposition building-up in plaques) (Hollander 1976). As in the case of dyslipidemias, the treatment of arterial hypertension should start with lifestyle changes (diet and exercise), and progress to pharmacological therapy when blood pressure values remain uncontrolled.

Diabetes mellitus influences atherosclerosis in such great extent that the condition is considered to be equivalent to the development of the atherosclerotic process. This is due partly to the fact that diabetes mellitus leads to the non-enzymatic glycation of lipoproteins (enhancing the uptake of LDL cholesterol by foam cells) and to a pro-thrombotic state which becomes permanent (Lilly 2011). Intense control of serum glucose levels in diabetic patients reduces the risk of vascular complications, such as myocardial infarction and stroke, and controlling associated dyslipidemia and/or hypertension lowers the overall cardiovascular risk in these patients.

Metabolic syndrome includes multiple risk factors, as: hypertension, hypertriglyceridemia, reduced HDL-cholesterol, insulin resistance syndrome and visceral obesity. These multiple conditions associate higher risk for developing atherosclerotic disease.

Sedentarism or low level of physical activity may mitigate atherogenesis in multiple ways. Exercise improves insulin sensitivity and endothelial production of nitric oxide, an endogenous vasodilator, lipid profiles and blood pressure values. Studies suggest that moderate-level activities, such as 30-minutes-a-day walking can lower cardiovascular mortality (Lilly 2011).

2.3.1.2 Pathophysiology of Coronary Artery Disease

Regulation of Coronary Blood Flow

The main physical factor influencing myocardial perfusion is the aortic pressure, which causes parallel changes in the coronary hemodynamics. In addition to this, changes in vessel caliber in response to the metabolic demands of the heart lead to changes in coronary blood flow.

Opposing this pressure is the coronary vascular resistance, a factor that influences the hemodynamics of coronary flow. In normal arteries, the resistance depends on external forces that compress the coronary artery and on factors that alter intrinsic vascular tone (Lilly 2011).

Coronary flow reserve represents the difference between maximal flow as caused by vasodilators and the flow in the physiological range.

Unlike other arterial beds where the highest blood flow occurs during systole, coronary perfusion takes place during diastole, when the small coronary arteries are no longer compressed, as they are during systole. In the case of the coronary arteries, the perfusion pressure is close to equal to the aortic diastolic pressure; conditions that decrease the aortic diastolic pressure, such as hypotension or aortic regurgitation, also decrease coronary artery perfusion pressure and therefore lower oxygen supply to the myocardium (Lilly 2011).

Sympathetic stimulation produces an increase in coronary blood flow through an increased metabolic demand and a predominance of β receptor activation. Alpha stimulation may play a role in the distribution of blood flow within the myocardium by restricting metabolically mediated flow increase and exerting an anti-steal effect (Ramanathan and Skinner 2005).

The supply of oxygen to the myocardium is determined by the oxygen content in the blood and the rate of coronary blood flow. Oxygen content is determined by the hemoglobin concentration and systemic oxygenation; the rate of coronary blood flow is proportional with the vessel's perfusion pressure and inversely correlated to coronary vascular resistance. Alterations of the balance between oxygen-supply and oxygen-demand generate areas of ischemia and eventually death of the involved tissue (infarction).

A decrease in the oxygen supply to oxygen-demand ratio (produced by a reduction in oxygen supply or an increase of oxygen demand) causing ischemia, leads to a metabolic regulation of blood flow with the release of vasodilator substances from the myocardium into the interstitial fluids, causing relaxation of the coronary vessels. The most important vasodilator agents are adenosine and nitric oxide (Pappano and Wier 2013).

Atherosclerotic plaque deposition decreases vessel lumen, thus reducing blood flow, which is the most important cause of ischemia at this site. If ischemia is present and prolonged, necrosis of affected cardiac cells develops. Myocardial ischemia produces alterations in the mechanical and electrical behavior of the heart. The mechanical impairment is not only due to lack of oxygen supply but also to the accumulation of harmful substances from the necrotic process, such as lactic acid, H+ or K+ (Pappano and Wier 2013).

Atherosclerotic Plaque Formation

The arterial wall is composed by three layers: the tunica intima (the inner layer), the tunica media (the middle layer) and the tunica adventitia (the outer layer). The inner layer consists of a thin layer of simple cells called the endothelium which forms an interface between circulating blood and its two more profound layers—the subendotelial proteoglycan-rich layer and the deeper musculo-elastic layer made of smooth muscle cells and elastic fibers (Theroux 2011).

Atherosclerosis is a chronic inflammatory proliferative disease of the intima of large and medium sized arteries. It is characterized by early retention and structural modification of atherogenic lipoproteins, recruitment of immune cells and accumulation of abundant fibrous tissue (Theroux 2011). An atherosclerotic plaque consists of a core of foam cells (immune cells which come to the site of plaque formation to address and solve what seems to them to be an inflammatory process but end-up integrating lipids and thus become lipid-engorged and die), covered by a fibrous cap (a region of the intimal layer that has become thickened and hardened as a result of collagen and elastin fibers deposition) (Ashley and Niuebauer 2004).

The first step in the atherosclerotic process is represented by the retention of apo-B containing lipoproteins, primarily LDL, to extracellular proteoglycans of the tunica intima. The accumulation of subendothelial lipoproteins is followed by

aggregation and oxidation in enzymatic reactions and by oxidative radicals (leading to oxidized LDL), generating the signaling-pathway to stimulate the recruitment, differentiation and replication of monocyte-derived macrophages (immune cells), acting as a pro-inflammatory trigger (Theroux 2011).

Inflammation plays a major role in the pathogenesis and clinical expression of atherosclerosis to the extent that the disease is now considered an inflammatory one (Buja and McAllister 2007). The recruited macrophages engulf LDL-particles through scavenger receptors, giving them the above mentioned name—foam cells. Cytokines produced by the macrophages create a pro-inflammatory environment that facilitates the recruitment of more and more inflammatory cells.

At this point, the process of foam cells production is reversible if the stimuli causing their formation disappear. If the accumulation of intracellular lipids continues, it is followed by accumulation of lipids in the musculo-elastic layer, beneath the foam cells, generating intermediate lesions, also reversible. Moreover, if the conversion of the isolated lipid areas into one or more confluent lipid-rich cores goes further, they are generating the necrotic core, a permanent lesion that disrupts the structure of the inner layer.

The lipid-rich core is separated from blood flow by a fibrous cap, a structure that plays an important role in the pathology and clinical consequences of the atherosclerotic process. This structure consists of fibrous tissue and calcifications, without any lipid particles (Theroux 2011). An excess of degradative enzymes leads to degradation and thinning of the fibrous capsule.

The two components of plaque, the inner lipid layer and the fibrous cap, are extremely important as they determine the risk for plaque complications such as rupture or erosion which lead to thrombus formation and complete artery occlusion. A stable plaque (poor lipid core, rich calcified fibrous cap) is less likely to rupture, while an unstable plaque (rich lipid core, thin fibrous cap) is highly likely to rupture or erode.

In the initial phase, atherosclerosis is a focal disease, generating plaques adjacent to branch points in areas of low-velocity flow and low shear stress areas, near high shear stress ones; this flow pattern promotes endothelial dysfunction (Gimbrone 2010). Areas of severe atherosclerosis of the coronary system include the proximal left anterior descending coronary artery and the proximal and distal right coronary arteries.

Atherosclerotic disease leads to extensive remodeling of the arteries, causing dilatation of the vessels initially without influencing lumen diameter; luminal narrowing occurs, however, but only in more advanced stages of the disease (Willerson and Holmes 2015).

2.3.1.3 Pathophysiology of Stable Angina (Stress Induced Angina)

With time plaque grows continuously, reducing the arterial lumen progressively and leading to a point where ischemia sets in, causing what is clinically known as angina pectoris—typical chest pain with exertion. If a stenosis never produces flow-limitation, it will never produce symptoms (Theroux 2011). Flow obstruction is determined by a series of factors such as: plaque size, vasospasm (vasoconstriction)

and vessel wall remodeling. Expansive or positive remodeling refers to the initial preservation of vessel lumen and is more common than the opposite constrictive remodeling (negative remodeling), that reduces vessel lumen area. Coronary artery remodeling is unrelated to sex or smoking and it is plaque specific (Varnava and Davies 2001). Also, multiple plaques at different stages of progression and of variable morphology coexist within the same patient or even artery (Koskinas et al. 2010). In addition to arterial remodeling, local paradoxical exercise-induced vasospasm may influence the blood flow, causing temporary obstruction and symptoms specific to stable angina (Gage et al. 1986).

The cut-off point of vessel lumen reduction at which coronary blood flow at rest becomes significantly influenced is 80%. The types of stenosis which cause such lumen reductions are highly calcified fibroatheromas or fibrous plaques (Ehara et al. 2004). A small percent of culprit plaques in patients with stable angina present residual thrombi that suffer recanalization with time (Mann et al. 1998). The severity of the stenosis correlates with the number of plaque events (Burke et al. 2001) and majority of plaque ruptures are not lethal, being clinically silent (Davies et al. 1989).

2.3.1.4 Pathophysiology Behind the Acute Coronary Syndromes

Acute coronary syndromes (unstable angina and acute myocardial infarction with or without ST segment elevation) are produced by a luminal thrombus attached to an atherosclerotic plaque, with possible concomitant vasospasm. Rare causes of acute coronary syndromes are embolic, subsequent arterial dissection, vasculitis, cocaine abuse and posttraumatic lesions (Theroux 2011).

Unstable angina is the clinical condition in which a patient manifests symptoms of myocardial ischemia (severe chest pain, sweating, anxiety) without an increase in serum levels of myocardial damage enzymes. When the myocardial ischemia leads to an infarction involving part of the heart wall, such enzymes are released in the circulation and the death of heart cells lead to electrical changes that can be observed on the electrocardiogram (ECG). When the lesion is more severe and crosses the entire heart wall, all the above mentioned conditions are met and the specific ECG changes called “ST-elevation” gives the name of the condition—ST Elevation Myocardial Infarction or STEMI. The other type of myocardial infarction (affecting only part of the heart wall) is thus called a non-STEMI (non-STEMI), as in this case all other conditions are met except the ST-elevation on the ECG tracing.

The thrombus formed on a ruptured or eroded plaque is usually occlusive and sustained in STEMI, whereas in non-STEMI, the thrombus is frequently non-occlusive and dynamic.

Coronary thrombosis is associated with plaque rupture, in which a structural defect of the fibrous cap is exposing the thrombogenic lipid-rich core to the blood flow; when no rupture is identified, the pathological insight is based on plaque erosion (Schaar et al. 2004).

The time between plaque rupture and syndrome onset is not known, because the first event is totally asymptomatic and the thrombotic process is highly unpredictable;

some studies suggest that severe thrombosis occurs immediately after plaque rupture (Falk 1983), others describe a dynamic response to a thrombotic event characterized by subsequent thrombolysis and vasospasm, with the tendency of creating a layered thrombus over days (Falk et al. 2004).

2.3.1.5 Plaque Vulnerability

On rupture-prone plaques, the rupture tends to occur at the cap margin, its thinnest and weakest area (Falk et al. 1995). Rupture of a thin cap and subsequent thrombosis may occur spontaneously, but in some cases, a temporary increase in emotional or physical stress provides the final triggering of the event. Recognized triggers include physical and sexual activity, heavy meals, psychological status (anger, anxiety, stress), earthquakes, war and terror attacks, temperature changes (cold exposures), acute infections, cocaine use (Mittleman and Mostofsky 2011) or just simple activities (Servoss et al. 2002). A specific circadian rhythm in the frequency of onset of acute coronary syndromes was detected, with a peak of events in the first ours of the morning. This statement was not characteristic in patients receiving beta-adrenergic blocking agents before myocardial infarction onset, but was present in those not receiving such therapy (Muller et al. 1985).

Very thin fibrous caps are at risk of rupturing and are influenced by the composition and gradual loss of smooth muscle cells, ruptured caps containing lower levels of smooth muscle cells and less collagen than intact caps (Kolodgie et al. 2001).

The lipid-rich core is essential for defining plaque rupture and its complications. A larger lipid-rich core promotes a higher risk, the influence on size being somewhat intuitive, as a large lipid-rich core may erode the fibrous cap and promote thrombosis after plaque rupture (Theroux 2011).

It has been considered that plaque size does not play an important role. Emerging evidence suggests that microcalcifications play a critical role in determining atherosclerotic plaque vulnerability (Hutcheson et al. 2014).

Multiple studies suggest that plaques causing significant stenosis are at a higher risk for clinical events. Conversely, it has been demonstrated that most acute coronary syndromes are induced by plaques that were not causing significant stenosis on angiography evaluations performed months before, a finding which may be that these lesions are much more prevalent than stenotic ones (Stone et al. 2011).

Lesions responsible for acute coronary syndromes are less calcified than plaques responsible for stable angina (Burke et al. 1997). In ruptured plaques there is more neovascularization and inflammation of the adventitia than in intact plaques (Virmani et al. 2005).

Erosion-prone plaques promote coronary thrombosis without rupture, but the mechanisms of erosion are not well known, and it is currently considered to involve multiple pathological ways. They generally involve endothelial denudation over pathological intimal thickening and fibroatheromas with thick cap (Virmani et al. 2000). A potential trigger of endothelial damage is the presence of vasospasm (Virmani et al. 2006).

2.3.1.6 Clinical Significance of Atherosclerotic Disease

Significant narrowing of the coronary arteries produces angina pectoris, its symptomatology consisting of acute chest pain during exercise, cold temperatures or emotional stress, lasting for 2–10 min. It may be described as retrosternal chest pressure, burning, squizzing, heaviness, radiating occasionally to the neck, jaw, epigastrium, shoulder or left arm (Mann et al. 2015).

It is usually produced by fixed stenosis on one or more coronary arteries. The pattern of symptoms is correlated to the degree of stenosis. During exertion, the sympathetic system increases heart rate, blood pressure and contractility, all these mechanisms eventually increasing the demand of myocardial oxygen; when exceeding the supply of oxygen, myocardial ischemia results, causing chest discomfort called angina pectoris. The symptomatology persists until oxygen balance is restored (Barry et al. 2014).

Endothelial dysfunction prevents appropriate vasoconstriction thus aggravating the already insufficient oxygen supply and the capacity to release local metabolites which induce vasodilatation in normal vessels. Therefore, the altered coronary vascular tone, which varies in different patients, contributes to the pre-existing physical arterial narrowing.

Symptoms are extremely variable, and "angina equivalents" have been described in different patient populations (women, elderly people, diabetics) who experience angina, in the absence of chest pain, as jaw or shoulder pain, dyspnea, nausea or vomiting and diaphoresis (Mann et al. 2015).

Unstable angina presents under three main forms: (a) rest angina or angina with minimal exertion usually defined as occurring within the last month; (b) new-onset angina, usually defined as occurring within the last month; (c) crescendo angina, defined as previously diagnosed angina that has become more frequent, longer in duration or more severe in nature (Betriu et al. 1992).

Usually, the pain in unstable angina frequently waxes and wanes, lasting for a few minutes to as long as, but usually less than, 20 min (Theroux 2011).

Non ST-segment elevation and ST-segment elevation myocardial infarction is diagnosed based on typical ischemic chest pain, typical ECG changes, including development of Q waves and elevated serum markers of myocardial injury, usually creatine-kinase myocardial band. In the recent years, the availability in clinical practice of serum troponin levels, being much more sensitive and specific to myonecrosis than creatine-kinase myocardial levels, has been associated with higher rates of rapid diagnostic and assessment (Fuster et al. 2011).

STEMI refers to the most lethal form of acute coronary syndromes, and develops when a completely occlusive thrombus interrupts coronary blood flow in the territory of the occluded artery. Specific changes on the ECG, such as ST segment elevation and development of Q waves, highly suggest full or nearly full thickness necrosis of the myocardium wall (Fuster et al. 2011). The fast and accurate diagnosis dictates the necessity for immediate therapeutic measures, such as reperfusion therapy, mechanical revascularization or thrombolysis. Mortality was proven to

significantly decrease in those who received reperfusion therapy within 12 h of symptom onset (Califf 1998).

Patients with acute myocardial infarction (both STEMI and NSTEMI) present ischemic pain that develops abruptly, is steady and lasts for more than 30 min. Patients frequently describe the pain as a pressure, burning, grawing, tightness, heaviness or crushing, when severe.

Typically patients describe center or left chest pain, radiating to classical areas (left shoulder, left elbow, jaw). Less commonly, they present with epigastric pain causing confusion and indigestion, which may lead to misdiagnosis. On the contrary, patients with acute coronary syndromes may have other accompanying symptoms, most commonly dyspnea, diaphoresis, nausea, vomiting and palpitations. Gastrointestinal symptoms are usually associated with inferior wall infarction. Other atypical presentations include syncope, acute heart failure with pulmonary edema, generalized weakness and acute mental status changes (Theroux 2011).

Clinical manifestations of atherosclerosis become evident in the middle-aged and elderly individuals, but atherosclerosis is a lifelong disease. Fatty streaks are present in most individuals arteries even after puberty, intermediate lesions occur in most people from 20 to 30 years of age, and fibroatheromas are frequent in those aged 30 years and older.

When coronary atherosclerosis begins to cause symptoms, it has already become a systemic disease affecting most of the epicardial portion of the coronary arteries.

The invasive approach (e.g. percutaneous coronary intervention) of acute coronary syndromes ensures, in many cases, rapid, complete, and sustained recanalization of the culprit lesion. The possibility to prevent future events by addressing, during the same intervention, other coexisting asymptomatic lesions which display characteristics of vulnerable lesions is currently being explored.

The optimal strategy to prevent and slow the progression of atherosclerosis is based on prevention and treatment of lifelong risk factors, which involves both population-wide risk reduction strategies and individual lifestyle changes. Currently available medical therapy is highly efficient in affected individuals and many other novel therapies are still in development for those who still remain at high risk of future cardiovascular events.

2.3.2 Diagnostic Imaging in Coronary Artery Disease: Echocardiography Studies

In the past 20 years, echocardiography has become an established and powerful tool for diagnosing the presence of CAD and defining its consequences in patients with acute ischemic syndromes or in those with chronic coronary atherosclerosis. There is little to no risk in performing a cardiac echo in a patient with suspected CAD whereas other modalities that can be used to assess ischemia have restrictions and higher risk factors. In addition, its bedside availability, made this method the most

used imagistic noninvasive method for diagnostic and risk stratification in CAD. With little exceptions, echocardiography represents the third step in the algorithm of management of a patient with CAD after clinical evaluation and resting ECG tracings.

It can provide vital information of the pathophysiology of CAD by using 2D, M-Mode, and Doppler applications, this techniques being generally sufficient for evaluating patients with suspected or documented cardiac ischemia. However, transesophageal echocardiography (TEE) may be needed in some patients, particularly those with serious hemodynamic compromise but non-diagnostic transthoracic echocardiography (TTE) studies. In these circumstances TEE can distinguish among extensive infarction with pump failure, mechanical complications of infarction, or hypovolemia and can guide prompt therapy. Stress echocardiography is useful for evaluating the presence, location, and severity of inducible myocardial ischemia as well as risk stratification and prognostic information. Newer echocardiographic techniques like speckle tracking echocardiography and three dimensional echocardiography aren't used yet in clinical practice, but only for research purposes.

2.3.2.1 Basic Principles of Echocardiography in Coronary Artery Disease

Echocardiography is not able to visualize directly the coronary blood flow through the coronary arteries, but can depict indirectly consequences of the imbalance between flow and consumption. The mainstay of this phenomenon are the changes in left ventricular wall motion characteristics. The changes are usually regional and may be detected by echocardiography considering that ultrasound beam traverses the affected area and image quality is satisfactorily. Unfortunately many ischemic patients are heavy smokers, obese, with hyperinflated lungs, making echocardiographic exam difficult.

History begun in 1935, when Tennant and Wiggers demonstrated that coronary occlusion resulted almost immediately in abnormalities of wall motion (Tennant and Wiggers 1935). Forty years later, experimental studies on canine models using ultrasonic crystals, demonstrated that during acute ischemia (Theroux et al. 1974) and infarction (Kerber and Abboud 1973), reduction in regional flow are followed closely by a reduction in contractile function, and set the use of ultrasound in CAD.

Myocardial ischemia results in a cascade of events in which various changes are hierarchically ranked in a well-defined time sequence (Picano 1989). Ischemic cascade starts in aerobic tissues after seconds to minutes of inadequate blood supply and begins with a series of biochemical reactions followed by changes in left ventricular function and only afterwards ECG changes and clinical manifestations (Fig. 2.2). Hence, echocardiography can detect ischemic heart disease before electrical and clinical signs occur, although in clinical practice assessing a patient with suspected cardiac ischemia begins rarely with ultrasound examination.

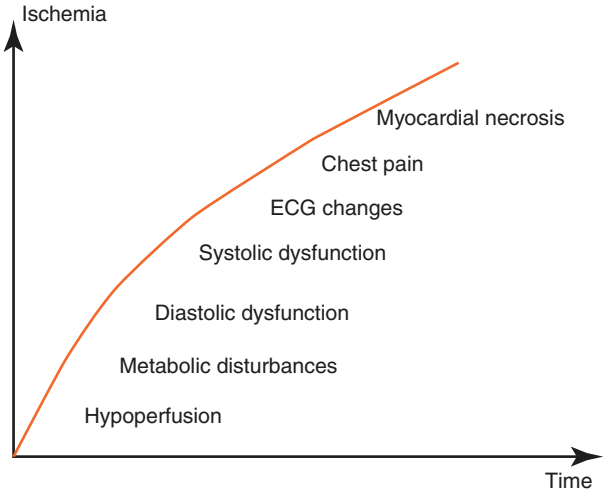

Fig. 2.2 Schematic depiction of ischemic cascade, showing that echocardiography can detect ischemia before ECG changes or clinical manifestation occur (Baskot 2011)

2.3.2.2 The Importance of Echocardiography in Patients with Coronary Artery Disease

In the light of this, echocardiography is very useful for assessing patients with chest pain in order to make a differential diagnosis, evaluating global and regional left ventricular function, determining the coronary artery that could be probably involved in the ischemic process, stratifying prognosis and guiding therapy.

Differential Diagnosis of Chest Pain

Echocardiography is very important in confirming the ischemic origin of chest pain by excluding other cardiac and noncardiac causes of chest pain (Wang and Fleischmann 2001), helping differentiate angina pain from aortic dissection, acute pericarditis, pulmonary embolism, pulmonary arterial hypertension, spontaneous pneumothorax, also life threatening conditions such as unstable angina or acute myocardial infarction. Echocardiographic findings like dilated aorta with intimal flap, pericardial effusion, and dilated right heart with elevated pulmonary pressure make acute coronary syndromes less probable. On the other hand, detecting left ventricular wall regional motion abnormalities and sometimes right ventricular wall kinetic changes confirms the suspicion of acute coronary syndromes and, together with ECG changes, allows for a more rapid diagnosis allowing the rapid establishment of invasive and noninvasive therapeutic measures. In addition, echocardiography has a high positive predictive value in patients with left bundle branch block (Cortigiano et al. 2001; Bouzas-Mosquera et al. 2009) or pacing in which ECG findings are not diagnostic for an ischemic process.

Diastolic Dysfunction in Ischemic Heart Disease

In the ischemic cascade, after the occurrence of metabolic changes, the next step represents the appearance of diastolic dysfunction. Diastole is the cardiac cycle phase during which the heart is relaxing and filling with incoming blood that is

being returned from the body through the inferior and superior venae cavae to the right atrium and from lungs through pulmonary veins to the left atrium. Diastolic failure occurs when the ventricle cannot be filled properly because it cannot relax or because its wall is thick or rigid. Diastolic failure is characterized by an elevated diastolic pressure in the left ventricle, despite an essentially normal/physiologic end diastolic volume (Lenihan et al. 1995).

To evaluate left ventricular diastolic function (Sherif et al. 2009), a PW Doppler sample volume is placed at the mitral valve leaflet tips and the following measurements are recorded: E wave representing early diastolic velocity, meaning the filling of the left ventricle due to left atrium-left ventricle gradient in early diastole; A wave representing late diastolic filling due to atrial systole; E/A ratio (normal values 1.1–1.5); E wave deceleration time (normal values 160–240 ms), isovolumic relaxation time (normal values 76 ± 13 ms) (Fig. 2.3). For further evaluation of left ventricular diastolic function, one should evaluate pulmonary vein flow by placing PW sample into the left upper pulmonary vein ostia, recording S and D wave velocities and the pulmonary vein "a" flow reversal (normal values <25 cm/s) (Fig. 2.4), together with left atrium size, preferably by measuring LA volume (normal values <20 mL/mp) (Fig. 2.5).

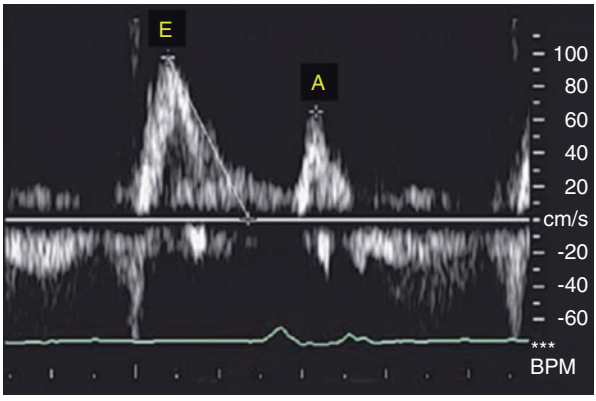

Fig. 2.3 Application of PW Doppler to the mitral valve for studying LV diastolic function

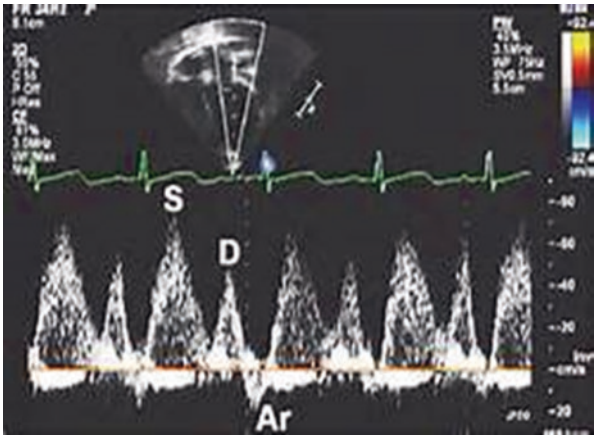

Fig. 2.4 Placing of a PW sample in the upper left pulmonary vein

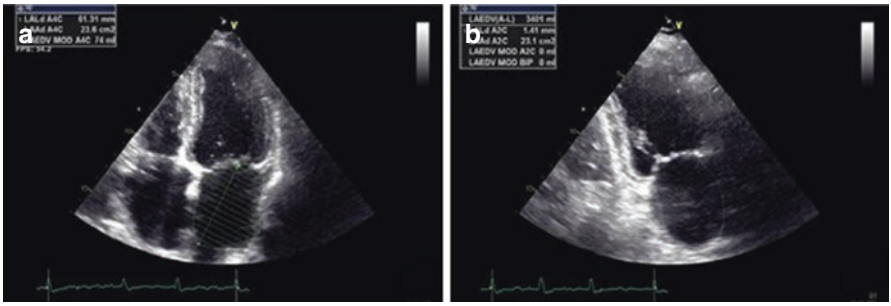

Fig. 2.5 Measuring left atrium size using biplane method, by measuring left atrium volume in apical 4 and 2 chamber views

Table 2.1 Stages of abnormal diastolic filling

Stage of diastolic dysfunction	Impaired early left ventricular relaxation	Pseudonormalization	Restricted filling pattern
Significance	Impaired (slow) early left ventricular relaxation	Suggests impaired (slow) early left ventricular with decreased left ventricular compliance	Severe decrease in left ventricular compliance and impaired (slow) early left ventricular relaxation
Signs and symptoms	None at rest	Exertional dyspnea	Dyspnea with minimal exertion
Functional status	Mild impairment	Moderate impairment	Marked impairment
Left atrium	Normal dimension (may be hypercontractile)	Enlarged and hypocontractile	Enlarged and hypocontractile
Filling pressures	Normal	Increased	Markedly increased
PW Doppler findings	E/A ratio < 1.0	E/A ratio: 1.0–1.5	E/A ratio: >1.5
	Deceleration time > 240 ms	Deceleration time: 160–240 ms	Deceleration time: <160 ms
	IVRT >90 ms	IVRT: 76 ± 13 (>40 years), 69 ± 12 (<40 years)	IVRT: <60 ms
	Pulmonary Vein "a" wave flow reversal <25 cm/s	Pulmonary vein "a" wave flow reversal: >25 cm/s	Pulmonary' vein "a" wave flow reversal: >25 cm/s (Variable: Depending on atrial systolic function)

In acute or chronic ischemia, three patterns or stages can indicate abnormal diastolic filling (Table 2.1).

In CAD, as well as in other pathologies, it is important to distinguish between the normal and the pseudonormal diastolic pattern, as therapeutic interventions can be

appropriate in reversing patients' condition. In this setting, methods of making this differentiation consist of applying the Valsalva maneuver to the Doppler transmitral inflow pattern together with using the pulmonary venous flow (a difference of >30 ms between pulmonary atrial reverse velocity and transmitral A velocity indicates increased left ventricle filling pressure).

During acute, transient ischemia, different stages of diastolic dysfunction can occur, from type I to type III. In case of a pre-existing diastolic dysfunction one can note its exacerbation instead. Once the ischemic process stops, diastolic dysfunction can reverse to normal or improve. However, it is characteristic for the ischemic cascade that diastolic dysfunction precedes systolic dysfunction.

After an acute myocardial infarction, the Doppler assessment of left ventricle diastolic function plays an important prognostic role regardless of other prognostic markers (e.g. NYHA class). A short transmitral Doppler deceleration in E velocity (<130 ms) is an early, independent marker of late left ventricle remodeling and confers an adverse prognosis; the predischarge persistency of a restrictive pattern is also prognostic (Temporelli et al. 2004). Left atrium dilation was also proved to hold prognostic value after acute myocardial infarction. The GISSI study found that that left atrium dilatation contributes to left ventricle remodeling (Popescu et al. 2004).

Global and Regional Systolic Left Ventricular Functional Changes in Coronary Artery Disease

Echocardiography can be used to assess global systolic left ventricle function and the regional wall motion abnormalities caused by transient ischemia or myocardial necrosis and identify their extent and site with great precision within just a few minutes of coronary occlusion and before onset of symptoms.

During an acute ischemic process in case of unstable angina or during the acute phase of a myocardial infarction evaluating global left ventricle function is mandatory, by assessing left ventricle ejection fraction which represents the ratio of left ventricle stroke volume (the difference between left ventricle end-diastolic volume and end-systolic volume) and left ventricle end-diastolic volume. End-diastole is defined as the first frame after mitral valve closure or the frame in the cardiac cycle in which the left ventricle linear dimensions or volume are the largest. End-systole is best defined as the frame after aortic valve closure or the frame in which L left ventricle V dimensions or volume are the smallest (Lang et al. 2015). In patients with a regular heart rhythm, measurements of the timing of openings and closures derived from M-mode echocardiography, pulsed wave (PW) or continuous wave Doppler (CW) may be used for accurate definitions of ventricular time intervals. Left ventricle volume estimates may be derived from two dimensional echocardiography (2D) or three dimensional echocardiography (3D). Volumetric measurements are based on tracing of the interface between the compacted myocardium and the left ventricle cavity. Left ventricle ejection fraction should be measured by means of 2D echocardiography using modified Simpsons method in apical four and two chamber view (Lang et al. 2015) (Fig. 2.6). 2D echocardiographic acquisition should aim to maximize left ventricle areas to avoid foreshortening and therefore

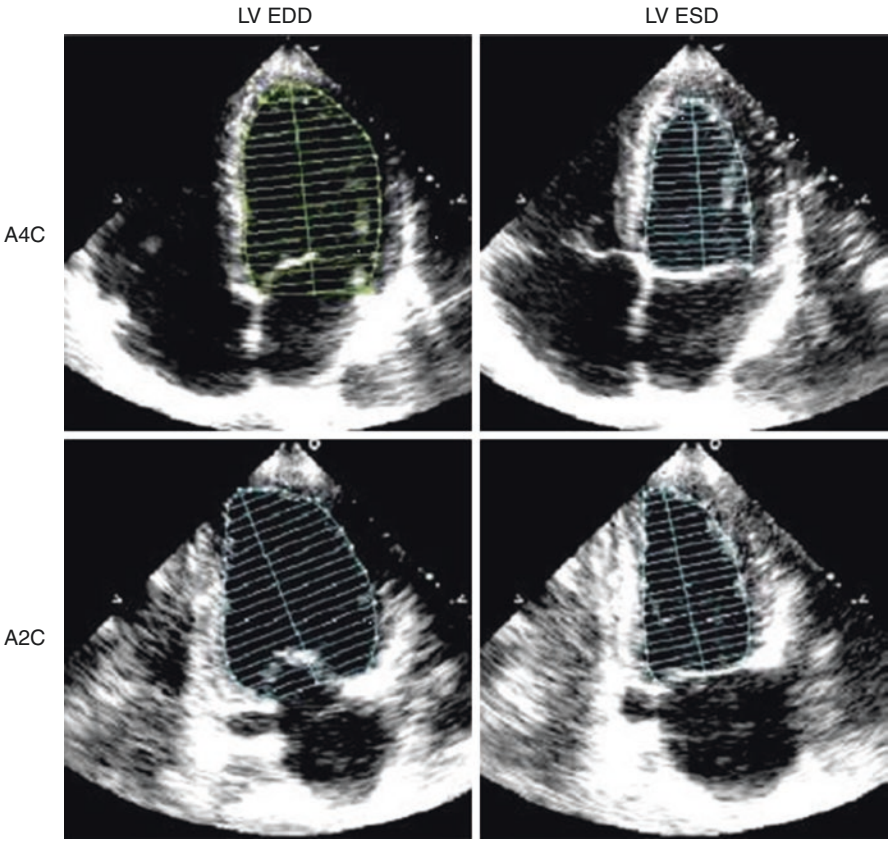

Fig. 2.6 Measuring left ventricle volumes through 2D echocardiography by modified Simpson method

underestimation of left ventricle volumes. This shortfall was avoided by introducing real-time 3D echocardiography which has led to very interesting perspectives for measuring left ventricle volumes and ejection fraction in ischemic heart disease, even when MRI is used as the gold standard (Jenkins et al. 2007). Thus, 3D echocardiography measurements of ejection fraction are accurate and reproducible and should be used when available and feasible (Fig. 2.7). Left ventricle ejection fraction <52% for men and <54% for women are suggestive of abnormal left ventricle global systolic function. The Teicholtz method for calculating left ventricle volumes from left ventricle linear dimensions is no longer recommended (Lang et al. 2015).

A number of disorders mimicking acute coronary syndromes (myocarditis/pericarditis, valvular heart diseases) or acute coronary syndromes caused by extensive ischemia (multicoronary vessel disease) can be associated with a globally reduced ejection fraction.

By means of 2D echocardiography regional myocardial function can be evaluated using the segmentation schemes that reflect the coronary perfusion territories.

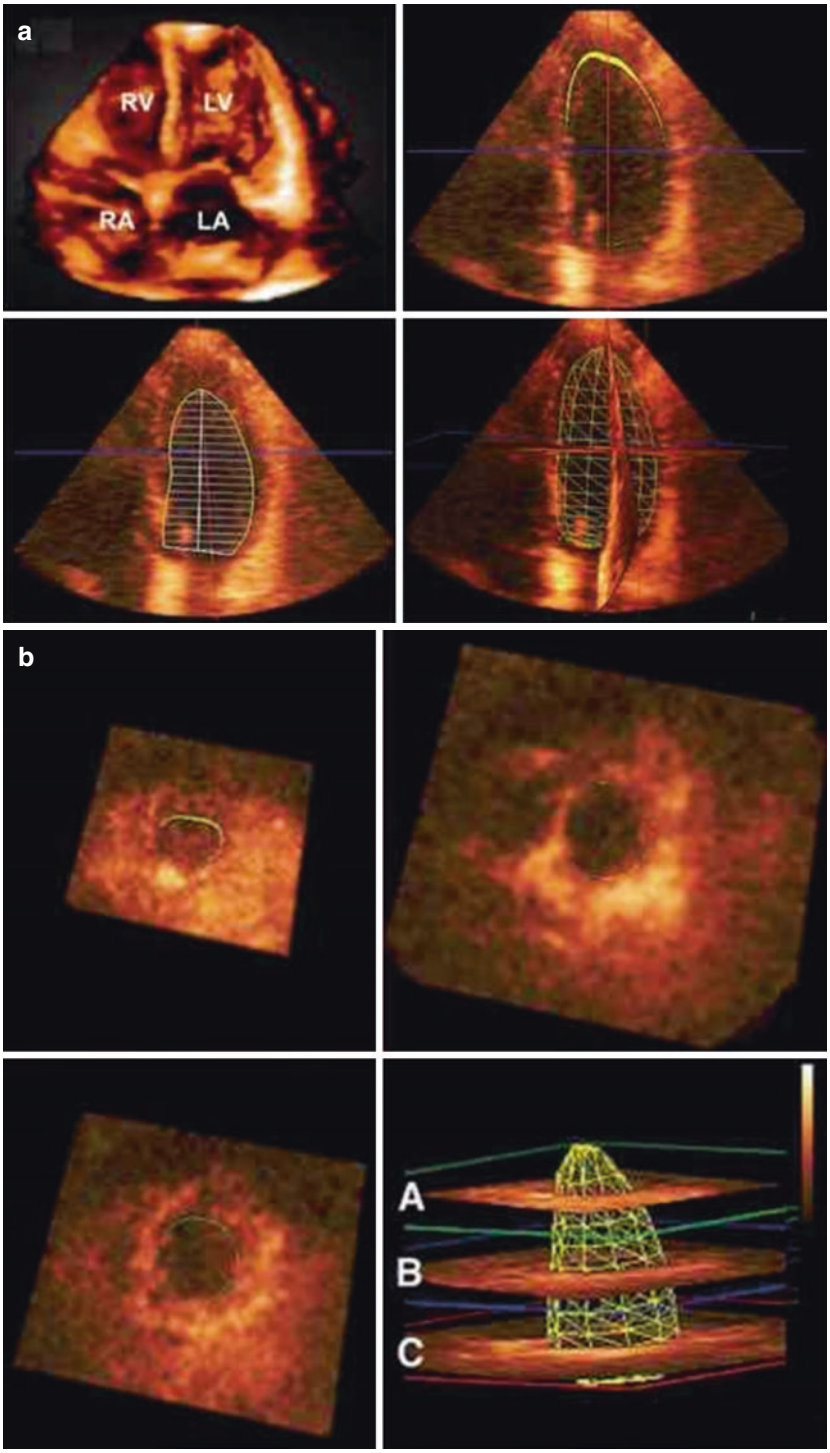

Fig. 2.7 Measuring LV volumes through real time 3D echocardiography

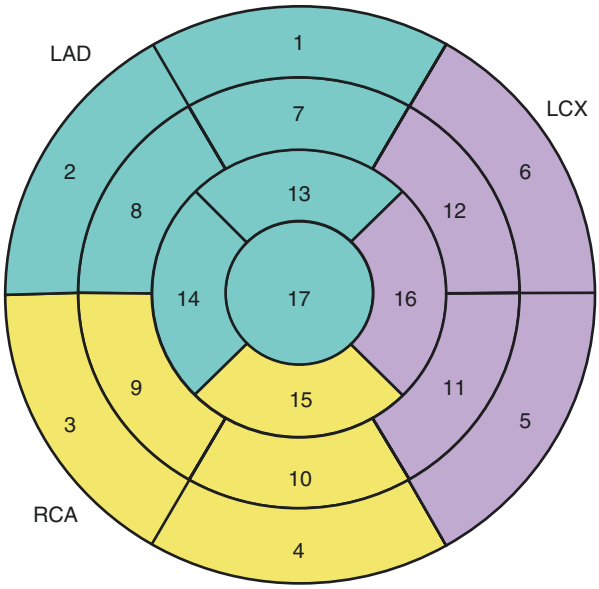

Fig. 2.8 Coronary artery distribution

In an attempt to establish a standard segmentation applicable to all types of cardiac imaging, a 17 segment model (including the apical cap) has been introduced and endorsed by the recent guidelines (Cerqueira et al. 2002). Despite the great variability in coronary artery supply, the assignment of individual segments to specific coronary arterial territories has been standardized (Fig. 2.8) (ASNCI 1999).

In echocardiography, regional myocardial function is assessed on the basis of the observed myocardial wall thickening and endocardial motion of the myocardial segment. It is recommended that each of the 17 segments be analyzed individually in multiple views. At least three wall motion abnormalities have been defined: hypokinezia—meaning reduced thickening, akinesia—meaning absent or negligible thickening, and dyskinesia—which refers to systolic thinning or stretching, such as in the case of an aneurysm. An aneurysm is characterized morphologically by focal dilatation and thinning with either akinezia or systolic deformation (Voigt et al. 2003b) (Fig. 2.9).

In clinical practice and for research purposes, a semiquantitative wall motion score index is used and is calculated as average of the scores of all segments visualized. Every normal or hyperkinetic segment receives one point, every hypokinetic segment receives two points, whereas akinetic myocardial regions receive three points and dyskinetic ones four points. The calculated sum is then divided by the number of segments. The wall motion score index has prognostic value after an acute myocardial infarction (Moller et al. 2006).

A regional wall motion abnormality at rest cannot be visualized until the stenosis exceeds 80–85% of the coronary lumen; with exercise or pharmacological stress, a 50% coronary artery lesion can lead to regional dysfunction. Studies show that in case of an acute ST elevation myocardial infarction, up to 90–100% of patients

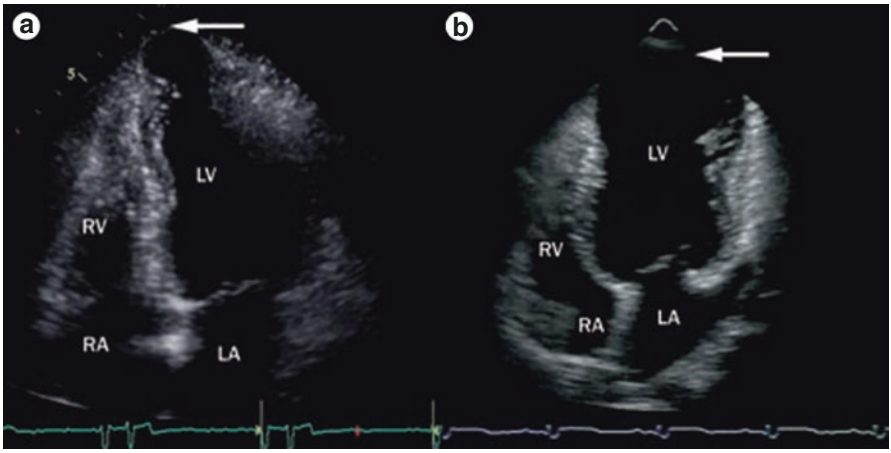

Fig. 2.9 Left ventricular aneurysm

show wall motion abnormalities, whereas in non ST elevation myocardial infarction, about 86% show wall motion disorders (Pierard et al. 1986; Ogawa et al. 1985). In general, wall thickening discriminates normal and infarcted myocardium better than wall motion, and transmural necrosis is better detected than subendocardial infarcts involving <20% of the whole myocardial thickness. In case of an acute myocardial infarction, the location of myocardial wall motion abnormalities is in accordance with the localization of the infarct deduced from ECG changes in 93–100% of patients, but discrepancies can appear in the context of previous myocardial scar/infarction, multivessel coronary artery disease or an overlap between the perfusion of the right and circumflex coronary arteries.

Besides 2D echocardiography, other echocardiographic methods derived from special techniques can be used for quantifying regional left ventricle dysfunction in ischemic heart disease. Doppler Tissue Imaging (DTI) and speckle tracking echocardiography are providing comparable data quality (Heimdal et al. 1998) (Leitman et al. 2004), although DTI is angle dependent and can underestimate motion that is not properly aligned to the ultrasound beam. Commonly used parameters are velocity, motion, deformation and deformation rate. Because velocity and motion are measured relative to the transducer, measurements may be influenced by overall heart motion. Therefore, the use of deformation parameters such as strain and strain rate are preferable. DTI assessment of mitral annulus can detect subclinical alterations in longitudinal systolic function (Sm) or in early myocardial relaxation (Em) (Fig. 2.10), even when conventional echocardiographic methods do not reveal changes. Such findings could be signs of mild subendocardial damage due to myocardial ischemia.

The term "deformation" refers to changes in shape and dimension of the myocardium during the cardiac cycle. If there is myocardial ischemia, or if a myocardial infarction had occurred in the past, this part of the heart muscle is weakened and shows reduced and altered systolic function. The most commonly used parameter to asses deformation is the ***longitudinal strain*** during LV systole. All four components

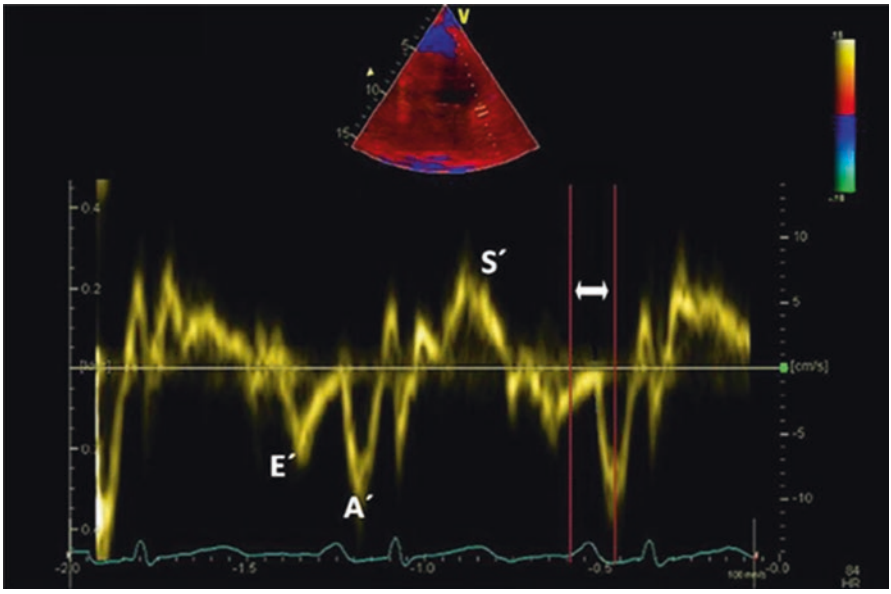

Fig. 2.10 DTI of the mitral annuls showing systolic and diastolic velocities

of strain can be expressed using three dimensional echocardiography, e.g. three dimensional strain, currently used only for research purposes, without having yet defined normal ranges. With currently available software, deformation parameters can vary in amplitude depending on the region, on the vendor or the methodology used. The temporal relationship of myocardial deformation is also important, while independent of the values obtained for strain. For example, longitudinal shortening or radial thickening of a myocardial region, occurring after aortic valve closure (sometimes called tardokinesia) is a sign of regional dysfunction, suggesting ongoing ischemia or the presence of an irreversible process (scar formation) (Voigt et al. 2009). The development of postsystolic shortening during a stress test has been proposed as an indicator of regional ischemia (Voigt et al. 2003a). Strain rate imaging is an imagistic method for measuring regional or global deformation of the myocardium. Strain rate imaging serves to assess longitudinal myocardial function in patients with acute myocardial infarction, where strain rate seems to predict regional wall motion recovery after percutaneous coronary intervention.

In a recent study, 3D real time color-flow Doppler transthoracic echocardiography was employed for the automated quantification of stroke volumes and mitral inlet flows (Thavendiranathan et al. 2012). Results were compared against measurements extracted from cardiac magnetic resonance imaging, and indicated the proposed method was accurate and reproducible. Due to its real-time capabilities it is well suited for clinical workflows.

Furthermore, since left ventricular stroke volume plays a significant role for the assessment of the circulation, an in vivo animal study was conducted for determining the accuracy of 3D real-time color-flow Doppler transthoracic

echocardiography for the evaluation of volumetric flow rates through the aortic and mitral valves (Shimada et al. 2015). The study has shown that real-time 3D color-flow Doppler is an accurate method for the evaluation of both mitral and aortic valve volumetric flow rates.

Another echocardiographic method, frequently used in ischemic heart disease, is stress echocardiography, the combination of 2D echocardiography or 3D echocardiography with the use of an ischemic stressor: physical, pharmacological or electrical (Rosa et al. 2008). The diagnostic endpoint of myocardial ischemia is the induction of a transient worsening in regional function during stress in a segment that is contracting normally at rest. In parallel, the stress echo sign of myocardial viability is a stress induced improvement of function during low levels of stress in a region that is contracting abnormally at rest.

Regardless of the kind of stress used, myocardial ischemia propagates centrifugally, involving first the subendocardial region and afterwards the subepicardial layer (Gallagher et al. 1984). In patients with normal epicardial coronary arteries, coronary flow reserve can be reduced in the presence of microvascular disease (microvascular angina or left ventricular hypertrophy). In this setting, angina can occur typically along with signs of subendocardial lesion on the ECG, but without wall motion abnormalities on stress testing. Therefore, wall motion abnormalities are more specific for the detection of epicardial coronary artery disease (Nihoyannopoulos et al. 1991).

The choice of stressors depends on the experience of the individual operator and laboratory with the agent and/or protocol. Exercise is the prototype of ischemic stress and the most widely used, combining echocardiography with pedaling on a supine bicycle. In patients who cannot exercise maximally one could use pharmacological stressors like dobutamine or dypiridamol. The use of pharmacological stressors is more convenient as it lacks the drawbacks imposed by factors hampering the image quality during exercise stress testing, such as hyperventilation and excessive chest wall motion movement frequent in physical stress testing. Dobutamine and dipyridamole act on different receptors: dobutamine stimulates adrenoreceptors, while dipyridamole stimulates adenosine receptors, therefore inducing ischemia through different mechanisms. Dobutamine increases myocardial oxygen demand, while dipyridamole decreases subendocardial flow. Dipyridamole provokes "vertical steal", which suggests the presence of an epicardial artery coronary stenosis while the subepicardium steals blood from the subendocardium (Rosa et al. 2008).

In terms of diagnostic criteria, in stress echocardiography, the fundamental stress response patterns are normal, ischemic, viabile and necrotic myocardium. In the normal model, a segment is normokinetic at rest and becomes hyperkinetic at stress. The ischemic segment's function deteriorates during stress (a stress test is usually positive when these findings are present in two adjacent segments). The necrotic segment has resting dysfunction which remains fixed during stress. The viable segment has resting dysfunction and during stress can show either a sustained improvement indicating a stunned myocardium, or first improve during early stress and then subsequently deteriorate at peak stress (biphasic response)

(Senior and Lahiri 1995), indicating a hibernating myocardium. The hibernating myocardium requires therapeutic revascularization to improve contractility. A resting akinetic segment becoming dyskinetic during stress usually indicates a passive, mechanical consequence of increased intraventricular pressure and is not a true sign of active ischemia.

Given the fact that the interpretation of contractile function is subjective, an improved image quality could reduce inter-operator variability. For this purpose, harmonic imaging and ultrasound contrast agents for LV opacification are recommended to enhance endocardial border detection and hence accuracy of the examination (Kirkpatrick et al. 2005).

More recently, it 3D echocardiography was validated for the assessment of left ventricular volumes. Specifically, automated methods for real-time border detection have been proposed, thus contributing to the integration of 3D echocardiography in routine clinical workflows (Barbosa et al. 2013).

In conclusion, echocardiography is the most commonly used imagistic method to assess myocardium functionality in coronary heart disease. It is crucial for diagnostic and risk stratification, and has become so because of its bedside availability, relatively low cost, repetabilty and lack of adverse effects. Although the method does not image the coronary arteries directly, it allows accurate visualization of wall motion abnormalities, allowing precise localization of culprit coronary artery in most cases of chronic ischemia or acute coronary syndromes. Newer echocardiographic techniques, such as deformation imaging or three dimensional echocardiography, can detect subtle changes in myocardial mechanics or function, before classical methods show any alterations. Stress echocardiography is a very valuable method for increasing sensibility and specificity in diagnostic and risk stratification in ischemic heart disease.

2.3.3 Invasive Diagnosis of Coronary Artery Disease: Angiography

The invasive coronary evaluation—coronary angiography and angioplasty—is nowadays the cornerstone in the complex treatment management of CHD. From the right heart catheterization of Forssmann in 1929 to the accidental injection of contrast dye in the coronary arteries of Sones in 1960 and to Gruentzig in 1977, coronary angiography and angioplasty have come a long way to become a leading worldwide method of diagnosis and treatment. With the invention of coronary stents and extensive research for minimizing the technology for better and easier access, the method has become readily available all around the world. The past 25 years have witnessed a great leap of technology in the field of interventional cardiology technology and methodology, allowing physicians to treat CHD less invasively and to treat acute myocardial infarctions before complete damage of the myocardium occurs. Moreover, the past decades have brought novel research and breakthroughs to understand the pathology of atherosclerosis and describe the intimate processes of intravascular coronary physiology.

2.3.3.1 The Coronary Angiography

In order to perform a coronary angiogram or percutaneous coronary intervention (PCI), first we must have an arterial access, usually through the femoral or radial artery. As the most common side effects of coronary catheterization are access-site related, recent years have brought a shift made towards the radial access, as this method has almost no access-site complications. The artery access is performed via an arterial introducer, usually 1.7 or 2 mm (5 or 6 French gauge) in diameter. For very complex PCIs a 2.3 mm introducer can be used (7 Fr gauge). Through the introducer, specific pre-shaped catheters are introduced under X-ray guidance all the way to the ascending aorta and the tip of the catheters are gently introduced in the coronary ostia. Either manually, or via an automated syringe, contrast dye is injected and the entire coronary artery circulation can be visualized (Serruys et al. 2010) (Figs. 2.11 and 2.12). Even to this day, despite the availability of many incredibly accurate methods of assessment of both intravascular physiology and anatomy, the decision to revascularize is still performed via a visual assessment of the coronary artery stenosis (Hannawi et al. 2014).

Owing to technological progress and miniaturization, the coronary angiography is considered a safe technique, with low rates of complications that vary greatly accordingly to patient comorbidities. Most complications are access-site related, the femoral artery having been the main access artery for more than 20 years. These problems include most often local haematoma, the formation of a pseudoaneurysm and an arterio-venous fistula and occur in 0.3–5% of patients (Alonso et al. 2003; Baim and Grossman 1996). These complications are minor, often self-limiting and easily treated via manual, interventional or local minimal surgery (Krueger et al. 2005; Paulson et al. 2000). These access related complications are almost absent in

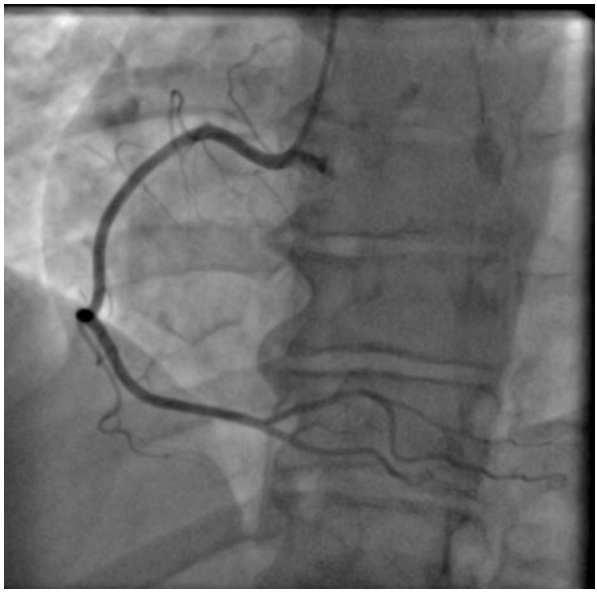

Fig. 2.11 Right coronary artery angiography—normal appearance

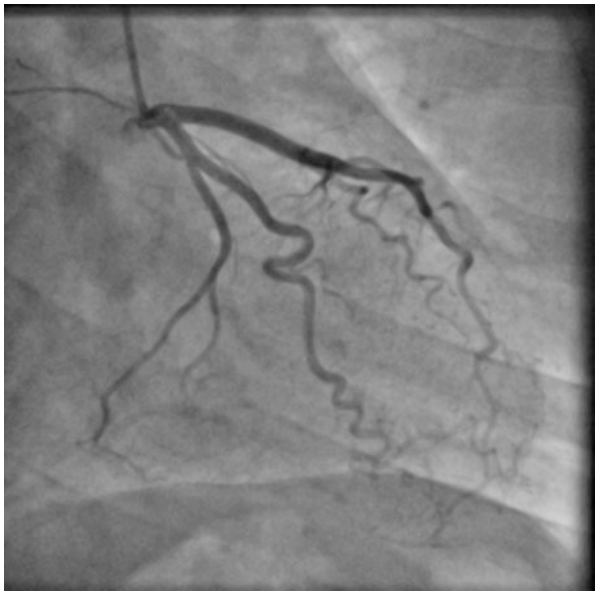

Fig. 2.12 Left coronary artery angiography with left anterior descending artery and left circumflex artery—normal appearance

the case of a radial access, but with slightly more radiation exposure for the operator and a longer learning curve. Other, more severe complications, include arrhythmias—the most severe being ventricular tachycardia or ventricular fibrillation and cardiac arrest, which is usually reversible—and complete atrioventricular block or asystole, also usually reversible. In addition, arterial embolism or dissection may occur as a severe complication followed by acute stroke (0.2–0.4%) (Kwok et al. 2015), or acute limb or renal ischemia, or even aortic dissection. Another significant complication is contrast-related nephropathy, with more than 5% of patients having a transient increase of serum creatinine, but usually less than 1% actually requiring haemodialysis. Myocardial infarction or death after a diagnostic procedure is quite rare, both being reported in less than 0.1% (Wyman et al. 1988; Johnson et al. 1989).

2.3.3.2 Percutaneous Coronary Interventions

The PCI is inextricably linked to the diagnostic coronary angiogram (Fig. 2.13). It is the cornerstone in the treatment of CHD because nowadays it is the main method of restoring normal coronary blood flow. The PCI follows after the decision to revascularize usually taken within the same procedure (Fig. 2.14).

If one can define the coronarography as a diagnostic method, the PCI is the treatment method that completes the coronary catheterisation spectrum. It is performed using the same type of vascular access, femoral or radial. Specific pre-shaped guiding catheters are used, with larger inner diameters and metallic wire reinforcements to compensate for thinner walls. These catheters are much stiffer than the diagnostic ones in order to provide the much needed support for the PCI. All PCIs commence with the gentle advance of a thin metallic wire called a guidewire. It has a diameter of 0.014 in. and its insertion is a main stage during the PCI. There are numerous

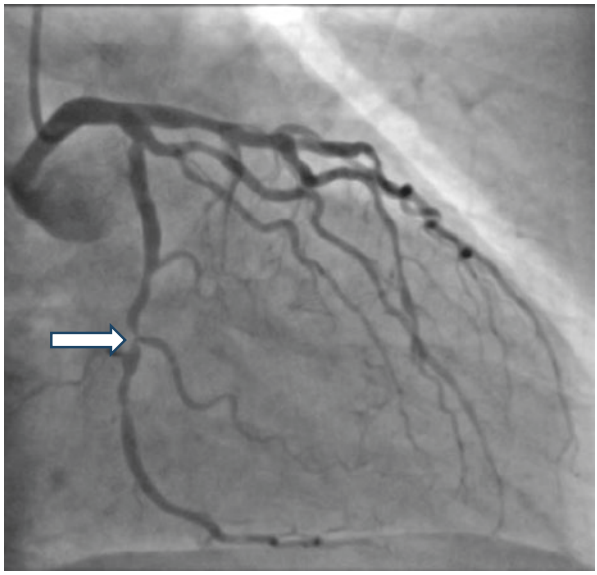

Fig. 2.13 Left circumflex artery severe stenosis—initial aspect

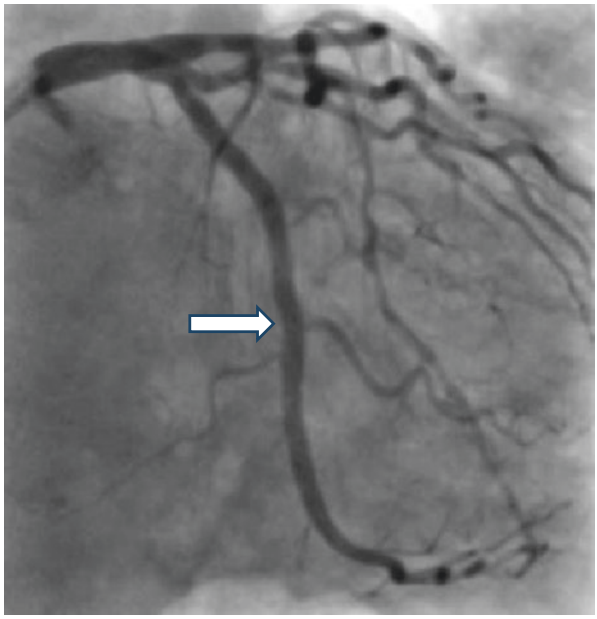

Fig. 2.14 Left circumflex artery—after PCI with stent implantation

types of guidewires, as they are classified by the guidewire coating (hydrophilic or non-hydrophilic), core material and structure, tip diameter and most importantly tip loading, steerability and trackability, torque and support. They act as a rail for subsequent material to be introduced in the coronary artery. After a wire is chosen and the target stenosis is crossed, usually a balloon catheter is then introduced on to the

wire to the stenosis. The balloon catheter is connected to a manual pump and is inflated with pressures from 6–8 to at least 20 atm, with a mixed liquid formed from saline and contrast media. This stage is called predilation and it has the purpose of preparing the lesion for subsequent stent placement. The balloon is then deflated and extracted from the guiding catheter. The balloon is usually provided with radio-opaque markers in order to have a landmark for a correct stent length placement. Each of these stages are performed using intermittent injection of contrast media (Serruys et al. 2010).

Once the lesion is prepared and the length and diameter of the vessel stenosis is established, usually a stent implantation follows. Coronary stents are advanced tube-shaped devices that help maintain a normal blood supply to the myocardium. All stents are basically formed of a metallic framework made from a very thin metal alloy strut of around 80 μm that is intertwined to form the tube. The stent comes folded onto another balloon catheter. After the stent is positioned, the balloon is inflated to at least 12 atm in order to fully expand the stent struts into the vessel wall. Sometimes, a postdilation is required, with a special fixed-diameter non-compliant balloon catheter in order to fully apposition the stent to the vessel wall.

After some time, usually 1 month to several years, the intracoronary stent becomes part of the vessel wall via endothelialization. This process influences the two main adverse effects of the stents: in-stent restenosis and acute thrombosis. Restenosis is a relatively slow-acting process (around 3 months to 1 year), by which the endothelial cells react abnormally to the vessel injury and the foreign body, and leads to neointimal hyperplasia. This process is a proliferation of vascular smooth cells inside the new intima and leads to the thickening of the arterial walls and a decrease in the arterial lumen. Restenosis presence varies from 30% to less than 3–5%, has numerous risk factors and is clinically relevant because of the need, in such cases, of repeated revascularization (Dangas et al. 2010). The other complication, acute thrombosis, is defined as sudden vessel closure by a locally formed thrombus, initiated by the exposure of the metallic stent struts to the arterial lumen. Usually, all patients must receive strong antiplatelet therapy for various periods of time after a stent is placed in order to prevent thrombosis, until the stent is covered by the newly formed endothelium. Sometimes the treatment is stopped before full endothelialization (usually 1 month to 1 year) and the patient is exposed to the risk of thrombosis. The in-stent acute thrombosis is a serious complication, with a mortality rate as high as 45%. The incidence of this complication varies nowadays from 0.5 to 2%, with higher numbers in the past (Stone et al. 2007).

There are different types of coronary stents and great effort has been put into research and development of the technology. The type of stent used is often linked to the patient outcome and adverse cardiovascular events. Historically, the first stent types used were the bare metal stents (BMS). These stents were plagued with high rates of restenosis in selected patients, as high as around 30%, making repeat revascularization a frequent intervention. Still, they were extensively used for many years, with significant better results regarding CAD outcome than medication, and often similar in terms of mortality with coronary arterial by-pass graft surgery (CABG) (Serruys et al. 2001). Today, the bare metal stents are still used in patients

who can receive a limited duration of antiplatelet treatment, because BMS are quickly endothelialized in 1 month, the risk of stent thrombosis decreasing after this period.

The next great leap in terms of stent design was the introduction of the drug eluting stents. These are regular bare metal stents coated with a drug that blocks cell proliferation and therefore restenosis. The drugs are slowly released over one to 6 months, in the time span when the restenosis occurs (Halkin et al. 2005). The first antiproliferative agents were paclitaxel and sirolimus, but nowadays zotarolimus, biolimus and everolimus are most often used. Thanks to the decreased need of revascularization and significant better outcomes, drug eluting stents now form the bulk of the coronary stents implanted worldwide (Sarno et al. 2012). Still, because of impeded endothelialization, drug eluting stents are prone to late and very late stent thrombosis (Lüscher et al. 2007).

The newest type of coronary stents are the bioresorbable vascular scaffolds (BVS). These are stents made not from metal alloys but from fully bioresorbable materials. The most used BVS is formed from a poly-L lactide material, coated with everolimus, in order to prevent restenosis. Over time, the material is broken down and it is dissolved by the organic processes in the vessel wall. The advantages of the BVS include vasomotion restoration, reduction in plaque area and late lumen gain, but with a more difficult intracoronary deployment and emergent data regarding late and very late in-stent thrombosis (Cassese and Kastrati 2016).

2.3.3.3 Indications of Coronary Angiography and PCI

The coronary heart disease comprises a wide spectrum of clinical presentations that can be divided in three clinical entities: stable coronary disease, non-ST-segment elevation acute coronary syndromes (non STEMI ACS—including unstable angina and non-ST-segment elevation myocardial infarctions) and ST-segment elevation acute myocardial infarctions (STEMI).

Nowadays, the introduction of the PCI as the main revascularization method in STEMI, has lowered the in-hospital mortality almost four-fold, to around 4%. The European Society of Cardiology (ESC) Guidelines for STEMI indicates the primary PCI is the recommended reperfusion therapy and must be performed as soon as possible, in the first 12 h or in selected cases, in the first 24 h. In order to obtain the maximum advantage of the primary PCI, a complex network involving patient education, the emergency service, transit hospitals and PCI-capable hospitals, must be put in place to bring the patient in the cath lab as soon as possible. The primary PCI is the best treatment of STEMI in terms of outcome because of the high rate of success in experienced centres, the prompt revascularization leading to a greater salvage of myocardium and extremely low reinfarction rates (Steg et al. 2012).

The non-STEMI ACS is a heterogeneous clinical entity, comprising from aggravating exertion angina to an abrupt coronary occlusion without the ECG manifestation of ST-segment elevation. The ESC Guidelines of non-STEMI ACS has established a risk stratification score with the invasive evaluation as the centre of the treatment strategy. In the highest risk group, the coronary angiogram must be performed immediately, in the second risk group it must be performed in the first 24 h, in the third risk group in the first 72 h, and in the least risk group a non-invasive evaluation must be performed first (Roffi et al. 2015).

All acute coronary syndromes are great medical emergencies that pose a real threat to human lives. Therefore, the invasive coronary evaluation is mandatory and its benefits, and that of subsequent revascularization, overwhelm the procedure and stent-associated risks. But the patients with acute coronary syndromes represent only a part of the great coronary atherosclerotic burden. In stable angina patients, the benefit of revascularisation compared to the optimal medical treatment is less pronounced, and in fact some clinical trials have showed that there is no benefit on mortality between the two groups. In all clinical studies comparing the two groups though, there was a pronounced and consistent benefit regarding the need for revascularisation.

The ESC Guidelines for stable angina argue that a coronary invasive evaluation should be performed only in patients with severe stable angina or in patients with a clinical profile suggesting a high clinical risk, in patients with a prior non-invasive test that suggest a high adverse event risk, or in patients with inconclusive or conflicting tests.

The guidelines also have some strict indications regarding revascularization. Because of the heterogeneity of the coronary anatomy and disease, prognostic indications have been made for the unstable angina. Revascularization is suited in patients with a left main disease stenosis of more than 50%, any proximal LAD stenosis >50%, two- or three-vessel disease associating an impaired left ventricle function, a large area of ischemia in the left ventricle (>10%) as defined by non-invasive studies, and a single remaining patent artery with a >50% stenosis. Besides anatomic prognostic criteria, there is also another criterion, regarding symptoms, the presence of a coronary stenosis of more than 50% with angina, unresponsive to medical therapy (Montalescot et al. 2013).

The non-invasive testing for coronary ischemia have their rationale in filtering out and also guiding patients with stable symptoms towards coronary invasive evaluation and subsequent revascularisation. Although a relatively safe procedure as shown above, there is no need to expose numerous patients to an invasive procedure if they do not need it. Non-invasive tests are grouped into three categories: the exercise stress ECG, imaging studies and coronary computed tomography angiography. The ECG stress test is widely available and cheap, but with the lowest sensitivity and specificity (Morise and Diamond 1995). The imaging studies comprise the exercise or pharmacological stress echocardiography, pharmacological stress magnetic resonance imaging, pharmacological stress PET and exercise or pharmacological SPECT (single photon emission computed tomography). These tests are highly accurate but expensive, they are not widely available, difficult to perform and necessitate highly trained personnel (Heijenbrok-Kal et al. 2007; de Jong et al. 2012). The coronary computer tomography angiography has difficulties in assessing the coronary anatomy if the vessel are calcified and has a high radiation dose (Miller et al. 2008).

2.3.3.4 Adjunctive Invasive Diagnostic Tools

Even nowadays, in most coronary procedures, angiograms and PCIs, visual assessment of the stenosis, the vessel diameter and the size of the stent is still the most widely used method. Numerous studies showed that visual assessment is not adequate

and is not well correlated with actual measurements and with a large inter-observer variability (Fischer et al. 2002; D'Ascenzo and Barbero 2015; Tonino et al. 2009).

Regarding coronary anatomy, there are two methods employed in correctly assessing the vessel diameter, extent of the lesion, stent deployment and apposition as well as important information regarding atherosclerotic plaque physiopathology.

The first method is the intravascular ultrasound (IVUS). A small probe is inserted in the coronary artery and using ultrasound technology the vessel wall is visualised. It has a penetrance of 4–8 mm and a resolution of 150 μm. The IVUS is the gold standard for accurate measurement of plaque burden and is used to determine the evolution of the plaque under different drugs. It is also used for stent implantation optimization and many clinical trials have assessed the clinical outcome of stent placement under IVUS guidance with mixed results. The high price of the probe limits its use and the routine IVUS evaluation is not recommended (Windecker et al. 2014; Mintz et al. 2001).

The other method uses optical coherence tomography (OCT). A probe is inserted in the coronary artery and using a light based technology, it accurately detects intraluminal structures, as it has a resolution of 15 μm, but a penetrance of only 2–3 mm. Because of such a high resolution, structures like lipid pools, fibrous plaque, white or red thrombi and even the thin fibrous cap of the vulnerable atherosclerotic plaque can be seen. It is the standard method of evaluating the BVS placement and optimization, as the BVS struts are echolucent (Prati et al. 2012).

Regarding coronary physiology, the most important breakthrough is the determination of the fractional flow reserve (FFR). It is the gold standard method for evaluation of the functional assessment of a lesion severity. The visual assessment on the angiogram is a poorly correlated method to the FFR, as many >70% (the classical threshold for revascularization) stenosis have a non-significant FFR and also many <70% stenosis on visual assessment have a positive FFR and a need to treat (Fischer et al. 2002). The method implies the introduction of a special coronary 0.0014″ guidewire, with a pressure sensor at its tip, distally to the stenosis to be assessed. Different drugs (papaverine, adenozine, ATP, isosorbid dinitrate) are then administered either intravenously or intracoronary in order to obtain a full microcirculation hyperemia, to mimic the maximal blood flow distally to the stenosis. The ratio between the pressure distally to the lesion and the aortic pressure is then calculated. A ratio bellow 0.75–0.80 shows that it is a functionally significant lesion and must be treated, while a ratio over 0.80 may be left untreated. Randomized clinical trials with hard endpoints established the safety and effectiveness of the 0.80 threshold (Tonino et al. 2009; Pijls et al. 2007; De Bruyne et al. 2012).

2.4 Aortic Pathologies

2.4.1 Background

Aortic pathologies comprise a wide spectrum of arterial diseases: aortic aneurysms, acute aortic syndromes including aortic dissection, intramural hematoma, penetrating atherosclerotic ulcer and traumatic aortic injury, pseudoaneurysm, aortic rupture,

atherosclerotic and inflammatory affections, as well as genetic diseases (e.g. Marfan syndrome) and congenital abnormalities, including the coarctation of the aorta (CoA) (Erbel et al. 2014).

This large spectrum of pathologies may be diagnosed after a long period of subclinical development or they may be discovered under an acute presentation, as acute aortic syndrome, a clinical condition that needs rapid diagnosis and decision-making to reduce major complications or even death.

Coarctation of the aorta, a congenital abnormality considered to be a complex disease of the vasculature, occurs in approximately 5–8% of patients with congenital heart disease. The prevalence of isolated forms is 3 per 10,000 live births (Erbel et al. 2014).

It occurs at least 1.5–2 times more often in males than in females (Warnes 2009). Although the majority of the cases are not inherited, there have been identified possible genetic associations with left-sided obstructive lesions that include coarctation of the aorta, left ventricular outflow obstruction, subaortic stenosis, bicuspid aortic valve and supravalvular aortic stenosis (Aboulhosn and Child 2006).

CoA covers multiple aspects of anatomy and physiology and the severity of the disease depends not only on the degree of aortic narrowing but also on associated heart lesions. Timely repair of coarctation with surgery or catheter intervention relieves symptoms and improves prognosis (Crawford 2010).

This chapter focuses on coarctation of the aorta, and, before presenting the evaluation strategies of this pathology, several physiopathological aspects are discussed.

2.4.2 Anatomy, Physiology and Physiopathology

The aorta, the largest artery in the body, is anatomically divided into thoracic and abdominal segments. The former, the thoracic segment, is subdivided into the ascending aorta, the aortic arch and the descending aorta. The latter has two distinct portions, in relation to the renal arteries, called supra- and infrarenal segments (Mann et al. 2015).

The aortic wall is histologically composed of three layers, playing an important role in the physiopathology of aortic diseases: tunica intima, a thin layer lined by the endothelium, tunica media, arranged as concentric sheets of elastic and collagen fibers with the border zone of the lamina elastica interna and externa, and also smooth muscle cells. The outer layer, called tunica adventitia, contains collagen fibers, vasa vasorum and lymphatics (Erbel et al. 2014).

The media gives the aorta its circumferential elasticity, necessary to resist hemodynamic stress. The adventitial collagen fibers ultimately govern the tensile strength of the aortic wall. Oxygen and nutrients are supplied to the aortic wall by diffusion from the lumen (Mann et al. 2015).

Coarctation of the aorta represents a narrowing of the aorta that causes a restriction of blood flow to the more distal vessels and organs, and hypertension proximal to the CoA (Warnes 2009).

In the typical form of coarctation of the aorta, the narrowing is located near the thoracic end of patent ductus arteriosus (PDA), usually in a distal point to the left

subclavian artery, depending on the length of the isthmus (Crawford 2010). In patients with coarctation the ascending aorta is usually dilated and the severity of the narrowing is variable. The dilatation may become aneurysmal and also involve sinuses of Valsalva. In many cases, coarctation of the aorta is often associated with other cardiac malformations, of which the most common is a bicuspid aortic valve, giving rise to another associated pathology: aortic stenosis or aortic regurgitation. It may associate shunt lesions, such as patent ductus arteriosus or ventricular septal defect (Willerson et al. 2007). It is also important to mention the possible coexistence of a noncardiac anomaly in this category of patients, the aneurysm of the circle of Willis (Hodes 1959).

Aortic coarctation can rarely occur in the ascending intrathoracic or abdominal aorta and it may be associated with systemic disease, such as Takayasu's aortitis, Williams syndrome and middle aortic syndrome (Crawford 2010).

Based on the elastic properties, the aorta transmits pulsatile arterial blood pressure to all points in the vascular tree (Mann et al. 2015). Through its elasticity, the aorta has the role of a second pump—Windkessel function/effect—during diastole, being essential to ensure coronary perfusion, and also perfusion for the rest of the organs (Erbel et al. 2014).

Coarctation of the aorta is a diffuse disease, an affirmation based on histologic examinations that show intimal and medial lesions consisting of a thickened shelf that protrudes posteriorly and laterally into the aortic lumen. This shelf is related to the wall of the ductus, and encircles the vessel. These histological aspects reveal that the coarctation develops as a result of migration of ductus smooth muscle cells into the periductal aorta, resulting in a subsequent constriction and narrowing of the aortic lumen (Crawford 2010).

The impedance of aortic narrowing in coarctation causes a chronic increase of afterload for the left ventricle. Blood flow to the head and upper extremities is preserved because the vessels supplying these areas branch off from the proximal segment of the aorta. Blood flow to the descending aorta and lower extremities is usually diminished. Compensatory mechanisms, such as left ventricular hypertrophy, dilatation of collateral blood vessels from the intercostal arteries, to provide blood flow to the descending aorta, will appear if the primary cause is not corrected (Lilly 2011).

2.4.3 Natural History and Clinical Presentation

Coarctation of the aorta is likely to produce consequences during two periods of life: in early infancy (if the lesion is severe) and between 20 and 30 years of age. If the coarctation is not corrected only 10% of the patients live beyond age 50 (Willerson et al. 2007).

The clinical aspects of coarctation depend largely on the nature of the associated cardiac lesions and the severity of the narrowing. In early infancy, severe coarctation and cardiac-associated anomalies may lead to congestive heart failure and cardiac shock, often occurring after the closure of PDA, which before had the role of

bypassing the narrowed area. Those cases must be managed under administration of intravenous prostaglandin to maintain patency of the ductus arteriosus, preserving systemic blood flow until surgery can be performed (Warnes 2009).

Isolated coarctation may be mostly asymptomatic and may have subtle clinical findings. In these cases, it is frequently misdiagnosed and treatment is delayed. In older children and adolescents, with less severe types of coarctation, systolic hypertension and heart murmur (most prominent in the left paravertebral region, near the left scapula) are the most common presentations (Crawford 2010).

A complete cardiovascular examination may strongly suggest the correct diagnosis. Normally, the lower extremity blood pressure is higher than that of the upper extremities. The classical coarctation patient presents lower blood pressure in the legs than in the right upper extremity. This diminishes the femoral pulse, combined with delayed timing, when compared with the right upper extremity pulses. The left arm may be variable depending on the area of the left subclavian artery relative to coarctation site (Warnes 2009). A significant blood pressure gradient (above 20 mmHg) between the upper and lower extremities indicates significant coarctation of the aorta (Erbel et al. 2014).

Another clinical finding is increased left ventricular impulse, that may be displaced, secondary to left ventricular hypertrophy, signs of collateral circulation and additional murmurs (Warnes 2009).

Aortic coarctation may also be associated with Marfan or Turner's syndrome. The somatic features in those cases should be correctly evaluated (Willerson et al. 2007).

2.4.4 Diagnostic Work-Up

If coarctation of the aorta is suspected, various tests enable a definitive diagnosis.

2.4.4.1 Chest Radiography

In infants with coarctation of the aorta, enlargement of the heart may be observed on the chest X-ray examination, but the outline may vary. If the child has an intracardiac lesion with left-to-right shunting, moderate to severe cardiomegaly with increased pulmonary vascular drawing may be observed (Crawford 2010). Rib notching can be seen as irregular areas on the undersurfaces of the posterior ribs. Those marks seldom appear before patients reach 7 years of age. The bilateral rib notching, usually confined to the third to eighth posterior rib, indicates that the area of coarctation is located just distal to the subclavian artery (Willerson et al. 2007). An indented aorta at the site of coarctation may also be visualized (Lilly 2011).

2.4.4.2 Electrocardiography

In general, right axis deviation and right ventricular hypertrophy can be seen in an infant. In adults, left ventricular hypertrophy is usually evident because of the long-term effects of left ventricular pressure overload. In case of associated right ventricular hypertrophy in adults, it is required to evaluate for another cardiac lesion (ventricular septal defect and pulmonary hypertension) (Crawford 2010).

2.4.4.3 Echocardiography

Ultrasound diagnosis for coarctation of the aorta represents a non-invasive, inexpensive investigation, readily accepted by every patient and it can be repeated as frequently as required. It is an important tool for quantification of left ventricular mass and for searching other possible intracardiac abnormalities (Sun et al. 2015).

In neonates and infants, echocardiography from the suprasternal axis view provides a useful method for evaluating the aortic arch, the branching arteries and possible cardiac anomalies. Color-flow mapping can assist the severity of the aortic coarctation. A turbulent flow which travels downstream is usually associated with the coarctation and studies on both pulse-wave Doppler and continuous-wave Doppler can provide a calculation of the pressure gradient across the narrowing, using the modified Bernoulli equation. This method is influenced by a series of variable parameters, such as aortic arch geometry, complex flow dynamics in the aortic arch, difficulty in aligning the Doppler beam with flow, or inability to measure flow velocity under certain circumstances, and the use of the Bernoulli simplified equation is not always reliable. In older adults, the suprasternal long-axis view may not offer as much information, due to poor imaging windows, but it can be useful to measure ascending aorta and detect aortic aneurysm (Crawford 2010). The peak and mean velocity detected with continuous wave Doppler through the coarctation site may help define the severity of the coarctation but may overestimate the gradient with long-segment stenosis or increased arterial stiffness (Warnes 2009).

2.4.4.4 Magnetic Resonance Imaging

The possibility of employing MRI to delineate the intrinsic contrast between flow and vessel wall makes an optimal choice for diagnosis of the aortic disease (Erbel et al. 2014). However, it is an expensive investigation for many countries, and it requires valuable experience in cardiac and vascular studies (Warnes 2009).

MRI in sagittal and parasagittal projections can appreciate the location and the severity of coarctation of the aorta and the anatomy of the transverse aortic arch, isthmus and poststenotic dilatation. It may also highlight the presence of a patent ductus arteriosus and the extent of collateral arteries (Crawford 2010).

2.4.4.5 Diagnostic Cardiac Catheterization and Angiography

Cardiac catheterization and angiography are invasive procedures, used for clinical evaluation and for cases in which clinical questions arise when referring to the severity of coarctation or associated cardiac lesions (Crawford 2010). For the majority of cases these investigations are rarely required because noninvasive imaging often ensures accurate evaluation. Through catheterization, the true pressure gradient across the arch is obtained; when the peak gradient exceeds 20 mmHg in noninvasive imaging, catheterization is reserved for therapeutic interventions (Warnes 2009).

2.4.5 Management of Coarctation of the Aorta

Once a diagnosis of coarctation is performed, both surgery and catheter interventions (balloon angioplasty and stent placement) can be considered for resolving the narrowing of the aorta. It is important to know that uncorrected aortic coarctation is

associated with a poor clinical course and short life expectancy—reaching an average of 30 years—and is usually secondary to clinical consequences of chronic arterial hypertension (Calderón-Colmenero and Attie 2008). Other common causes of death in the case of unrepaired coarctation cases are congestive heart failure, endocarditis and aortic rupture, as well as intracranial hemorrhage (due to rupture of aneurysm of Willis circle) (Warnes 2009).

Medical treatment implies drugs for controlling arterial hypertension with the inhibitors of the renin-angiotensin-aldosterone system (ACE inhibitors), angiotensin II type 1 receptor antagonists, or aldosterone antagonists (such as spironolactone, eplerenone), betablockers or centrally acting α-adrenergic agonists (clonidine) (Willerson et al. 2007). Neonates and infants with aortic coarctation should be admitted in the hospital for intravenous administration of prostaglandin E1 as soon as the diagnosis is confirmed, in order to reopen the ductus arteriosus for improving lower body perfusion (Moodie 2014).

The mortality rate of surgical repair for isolated coarctation of the aorta is very low in infants and older children, but it may be higher in the presence of associated lesions. Also, the morbidity after the correction may imply a rebound of arterial hypertension, neurological disorders, as paralysis due to spinal cord lesion or vocal cord paralysis, due to recurrent laryngeal nerve injury or immediate postoperative complications, like hemorrhage caused by the suture line or infections (Crawford 2010).

In a recent multicenter study, endovascular repair represented a safe and effective treatment for de novo coarctation and post-surgical complications of coarctation repair in adults, together with the lowest rates of complications and long-term clinical success (Erben et al. 2015).

In native coarctation of the aorta with appropriate anatomy, stenting has become the first choice treatment in adults in many centers. In these cases, appropriate antihypertensive treatment may still be necessary for controlling hypertension (Erbel et al. 2014).

2.4.6 Long Term Prognosis

Long term prognosis after CoA repair depends on age, associated lesions and systemic complications. Despite successful repair, the prevalence of hypertension in adults under 20 years varies from 20 to 40% and it may be higher in some cases. In addition to persisting arterial hypertension, a considerable number of patients with repaired coarctation are normotensive at rest, but develop a hypertensive response to exercise (Crawford 2010).

Clearly, the coarctation of the aorta represents a lifelong disorder consisting of more than a narrowing of an aortic segment. After surgical or catheter-based intervention these patients require persistent follow-up, preferably in a center that specializes in adults with congenital heart disease. Along with the regular follow-up and specific medical therapy, it is recommended that such patients undergo physical exercise and cardiovascular prevention training in order to lower their cardiovascular risk.

References

Aboulhosn J, Child JS (2006) Left ventricular outflow obstruction: subaortic stenosis, bicuspid aortic valve, supravalvar aortic stenosis, and coarctation of the aorta. Circulation 114(22):2412–2422. http://circ.ahajournals.org/cgi/pmidlookup?view=long&pmid=17130357

Alonso M, Tascón J, Hernández F, Andreu J, Albarrán A, Velázquez MT (2003) Complications with femoral access in cardiac cathetization. Impact of previous systematic femoral angiography and hemostasis with VasoSeal-ES® collagen plug. Rev Esp Cardiol 56(6):569–577

American Society of Nuclear Cardiology Images (1999) Imaging guidelines form nuclear cardiology procedures part II. J Nucl Cardiol 6:G47–G84

Anderson RH, Baker EJ et al (2010) Paediatric cardiology, 3rd edn. Churchill Livingstone, London

Anderson RH, Spicer DE et al (2013) Wilcox's surgical anatomy of the heart, 4th edn. Cambridge University Press, Cambridge

Arciero TJ, Jacobsen SJ, Reeder GS et al (2004) Temporal trends in the incidence of coronary disease. Am J Med 117:228

Ashley EA, Niuebauer J (2004) Cardiology explained. Remedica, London

Baim DS, Grossman W (1996) Complications of cardiac catheterization. In: Cardiac catheterization, angiography and intervention. Williams & Wilkins, Baltimore, p 17

Barbosa D, Dietenbeck T, Heyde B, Houle H, Friboulet D, D'hooge J, Bernard O (2013) Fast and fully automatic 3-d echocardiographic segmentation using B-spline explicit active surfaces: feasibility study and validation in a clinical setting. Ultrasound Med Biol. 39(1):89–101. doi:10.1016/j.ultrasmedbio.2012.08.008

Barry FA et al (2014) Impact of diet and exercise on lipid management in the modern era. Best Pract Res Clin Endocrinol Metab 28(3):405–421. http://www.bprcem.com/article/S1521-690X(14)00021-9/abstract

Baskot B (2011) Coronary angiography—advances in noninvasive imaging approach for evaluation of coronary artery disease. ISBN 978-953-307-675-1. https://www.intechopen.com/books/coronary-angiography-advances-innoninvasive-imaging-approach-for-evaluation-of-coronary-artery-disease/contrast-echocardiography-incoronary-artery-disease. Published 15 Sept 2011 under CC BY-NC-SA 3.0 license

Betriu A, Heras M, Cohen M et al (1992) Unstable angina: outcome according to clinical presentation. J Am Coll Cardiol 19:1659–1663

Bouzas-Mosquera A, Peteiro J, Alvarez-García N et al (2009) Prognostic value of exercise echocardiography in patients with left bundle branch block. JACC Cardiovasc Imaging 2:251–259

Buja LM, McAllister HA Jr (2007) Atherosclerosis: pathologic anatomy and pathogenesis. In: Willerson JT, Cohn JN, Wellens HJJ, Holmes DR Jr (eds) Cardiovascular medicine, 3rd edn. Springer, London, pp 1581–1591

Burke AP, Farb A, Malcom GT et al (1997) Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. N Engl J Med 336:1276–1282

Burke AP, Kolodgie FD, Farb A et al (2001) Healed plaque ruptures and sudden coronary death: evidence that subclinical rupture has a role in plaque progression. Circulation 103:934–940

Calderón-Colmenero J, Attie F (2008) Aortic coarctation. important considerations in long-term follow-up after correction. Rev Esp Cardiol 61(11):1117–1119. Available from http://linkinghub.elsevier.com/retrieve/pii/S1885585709600232

Califf RM (1998) Ten years of benefit from a one-hour intervention. Circulation 98:2649–2651

Cassese S, Kastrati A (2016) Bioresorbable vascular scaffold technology benefits from healthy skepticism. J Am Coll Cardiol 67(8):932–935. doi:10.1016/j.jacc.2015.12.020

Cerqueira MD, Weissman NJ, Dilsizian J et al (2002) Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals form the Cardiac Imaging Comitee of the Council of Clinical Cardiology of the American Heart Association. Circulation 105:539–542

Cortigiano L, Picano E, Vigna C et al (2001) Prognostic value of pharmacologic stress echocardiography in patients with left bundle branch block. Am J Med 110:361–389

Crawford MH (ed) (2010) Cardiology. Elsevier Saunders, Philadelphia

D'Ascenzo F, Barbero U (2015) Accuracy of intravascular ultrasound and optical coherence tomography in identifying functionally significant coronary stenosis according to vessel diameter. Am Heart J 169(5):663–673

Dangas GD, Claessen BE, Caixeta A, Sanidas EA, Mintz GS, Mehran R (2010) In-stent restenosis in the drug-eluting stent era. J Am Coll Cardiol 56(23):1897

Davies MJ, Bland JM, Hangartner JR et al (1989) Factors influencing the presence or absence of acute coronary artery thrombi in sudden ischaemic death. Eur Heart J 10:203–208

De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Mobius-Winkler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engstrom T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Juni P, Fearon WF, Investigators FT (2012) Fractional flow reserve-guided PCI vs. medical therapy in stable coronary disease. N Engl J Med 367(11):991–1001

Dewey M (2009) Coronary CT angiography. Springer, Heidelberg

Ehara S, Kobayashi Y, Yoshiyama M et al (2004) Spotty calcification typifies the culprit plaque in patients with acute myocardial infarction: an intravascular ultrasound study. Circulation 110:3424–3429

Erbel R, Aboyans V, Boileau C, Bossone E, Di Bartolomeo R, Eggebrecht, et al (2014) 2014 ESC guidelines on the diagnosis and treatment of aortic diseases. Eur Heart J 35(41):2873–2926. https://academic.oup.com/eurheartj/article-lookup/doi/10.1093/eurheartj/ehu281

Erben Y, Oderich GS, Verhagen HJ, Witsenburg M, Van den Hoven AT, Debus ES et al (2015) Abstract 10340: multi-center experience with endovascular treatment of aortic coarctation and post-surgical complications of coarctation repair in adults. Circulation 132(suppl 3):A10340–A10340

Estruch R et al (2013) Primary prevention of cardiovascular disease with a mediterranean diet. N Engl J Med 368:1279–1290

Falk E (1983) Plaque rupture with severe pre-existing stenosis precipitating coronary thrombosis. Characteristics of coronary atherosclerotic plaques underlying fatal occlusive thrombi. Br Heart J 50:127–134

Falk E, Shah PK, Fuster V (1995) Coronary plaque disruption. Circulation 923:657–671

Falk E, Shah PK, Fuster V (2004) Atherothrombosis and thrombosis-prone plaques. In: Fuster V, Alexander RW, O'Rourke RA (eds) Hurst's the heart, 11th edn. McGraw-Hill, New York, pp 1123–1139

Fischer JJ, Samady H, McPherson JA, Sarembock IJ, Powers ER, Gimple LW, Ragosta M (2002) Comparison between visual assessment and quantitative angiography versus fractional flow reserve for native coronary narrowings of moderate severity. Am J Cardiol 90(3):210–215

Ford ES, Ajani UA, Croft JB et al (2007) Explaining the decrease in U.S. deaths from coronary disease, 1980–2000. N Engl J Med 356:2388

Fuster V, Walsh RA, Harrington RA (eds) (2011) Hurst's the heart, 13th edn. McGraw-Hill, New York

Gage JE, Hess OM, Murakami T et al (1986) Vasoconstriction of stenotic coronary arteries during dynamic exercise in patients with classic angina pectoris: reversibility by nitroglycerin. Circulation 73:865–876

Gallagher KP, Matsuzaki M, Koziol JA et al (1984) Regional myocardial perfusion and wall thickening during ischaemia in conscious dogs. Am J Phys 247:H727–H738

Gimbrone MA (2010) The Gordon Wilson lecture. Understanding vascular endothelium: a pilgrim's progress. Endothelial dysfunction, biomechanical forces and the pathobiology of atherosclerosis. Trans Am Clin Climatol Assoc 121:115–127

Halkin A, Mehran R, Casey CW et al (2005) Impact of moderate renal insufficiency on restenosis and adverse clinical events after paclitaxel-eluting and bare metal stent implantation: results from the TAXUS-IV Trial. Am Heart J 150:1163

Hannawi B, Lam WW, Wang S, Younis GA (2014) Current use of fractional flow reserve: a nationwide survey. Tex Heart Inst J 41(6):579–584. doi:10.14503/THIJ-13-3917

Heijenbrok-Kal MH, Fleischmann KE, Hunink MG (2007) Stress echocardiography, stress single-photon-emission computed tomography and electron beam computed tomography for the assessment of coronary artery disease: a meta-analysis of diagnostic performance. Am Heart J 154:415–423

Heimdal A, Stoylen A, Storp H et al (1998) Real time strai rate imaging of the left ventricle by ultrasound. J Am Soc Echocardiogr 11:1013–1019

Hodes HL, Steinfeld L, Blumenthal S (1959) Congenital cerebral aneurysms and coarctation of the aorta. Arch Pediatr 76(1):28–43. Available from http://www.ncbi.nlm.nih.gov/pubmed/13618092

Hollander W (1976) Role of hypertension in atherosclerosis and cardiovascular disease. Am J Cardiol 38(6):786–800

Hutcheson JD, Maldonado N, Aikawa E (2014) Small entities with large impact: microcalcifications and atherosclerotic plaque vulnerability. Curr Opin Lipidol 25(5):327–332

Jenkins C, Bricknell K, Chan J et al (2007) Comparision of two and three dimensional echocardiography with sequential magnetic resonance imaging for evaluating left ventricular volume and ejection fraction over time in patients with healed myocardial infarction. Am J Cardiol 99:300–306

Johnson LW, Lozner EC, Johnson S, Krone R, Pichard AD, Vetrovec GW, Noto TJ (1989) Coronary arteriography 1984–1987: a report of the registry of the society for cardiac angiography and interventions. I. Results and complications. Catheter Cardiovasc Diagn 17(1):5

de Jong MC, Genders TS, van Geuns RJ, Moelker A, Hunink MG (2012) Diagnostic performance of stress myocardial perfusion imaging for coronary artery disease: a systematic review and meta-analysis. Eur Radiol 22:1881–1895

Kerber RE, Abboud FM (1973) Echocardiographic detection of regional myocardial infarction. An experimental study. Circulation 4:997–1005

Kirkpatrick JN, Lang RM, Savitri E (2005) Automated border detection on contrast enhanced echocardiographic images. Int J Cardiol 103:164–167

Klabunde RE (2012) Cardiovascular physiology concepts. Lippincot Williams & Wilkins, Baltimore, p 257

Kolodgie FD, Burke AP, Farb A et al (2001) The thin-cap fibroatheroma: a type of vulnerable plaque: the major precursor lesion to acute coronary syndromes. Curr Opin Cardiol 16:285–292

Koskinas KC et al (2010) Natural history of experimental coronary atherosclerosis and vascular remodeling in relation to endothelial shear stress: a serial, in vivo intravascular ultrasound study. Circulation 121(19):2092–2101

Krueger K, Zaehringer M, Strohe D, Stuetzer H, Boecker J, Lackner K (2005) Postcatheterization pseudoaneurysm: results of US-guided percutaneous thrombin injection in 240 patients. Radiology 236(3):1104

Kwok CS, Kontopantelis E, Myint PK, Zaman A, Berry C, Keavney B, Nolan J, Ludman PF, de Belder MA, Buchan I, Mamas MA (2015) Stroke following percutaneous coronary intervention: type-specific incidence, outcomes and determinants seen by the British Cardiovascular Intervention Society 2007–12. Eur Heart J 36(25):1618–1628. doi:10.1093/eurheartj/ehv113. Epub 2015 Apr 20

Lang RM, Badano LP, Mor Avi V et al (2015) Recommendation for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 28:1–39

Leitman M, Lysysansky P, Sidenko S et al (2004) Two-dimensional strain – a novel software for real time quantitative echocardiographic assessment of myocardial function. J Am Soc Echocardiogr 17:1021–1029

Lenihan DJ, Gerson MC, Hoit BD et al (1995) Mechanisms, diagnosis, and treatment of diastolic heart failure. Am Heart J 130:153–166

Lilly LS (ed) (2011) Pathophysiology of heart disease: a collaborative project of medical students and faculty, 5th edn. Lippincott Williams & Wilkins, Baltimore

Lüscher TF, Steffel J, Eberli FR et al (2007) Drug-eluting stent and coronary thrombosis: biological mechanisms and clinical implications. Circulation 115:1051

Lyoyd-Jones D, Adams RJ, Brown TM et al (2010) Executeve summary: heart disease and stroke statistics-2010 update: a report from American Heart Association. Circulation 121:948

Mann JM, Kaski JC, Pereira WI et al (1998) Histological patterns of atherosclerotic plaques in unstable angina patients vary according to clinical presentation. Heart 80:19–22

Mann DL, Zipes DP, Libby P, Bonow RO, Braunwald E (2015) Braunwald's heart disease: a textbook of cardiovascular medicine, 10th edn. Elsevier-Saunders, Philadelphia. https://www.amazon.com/Braunwalds-Heart-Disease-E-Book-Cardiovascular-ebook/dp/B00MEIYKXY/ref=mt_kindle?_encoding=UTF8&me=

Martin JM, Stephens JC (2013) Cardiovascular hemodynamics [Internet]. 204:742. Available from http://link.springer.com/10.1007/978-1-60761-195-0

McEvoy JW, Blaha MJ et al (2015) Cigarette smoking and cardiovascular events. role of inflammation and subclinical atherosclerosis from the multiethnic study of atherosclerosis. Arterioscler Thromb Vasc Biol 35:700–709

Miller JM, Rochitte CE, Dewey M, Arbab-Zadeh A, Niinuma H, Gottlieb I, Paul N, Clouse ME, Shapiro EP, Hoe J, Lardo AC, Bush DE, de Roos A, Cox C, Brinker J, Lima JA (2008) Diagnostic performance of coronary angiography by 64-row CT. N Engl J Med 359:2324–2233

Mintz GS, Nissen SE, Anderson WD, Bailey SR, Erbel R, Fitzgerald PJ, Pinto FJ, Rosenfield K, Siegel RJ, Tuzcu EM, Yock PG (2001) American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement, Reporting of Intravascular Ultrasound Studies (IVUS). A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 37(5):1478–1492

Mittleman MA, Mostofsky E (2011) Physical, psychological and chemical triggers of acute cardiovascular events: preventive strategies. Circulation 124:346–354

Moller JE, Hillis GS, Jae KO (2006) Wall motion score index and ejection fraction for risk stratification after acute myocardial infarction. Am Heart J 151:419–425

Montalescot G, Sechtem U, Achenbach S et al (2013) ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 34:2949

Moodie DS (ed) (2014) Clinical management of congenital heart disease from infancy to adult. Cardiotext Publishing, Minneapolis

Morise AP, Diamond GA (1995) Comparison of the sensitivity and specificity of exercise electrocardiography in biased and unbiased populations of men and women. Am Heart J 130:741–747

Moscucci M (ed) (2014) Grossman & Baim's cardiac catheterization, angiography and intervention, 8th edn. Lippincot Williams & Wilkins, Baltimore

Mukherjee D, Bates ER, Roffi M, Moliterno DJ (2010) Cardiovascular catheterisation and intervention. In: A textbook of coronary, peripheral and structural heart disease. Informa Healthcare, New York

Muller JE, Stone PH, Turi ZG, Rutherford JD, Czeisler CA, Parker C, Poole WK, Passamani E, Roberts R, Robertson T (1985) Circadian variation in the frequency of onset of acute myocardial infarction. N Engl J Med 313:1315–1322

Nihoyannopoulos P, Kaski J-C, Crake T et al (1991) Absence of myocardial dysfunction during stress in patients with syndrome X. J Am Coll Cardiol 18:1463–1470

Ogawa S, Fujii I, Yoshino H et al (1985) Values of electrocardiography and two dimensional echocardiography to identify myocardial infarction due to left circumflex and right coronary artery disease. Clin Cardiol 8:269–275

Ohman EM et al, REACH Registry Investigators (2006) The REduction of atherothrombosis for continued health (REACH) Registry: an international, prospective, observational investigation in subjects at risk for atherothrombotic events-study design. Am Heart J 151(4):786.e1–10

Oudkerk M, Reiser MF (2008) Coronary radiology, 2nd revised edn. Springer, New York

Pappano AJ, Wier WG (2013) Cardiovascular physiology, 10th edn. Elsevier-Mosby, Philadelphia

Paulson EK, Sheafor DH, Kliewer MA, Nelson RC, Eisenberg LB, Sebastian MW, Sketch MH Jr (2000) Treatment of iatrogenic femoral arterial pseudoaneurysms: comparison of US-guided thrombin injection with compression repair. Radiology 215(2):403–408

Picano E (1989) Dipyridamole-echocardiography test: historical background and physiologic basis. Eur Heart J 10:365–376

Pierard LA, Sprynger M, Gilis F (1986) Significance of precordial ST segment depression in inferioa acute myocardial infarction as determined by echocardiography. Am J Cardiol 57:82–85

Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, Bar F, Hoorntje J, Koolen J, Wijns W, de Bruyne B (2007) Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. J Am Coll Cardiol 49(21):2105–2111

Popescu BA, Antonini Canterin F, Gianuzii P et al (2004) Left atrium remodeling after acute myocardial infarction: results of the GISSI-3 echo sub-study. J Am Coll Cardiol 43(9):1156

Prati F, Guagliumi G, Mintz GS, Costa M, Regar E, Akasaka T, Barlis P, Tearney GJ, Jang IK, Arbustini E, Bezerra HG, Ozaki Y, Bruining N, Dudek D, Radu M, Erglis A, Motreff P, Alfonso F, Toutouzas K, Gonzalo N, Tamburino C, Adriaenssens T, Pinto F, Serruys PW, Di Mario C (2012) Expert review document part 2: methodology, terminology and clinical applications of optical coherence tomography for the assessment of interventional procedures. Eur Heart J 33(20):2513–2520

Ramanathan T, Skinner H (2005) Coronary blood flow. Contin Educ Anaesth Crit Care Pain 5(2):61–64

Reiner Z et al (2011) ESC/EAS Guidelines for the management of dyslipidemias. Eur Heart J 32(14):1769–1818

Roffi M, Patrono C, Collet JP et al (2015) 2015 ESC guidelines for the management of acute coronary syndrome in patients presenting without persistent ST-segment elevation. Eur Heart J. doi:10.1093/eurheartj/ehv320

Rosa S, Nihoyannopoulos P, Evangelista A et al (2008) Stress echocardiography expert consensus statement. Eur J Echocardiogr 9:415–437

Sarno G, Lagerqvist B, Fröbert O et al (2012) Lower risk of stent thrombosis and restenosis with unrestricted use of 'new-generation' drug-eluting stents: a report from the nationwide Swedish Coronary Angiography and Angioplasty Registry (SCAAR). Eur Heart J 33:606

Schaar JA, Muller JE, Falk E et al (2004) Terminology for high-risk and vulnerable coronary artery plaques. Report of a meeting on the vulnerable plaque, June 17 and 18, 2003, Santorini, Greece. Eur Heart J 25:1077–1082

Senior R, Lahiri A (1995) Enhanced detection of myocardial ischaemia by stress dobutamine echocardiography utilizing the 'biphasic' response of wall thickening during low and high dose dobutamine infusion. J Am Coll Cardiol 26:26–32

Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJ, Schonberger JP, Buller N, Bonser R, van den Brand MJ, van Herwerden LA, Morel MA, van Hout BA (2001) Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med 344(15):1117–1124

Serruys PW, Wijns W, Vahanian A, van Sambeek A, Rodney de Palma Eric Eeckhout (2010) Percutaneous interventional cardiovascular medicine—The PCR-EAPCI textbook. https://www.pcronline.com/eurointervention/textbook/pcr-textbook/table-of-contents/

Servoss SJ, Januzzi JL, Muller JE (2002) Triggers of acute coronary syndromes. Prog Cardiovasc Dis 44:369–380

Sherif FN, Christopher PA, Thierry CG et al (2009) Al recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 22:107–133

Shimada E, Zhu M, Kimura S, Streiff C, Houle H, Datta S, Sahn DJ, Ashraf M (2015) Quantitative assessment of mitral inflow and aortic outflow stroke volumes by 3-dimensional real-time full-volume color flow doppler transthoracic echocardiography: an in vivo study. J Ultra Med 34(1):95–103

Smith DL, Fernhall B (2011) Advanced cardiovascular exercise physiology [Internet], p 227. Available from http://books.google.com/books?id=gBExM6v-XPcC&pgis=1

Steg G, James SK, Atar D, Badano LP, Lundqvist C, Borger MA et al (2012) ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 33:2569–2619

Stone GW, Moses JW, Ellis SG, Schofer J, Dawkins KD, Morice MC, Colombo A, Schampaert E, Grube E, Kirtane AJ, Cutlip DE, Fahy M, Pocock SJ, Mehran R, Leon MB (2007) Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. N Engl J Med 356(10):998

Stone GW et al, PROSPECT Investigators (2011) A prospective natural-history study of coronary atherosclerosis. N Engl J Med 364:226–235

Sun Z, Cheng TO, Li L, Zhang L, Wang X, Dong N et al (2015) Diagnostic value of transthoracic echocardiography in patients with coarctation of aorta: the Chinese experience in 53 patients studied between 2008 and 2012 in one major medical center. PLoS One 10(6):e0127399

Temporelli PL, Gianuzii P, Nicolosi GL et al (2004) Doppler derived decelaration time as a strong prognostic marker of left ventricular remodeling and survival aftare acute myocardial infarction: results of the GISSI-3 echo sub-study. J Am Coll Cardiol 43:1646–1653

Tennant R, Wiggers CJ (1935) The effect of coronary occlusion on myocardial contraction. Am J Phys 112:351–361

Thavendiranathan P, Liu S, Datta S, Walls M, Nitinunu A, Van Houten T, Tomson NA, Vidmar L, Georgescu B, Wang Y, Srinivasan S, De Michelis N, Raman SV, Ryan T, Vannan MA (2012) Automated quantification of mitral inflow and aortic outflow stroke volumes by three-dimensional real-time volume color-flow Doppler transthoracic echocardiography: comparison with pulsed-wave Doppler and cardiac magnetic resonance imaging. J Am Soc Echocardiogr 25(1):56–65. doi:10.1016/j.echo.2011.10.004. Epub 2011 Nov 21

Theroux P (2011) Acute coronary syndromes. Companion to Braunwald's heart disease, 2nd edn. Elsevier-Saunders, Philadelphia

Theroux P, Franklin D, Ross J Jr, Lemper WS (1974) Regional myocardial function during acute coronary artery occlusion and its modification by pharmacological agent in the dog. Circ Res 34:896–908

Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van't Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF, Investigators FS (2009) Fractional flow reserve vs. angiography for guiding percutaneous coronary intervention. N Engl J Med 360(3):213–224

Varnava AM, Davies MJ (2001) Relation between coronary artery remodelling (compensatory dilatation) and stenosis in human native coronary arteries. Heart 86:207–211

Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM (2000) Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. Arterioscler Thromb Vasc Biol 20:1262–1275

Virmani R, Kolodgie FD, Burke AP, Finn AV, Gold HK, Tulenko TN, Wrenn SP, Narula J (2005) Atherosclerotic plaque progression and vulnerability to rupture: angiogenesis as a source of intraplaque hemorrhage. Arterioscler Thromb Vasc Biol 25:2054–2061

Virmani R, Burke AP, Farb A, Kolodgie FD (2006) Pathology of the vulnerable plaque. J Am Coll Cardiol 47:C13–C18

Voigt JU, Exner B, Schmiedehauser K et al (2003a) Strain rate imaging during dobutamine stress echocardiography provides objective of inducible ischemia. Circulation 107:2120–2126

Voigt JU, Lindenmeier G, Exner B et al (2003b) Incidence an characteristics of segmental postsystolic longitudinal shortening in normal, acutely ischemic and scarred myocardium. J Am Soc Echocardiogr 16:415–423

Voigt JU, Scheider TM, Korder S et al (2009) Apical transverse motion as surrogate parameter to determine left ventricular function inhomogeneities: a new integrative approach to left ventricular asynchrony assessment. Eur Heart J 30:959–968

Wang S, Fleischmann EK (2001) The role of echocardiographic evaluation in patients with acute chest pain in the emergency room. In: Otto C (ed) The practice of clinical echocardiography. WB Saunders, Philadelphia

Warnes CA (2009) Coarctation of the aorta and aortic disease. In: Michelle Z (ed) Gurvitz. http://eu.wiley.com/WileyCDA/WileyTitle/productCd-1405178205.html

WHO (2011) Global atlas on cardiovascular disease prevention and control. World Health Organization, Geneva

Wier WG, Pappano AJ (2013) Cardiovascular physiology, 10th edn, p 292. https://elsevier.ca/product.jsp?isbn=9780323086974

Willerson JT, Holmes DR (2015) Coronary artery disease. Springer, London, pp 3–4

Willerson JT, Wellens HJJ, Cohn JN, Holmes DR (eds) (2007) Cardiovascular medicine, 3rd edn. J Chem Inf Modeling, vol 53. Springer. http://www.springer.com/la/book/9781846281884

Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Juni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A, Authors/Task Force members (2014) 2014 ESC/EACTS guidelines on myocardial revascularization: the task force on myocardial revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 35(37):2541–2619

Wyman RM, Safian RD, Portway V, Skillman JJ, McKay RG, Baim DS (1988) Current complications of diagnostic and therapeutic cardiac catheterization. J Am Coll Cardiol 12(6):1400–1406