Chapter

Ischemic Heart Disease

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Abstract

All over the world ischemic heart disease remains as the leading cause of death, followed by stroke. Ischemic heart disease, also called coronary artery disease has a broad spectrum of clinical manifestations from the acute coronary syndromes which include, unstable angina pectoris and acute myocardial infarction with and without elevation of the ST segment and chronic coronary disease. In patients with diabetes mellitus the cardiovascular complications mainly ischemic heart disease, are the main cause of morbidity and mortality. However, in population-based studies, the risk of heart failure in patients with diabetes mellitus is significantly increased following adjustment for well-established heart failure risk factors such as hypertension or ischemic heart disease. Ischemic heart failure angiographically diagnosed is associated with a shorter survival than non-ischemic heart failure. Coronary artery disease is independently associated with higher mortality.

Keywords: myocardial infarction, coronary artery disease, heart failure, Ischemic heart disease

1. Introduction

Ischemic disorders, such as peripheral vascular disease, stroke and myocardial infarction, are the most common causes death in the world. Cardiovascular diseases are the main cause of death globally, with an estimated 17.9 million deaths each year, representing 31% of all global deaths. Of these deaths, 85% are a consequence of myocardial infarction and stroke. Over 75% of cardiovascular disease deaths take place in low- and middle-income countries [1]. The main cause of myocardial infarction is coronary artery disease, and in turn the main cause of coronary artery disease is atherosclerosis. The rupture of atheroma plaque is the event that lead to the thrombus formation with the subsequent occlusion of the blood supply distal to the affected vessel segment. The magnitude of the tissue injury is directly related to the extent of the territory affected by the reduction in blood flow and the length of the ischemic period, which influences the levels at which intracellular pH and ATP are reduced. Follow-up of groups of patients with characteristics that favor the appearance of atherosclerosis over time, has allowed the identification of risk factors for cardiovascular disease, as well as the development of various predictive models, such as the Framingham score.

The main cause of ischemic heart disease is coronary artery disease caused by atherosclerosis. There are secondary causes of ischemia, these can cause ischemic heart disease and non-obstructive myocardial infarction of the coronary arteries (INOCA and MINOCA), these secondary causes are classified in coronary, myocardial and non-cardiac causes.

2. Atherosclerotic artery disease

The term atherosclerosis is rooted in the Greek word αθερα ("athero", which means crushed food in the form of a mass) for the aspect of the necrotic core area and the word σκλεροζ ("scleros" which means hard) for hardening or induration, referring to the fibrous layer of the luminal edge. Atherosclerosis is an inflammatory process that begins from childhood and develops over the years, is asymptomatic most of the time; is distinguished by retention, oxidation and modification of lipids in the form of fatty streaks on the walls of the arteries that later evolve to fibrous plaques causing wall thickening in the affected artery, decreasing its internal diameter over time. Rupture of this plaque cause thrombosis and occlusion of the blood supply to the myocardial tissue irrigated by the affected artery [2].

The main cause of Ischemic heart disease is atherosclerosis. Coronary atherosclerotic disease can be classified into three types: obstructive coronary artery disease, non-obstructive coronary artery disease, and microvascular coronary artery disease. In addition to arteriosclerosis and thrombosis of the coronary arteries, other causes of acute myocardial infarction are extremely rare. Cases have been described of infarction caused by embolization within the coronary arteries from clot fragments from elsewhere, or septic embolization due to endocarditis of the aortic valve.

3. Definition of myocardial infarction

The introduction of more sensitive cardiac biomarkers has led the American College of Cardiology (ACC) and the European Society of Cardiology (ESC) to collaborate for the redefinition of myocardial infarction using a clinical and biochemical approach. These societies reported that myocardial injury detected by abnormal biomarkers in the context of acute myocardial ischemia should be labeled as in the fourth universal definition of myocardial infarction. In other words, myocardial infarction is defined as the presence of acute myocardial damage detected by the elevation of cardiac biomarkers in the context of evidence of acute myocardial ischemia [3].

Myocardial infarction can be defined from the point of view of pathological anatomy as myocardial cell death due to prolonged ischemia. The first ultrastructural changes are diminished cellular glycogen, sarcolemmal disruption, and relaxed myofibrils and they are seen as early as 10–15 min after the onset of ischemia. Mitochondrial abnormalities are observed as early as 10 minutes after coronary occlusion by electron microscopy [4, 5].

Cardiac troponins are regulatory proteins that mediate interaction between actin and myiosin, there are two types of cardiuacx troponins; troponin T (cTnT) and troponin I (cTnI), The cTnI has not been identified outside the myocardium. Cardiac troponin T is expressed to a small extent in skeletal muscle; however, the current cTnT assay does not identify skeletal troponins Myocardial injury is defined by detection of an elevated cardiac troponin (cTn) value above the 99th percentile URL. The injury is considered acute if there is a rise and/or fall of cTn values. The biomarkers of choice for the evaluation of myocardial damage are cTnI and cTnT; the use of high-sensitivity cTn (hs-cTn) is recommended in routine clinical practice [6]. Other biomarkers, such as the MB fraction of creatine kinase (CK-MB), are less sensitive and specific (**Table 1**).

Of patients with acute coronary syndrome, 1 to 14% do not have identifiable obstructive coronary lesions on coronary angiography.

Classification of myocardial infarction	
Myocardial infarction type I	Usually precipitated by atherosclerotic plaque disruption in atherothrombotic coronary artery disease.
Myocardial infarction type 2	Caused by mismatch between oxygen supply and demand, the pathophysiological mechanism lead to ischaemic myocardial injury.
Myocardial infarction type 3	Patients that manifest with a typical presentation of myocardial ischemia/infarction, including presumed new ischaemic ECG changes or ventricular fibrillation, and die before it is possible to obtain blood for cardiac biomarker determination; or the patient may succumb soon after the onset of symptoms before an elevation of biomarker values has occurred.
Myocardial infarction type 4	Type 4a. Associated with percutaneous coronary intervention.
	Type 4b. Stent/scaffold thrombosis associated with percutaneous coronary intervention.
	Type 4c. Restenosis associated with percutaneous coronary intervention.
Myocardial infarction type 5	Associated with coronary artery bypass grafting.

Table 1.
Classification of myocardial infarction according the fourth universal definition of myocardial infarction.

Patients with myocardial infarction and non-obstructive coronary arteries (MINOCA), represent a conundrum given the many potential underlying etiologies. MINOCA is defined as angiographic stenosis <50% and myocardial infarction Possible causes of MINOCA can be subdivided into coronary, myocardial, and non-cardiac disorders (**Figure 1**).

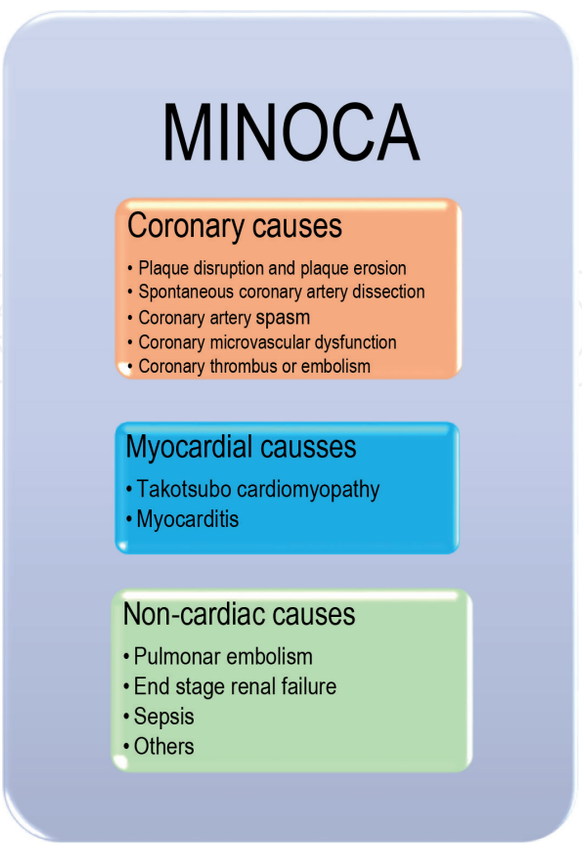

Figure 1.
Etiologies of MINOCA.

MINOCA is found in up to 14% of patients presenting with an acute coronary syndrome. Many terms have been used to describe patients with acute myocardial infarction or acute coronary syndrome with normal or near-normal coronary arteries, such as MINOCA, MINCA (MI with normal coronary arteries) and INOCA (ischemia and no obstructive coronary artery disease) The most common pathologies associated with an acute coronary syndromes are plaque rupture, erosion and calcified nodules which are present in 44%, 31% and 8% respectively.

Plaque formation starts with the formation of fatty streaks and intimal thickening, leading to fibrous cap atheroma and eventually to fibrous cap thinning. This so-called thin-cap fibroatheroma can rupture. In plaque erosion, there is an abundance of smooth muscle cells without an extensive necrotic core, hemorrhage or calcification. It differs from plaque rupture, as there is an absence of fibrous cap disruption. Identification of vulnerable plaques on coronary angiography can be challenging. Intravascular coronary imaging and computed tomography angiography could play an important role in finding these plaques in the future.

An elevated troponin beyond the 99th percentile of the upper reference level is a hallmark of myocardial injury in the same way that it is for myocardial infarction. However, myocardial injury is attributable to non-ischemic mechanisms of myocyte injury and in this way these entities differ conceptually from ischemic heart disease.

The diagnosis of MINOCA requires the fulfillment of the following criteria:

1. Acute myocardial infarction. Detection of a rise or fall of cTn value with at least one value above the 99th percentile upper reference limit and corroborative clinical evidence of infarction evidenced by at least one of the following criteria:

   - Symptoms consistent with myocardial ischemia.
   - New electrocardiographic changes consistent with ischemia.
   - Development of pathological Q waves.
   - Evidence of a new loss of viable myocardium or a new regional wall motion abnormality with a pattern consistent with an ischemic cause on imaging studies.
   - Evidence by angiography or autopsy of a coronary thrombus.

2. Evidence on angiography of non-obstructive coronary arteries, defined as the absence of obstructive disease (no coronary artery stenosis ≥50% in any major epicardial vessel). This includes the following cases:

   - Normal coronary arteries with no angiographic stenosis.
   - Angiographic stenosis with <30% stenosis and mild luminal irregularities.
   - Moderate coronary atherosclerotic lesions defined as stenosis >30% but <50%.

3. Absence of an alternate clinical diagnosis to explain the presentation

   - Alternate diagnoses include but are not limited to non-ischemic causes such as pulmonary embolism, sepsis, and myocarditis.

Among MINOCA patients coronary plaque disruption is common. The terms plaque rupture, plaque erosion, and calcific nodules are included in the term plaque disruption. Plaque rupture is an event that can trigger the formation of a thrombus that leads to myocardial infarction due to superimposed coronary spasm, distal embolization, or in some cases, transient complete thrombosis that resolves with spontaneous thrombolysis.

Coronary artery spasm is an intense vasoconstriction with more than 90% lumen occlusion of an epicardial coronary artery that compromises myocardial blood flow. Hyperresponsiveness to toxins or drugs of vascular smooth muscle cells can lead to vasospasm of the coronary arteries, or it can occur spontaneously due to disorders in coronary vasomotor tone.

In 30–50% of patients with non-obstructive coronary artery disease documented by invasive coronary angiography and presenting with chest pain or discomfort, coronary microvascular dysfunction can be detected. Microvascular dysfunction is seen more frequently in women and patients with classic cardiovascular risk factors. Microvascular dysfunction can be a cause of ischemia, but it can also be a consequence of myocardial injury.

Coronary embolism or thrombosis can cause MINOCA if it involves the microcirculation or if there is partial lysis of the epicardial coronary thrombus it can result in coronary disease that is not obstructive by coronary angiography. This can occur with or without a hypercoagulable state. Disorders with increased coagulability that cause coronary thrombosis can be classified as inherited or acquired. Among these disorders is the antiphospholipid syndrome, which is a heterogeneous disorder characterized by the presence of autoantibodies against protein-phospholipid complexes. Hereditary thrombophilia is prevalent in the general population, with a variable prevalence depending on race/ethnicity. Acquired hypercoagulable states include thrombotic thrombocytopenic purpura, antiphospholipid syndrome, heparin-induced thrombocytopenia, and myeloproliferative neoplasms.

Spontaneous coronary artery dissection is a relatively rare non atherosclerotic mechanism of myocardial infarction. The separation of the medial and adventitial vascular walls associated with intramural hematoma protrusion into the lumen cause obstruction to coronary blood flow. The primary source of the dissection is still controversial and the exact mechanism is not entirely known.

4. Myocardial ischemia-reperfusion injury

Occlusion of a coronary artery causes sudden cessation of regional perfusion, rapidly leading to the cessation of aerobic metabolism, creatine phosphate depletion, and the onset of anaerobic glycolysis; this continues to build up of lactate and catabolites and progressively reduces ATP levels. If ischemia continues, tissue acidosis develops and cellular ion exchange is impaired, the function of the cell membrane is impaired, triggering the onset of myocyte death. Irreversible myocardial damage begins in the subendocardium 20 minutes after coronary occlusion and extends as a wave front towards the subepicardial layers; after one hour of coronary occlusion, the dependent subendocardium and part of the myocardium are irreversibly damaged; transmural extension is completed with 4–6 h of ischemia.

Reperfusion entails a replenishment of substrates, mainly oxygen, which will intervene in the oxidation of fatty acids at the mitochondrial level. Complete restoration of contractile function is achieved when adenosine triphosphate (ATP) levels normalize and excess adenosine diphosphate (ADP, platelet aggregation agonist) disappears. There are other factors, such as changes in calcium flux due to membrane alterations or alterations in the metabolism of free fatty acids, which

are responsible for the prolonged abnormality of contraction after ischemia [7–9]. Endothelial damage activates the coagulation cascade with platelet and red cell aggregation that contribute to microvascular dysfunction [10]; the inflammatory response with complement activation also influences myocardial perfusion dysfunction [11] and other changes such as glycogen and ATP depletion, mitochondrial edema and nuclear chromatin clumping correlate with worsening myocardial function after ischemia (stunned myocardium) [12–14].

Reperfusion of the affected vessel during an acute myocardial infarction is crucial to save the ischemic myocardium, but it also causes a metabolic injury that can be reversible, as in the case of myocardial stunning [15–17], but it can also be irreversible and manifest as microvascular dysfunction and an increase in the size of the infarcted myocardium. This phenomenon is known as myocardial ischemia–reperfusion injury.

Several molecular mechanisms have been shown to be involved in the etiology of myocardial ischemia–reperfusion injury including defects in calcium handling, mitochondrial damage, reactive oxygen species production, and inflammation.

5. Apoptosis

Both calcium overload and oxidative stress can induce on the mitochondrial permeability transition pores abrupt opening. This abrupt opening of these pores causes uncoupling of oxidative phosphorylation and mitochondrial swelling, thereby inducing apoptosis and cell necrosis [18–19]. The apoptosis process is energy-dependent. It gets activated during ischemia, but it is not effected until the oxygen supply is reinitiated during reperfusion. Caspase activation is a primordial event in apoptosis. Caspase inhibition during early reperfusion has been demonstrated to protect the myocardium against reperfusion injury in a murine model [20].

6. Defects in calcium handling

For the maintenance of the excitation-contraction coupling in cardiomyocytes, calcium homeostasis plays an essential role. During the cardiac action potential, extracellular calcium enters the cell through L-type calcium channels, the ryanodine receptor 2 (RyR2) is activated by intracellular calcium leading to increased release of calcium from the sarcoplasmic reticulum. Intracellular calcium present at a certain level cause myocardial contraction, by binding to the myofilament of the contractile protein troponin C. On the one hand, the sarcoplasmic reticulum calcium-ATPase (SERCA) recaptures intracellular calcium, bringing it back to the sarcoplasmic reticulum. On the other hand, the sodium-calcium exchanger (NCX) expels calcium from the cells and the dissociation of calcium from the myofilament protein leads to cardiomyocite relaxation. SERCA, NCX, RyR2, and mitochondria regulate the calcium levels in myocardial cells, and also participate in calcium overload during ischemic injury. The common clinical characteristics of the myocardial induced reperfusion injury are myocardial reperfusion arrhythmias, stunning, intramyocardial hemorrhage, microvascular obstruction, and enlargement of the myocardial infarction [21–24].

After a period of hypoxia and ischemia, myocardial cells have an increase in anaerobic metabolism, this leads to the intracellular aggregation of hydrogen ions, which causes a low intracellular pH and an increase in intracellular sodium through hydrogen-sodium exchange (HNX). Excess intracellular sodium leads to sodium

excretion and calcium uptake by the sodium calcium exchanger ultimately resulting in calcium overload.

Calcium plays a fundamental role in the coupling of cardiac excitation-contraction. Thus, the calcium overload will increase the reperfusion injury and the size of the infarcted myocardium. Excess intracellular calcium will enter the mitochondria and this excess mitochondrial calcium inhibits ATP production, exacerbates energy metabolism disorders, and ultimately leads to apoptosis of myocardial cells. Mitochondrial damage is known to be a marker of irreversible damage in cardiomyocytes [25–26].

Disturbances of calcium homeostasis play a key role in the development of reperfusion arrhythmias, including idioventricular rhythm, ventricular tachycardia, and ventricular fibrillation [27]. Inhibition of intracellular calcium overload improves recovery of cardiac function [28].

7. Autophagy and mitophagy

The phenomenon called "mitophagy" consists of the activation of cellular autophagy and degradation of damaged mitochondria by lysosomes and is generally beneficial because they reduce the reperfusion injury [29].

Ischemia is known to stimulate autophagy. This occurs through a mechanism dependent on adenosine monophosphate activated protein kinase (AMPK), while ischemia–reperfusion causes left ventricular dysfunction and autophagic myocardial cell death through a Beclin-1 dependent mechanism, but independent of AMPK. The increase in autophagosomes containing damaged mitochondria is associated with the latter event [30, 31].

8. Inflammation

A sequence of cellular events leading to collagen-based scar formation leads to healing of the infarcted myocardium. This is a consequence of the fact that the heart of adult mammals has little regenerative capacity. Three overlapping phases describe the repair of the infarcted myocardium: the inflammatory, the proliferative and the maturation phases. Inflammation exerts a key role in cardiovascular diseases, as extensively reported in the literature. Inflammatory responses exert a different effect in the acute and chronic phase. Activation of inflammatory responses acutely contributes to the healing process including release of cytokines and infiltration of inflammatory cells into the myocardium, while prolonged activation of inflammation triggers pro-apoptotic pathways [32–34].

Reperfusion of the infarcted area of the myocardium triggers a complex inflammatory reaction accompanied by infiltration of inflammatory leukocytes into the compromised myocardial region and the release of cytokines. This release of cytokines and the inflammatory response after myocardial infarction are an integral part of the healing process and contribute to the remodeling of cardiac tissue, however, excessive inflammatory responses are detrimental to the integrity of the extracellular matrix and to cell survival. This occurs through enhanced activation of pro-apoptotic signaling pathways, with a subsequent poor clinical outcome [35–37].

Tissue injury generates endogenous signals that activate the innate immune system; these molecules belong to a large group of mediators that warn the body of injury and are known as damage-associated molecular patterns (DAMPs). A group of structurally diverse endogenous signals are released after tissue necrosis occurs, promoting cell activation of innate immune systems through binding to recognition

pattern receptors, these are known by the term alarmins. High mobility group B1 (HMGB1) is the best characterized alarmin and is a key initiator of inflammatory injury following myocardial ischemia through actions that might involve the receptor for advanced glycation end products (RAGE) and toll-like receptors (TLRs). The fact that both harmful and beneficial effects of HMGB1 have been reported in the infarcted myocardium is not surprising given the critical role of alarmin-mediated signaling in inflammation and repair of myocardial tissue. The identification of danger signals by innate immune cells occurs through participation of TLRs, a family of transmembrane receptors that activate subsequent pro-inflammatory cascades. Studies of loss of genetic function indicate that TLR2 and TLR4, both located on the cell surface, are important mediators of the post-infarction inflammatory reaction.

A molecular program that leads to the recruitment of inflammatory cells in the healing infarct is activated by alarmin-mediated signaling. The pro-inflammatory chemokines induced in the infarcted heart generate chemotactic gradients that lead to the recruitment of subpopulations of leukocytes through interactions with the corresponding chemokine receptors. Upregulation of pro-inflammatory cytokines (such as IL-1β, members of the IL-6 family and tumor necrosis factor [TNF]) induce molecule synthesis, endothelial cell adhesion, and activate leukocyte integrins, mediating strong adhesive interactions that ultimately lead to extravasation of inflammatory cells into the infarct.

In the infarcted myocardium the expression of the two main chemokine sub families (C-C y C-X-C) mediate the inflammatory leukocyte recruitment, The neutrophyl recruitment is mediated by the chemokines CX-C with amminoacid secuence Glu-Leu-Arg which are quickly induced by the infarcted myocardium.

9. Oxidative stress

Oxidative stress can be produced from enzymatic sources and non-enzymatic sources. Common enzymatic sources include the xanthine oxidase system, mitochondrial electron transport chain, NADPH oxidase system, and uncoupled nitric oxide synthase (NOS) system. Non-enzymatic sources are a minor source of oxidative stress, and include hemoglobin and myoglobin. The xanthine oxidase system, NADPH oxidase system, and mitochondrial electron transport chain are broadly implicated in oxidative stress in several organs, including the heart, lung, brain, muscle, intestine, liver, pancreas, stomach, and kidney. NOS is a major oxidative stress factor in the liver, heart, and aortic endothelial cells [38–40].

The onset of acute myocardial ischemia during an acute myocardial infarction induces cell damage and the death of different constituents of the myocardium. This, in turn, initiates an acute pro-inflammatory response through the concerted action of several processes including the production of reactive oxygen species, the activation of the complement cascade, and the damage-associated molecular patterns that serve as ligands for pattern recognition receptors (PRRs) a family of cytosolic nucleotide-binding oligomerization domain receptors (NLRP3, also known as Nod-like receptors) and toll like receptors This result in the release of a variety of pro-inflammatory mediators such as cytokines and chemokines, which induce the recruitment of inflammatory cells into the infarcted zone, and augment the pro-inflammatory response following acute myocardial infarction.

Infiltrating leukocytes can induce cardiomyocyte death by targeting the viable borderline area of the infarct, thus extending the ischemic lesion beyond the area of the original infarction.

10. Heart failure

Heart failure is a complex syndrome responsible for high rates of death and hospitalization among the general population worldwide. One of the most frequent causes of HF is ischemic heart disease.

Heart failure is a clinical syndrome characterized by typical symptoms (breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress. Demonstration of an underlying cardiac cause is central to the diagnosis. This is usually a myocardial abnormality causing systolic and/or diastolic ventricular dysfunction (**Figure 2**).

The two main types of heart failure are the acute and chronic forms. In chronic heart failure which is the most common type, symptoms appear slowly over time and gradually worsen with various underlying mechanisms such as mechanical stress, ischemia, infections, autoimmune diseases, and genetic diseases [41–45].

The regeneration process in ischemic heart disease after myocardial infarction begins with the infiltration of leukocytes. This is triggered by ischemia and the presence of necrotic cardiomyocytes to eliminate irreparably damaged or dead cells and allows repair of the infarcted area through the formation of scars to maintain cardiac integrity [46, 47].

A significant number of inflammatory cells, including monocytes/macrophages and neutrophils that infiltrate the infarct area, are considered to be an essential component of very early wound healing processes. It is through the polarization of macrophages towards a reparative phenotype that neutrophils orchestrate post-infarction healing. The polarization of neutrophils is mediated by DAMPs and the neutrophils themselves can polarize towards different phenotypes, for example, neutrophils N1 and N2 in the infarct region [48–51]. The cellular immune response and the subsequent inflammatory response are considered a key factor in adverse left ventricular remodeling after an acute myocardial infarction. The New York Heart Association (NYHA) functional classification has been used to describe the

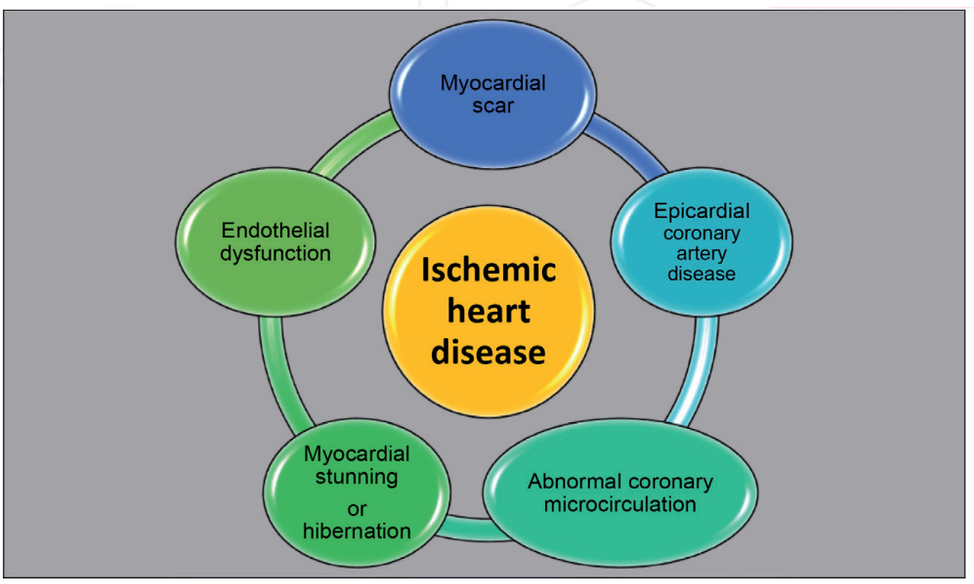

Figure 2.
Ischemic heart disease features in the etiology of heart failure.

severity of symptoms and exercise intolerance in heart failure. Although there is a clear relationship between the severity of symptoms and survival, the severity of symptoms is poorly correlated with many measures of left ventricular function, and patients with mild symptoms may be at high risk of hospitalization and death (**Figure 3**) [52–54].

Estimation of prognosis for morbidity, disability and death helps patients, their families and clinicians decide on the appropriate type and timing of therapies (in particular, decisions about a rapid transition to advanced therapies) and assists with planning of health and social services and resources (**Figure 3**) [55].

Virtually any measurement that can be performed in a biological system is included in the definition of a biomarker, this term in the context of heart failure is limited to substances measured in the blood other than electrolytes and commonly used markers of kidney or liver function. The plasma concentration of natriuretic peptides (NPs) can be used as an initial diagnostic test, especially in the non-acute setting when echocardiography is not immediately available. Elevated NPs help establish an initial working diagnosis, identifying those who require further cardiac investigation; patients with values below the cut-point for the exclusion of important cardiac dysfunction do not require echocardiography [55].

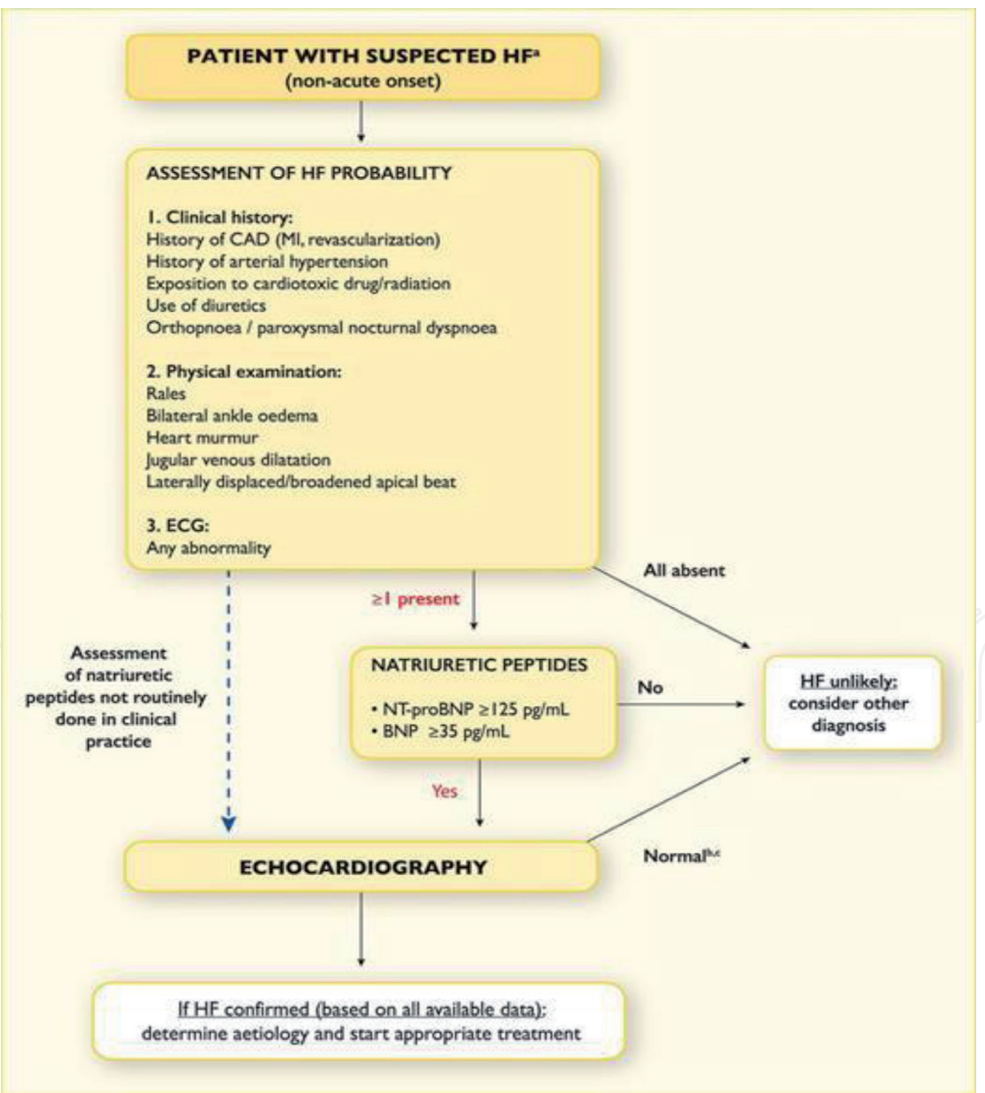

Figure 3.
Diagnostic algorithm from the ESC guidelines for the diagnosis and treatment of acute and chronic heart failure for the diagnosis of heart failure of non-acute onset [55]. BNP = B-type natriuretic peptide; CAD = coronary artery disease; HF = heart failure; MI = myocardial infarction; NT-proBNP = N-terminal pro-B type natriuretic peptide.

The fact that several drugs for HF have shown detrimental effects on long-term outcomes, despite showing beneficial effects on shorter-term surrogate markers, has led regulatory bodies and clinical practice guidelines to seek mortality/morbidity data for approving/recommending therapeutic interventions for HF. However, it is now recognized that preventing HF hospitalization and improving functional capacity are important benefits to be considered if a mortality excess is ruled out.

After of myocardial infarction the presence of ischemic heart failure mortality is a frequent complication. Several factors, such as infarct size, recurrent myocardial ischemia, ventricular remodeling, mechanical complications, stunned myocardium, and hibernating myocardium influence the appearance of left ventricular systolic dysfunction with or without clinical heart failure [56–58].

In 30–40% patients, the etiology of heart failure is nonischemic, the ischemic etiology is a significant independent predictor of mortality in patients with heart failure [59]. In the VALIANT registry were included 5573 consecutive MI patients at 84 hospitals in nine countries from 1999 to 2001. A multivariable logistic survival model was constructed using baseline variables to determine the adjusted mortality risk for those with in-hospital heart failure and/or left ventricular systolic disfunction. The presence of heart failure precedes 80.3% of all in-hospital deaths after myocardial infarction, and the survivors. Heart failure post high risk myocardial infarction occurs in a time-dependent fashion and is usually not directly related to re-infarction [60, 61].

11. Conclusions

Ischemic heart disease remains as the leading cause of death in the world. Coronary atherosclerosis and related ischemic heart failure is a leading cause of heart failure with reduced ejection fraction, the heart failure of ischemic ethiology is associated with a shorter survival and more complications than non-ischemic heart failure. The heart failure and systolic left ventricle dysfunction are present in more than the 80% of in-hospital deaths after myocardial infarction. Substantial improvements in the prevention and management of heart failure present formidable challenges, but these challenges may be met because much of the necessary ground work has already been carried out.

It is important to highlight that for the clinician who faces the challenge of treating patients with ischemic heart disease, it is important to know its mechanisms and the therapies aimed at both the management of patients with acute myocardial infarction and heart failure. The goals of treatment in patients with HF are to improve their clinical status, functional capacity, quality of life, prevent hospital admission, and reduce mortality.

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