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Chapter 7

Ischemic Cardiomyopathy: Contemporary Clinical Management

Burhan Sheikh Alkar, Gustav Mattsson and Peter Magnusson

Additional information is available at the end of the chapter

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Abstract

Ischemic cardiomyopathy, disease of the heart muscle due to coronary artery disease, is the most common cardiomyopathy. It is often difficult to discern the etiology of heart failure, and often there are multiple underlying causes. Ischemic cardiomyopathy most often presents with a dilated morphology with wall motion defects and a history of previous myocardial infarction or confirmed coronary artery disease. Mechanisms of myocardial depression in ischemia are necrosis of myocardial cells resulting in irreversible loss of function or reversible damage, either short term through myocardial stunning or long term through hibernation. In ischemic cardiomyopathy, echocardiography may be extended with stress testing or other imaging modalities such as myocardial scintigraphy and cardiac magnetic resonance tomography. Coronary angiography is often considered a gold standard; however, other modalities such as positron emission tomography can be needed to detect small vessel disease. Cardiac revascularization, through percutaneous coronary intervention and coronary artery bypass grafting, both in acute coronary syndrome and in stable coronary artery disease, relieves symptoms and improves prognosis. Therapy should aspire to treat ischemia, arrhythmias in addition to heart failure management, which includes device therapy with cardiac resynchronization therapy, implantable cardioverter defibrillators, and mechanical support as bridging or destination therapy in end-stage disease.

Keywords: cardiomyopathy, coronary artery disease, heart failure, ischemic, myocardial infarction

1. Introduction

Disease of the heart muscle, cardiomyopathy, appears in various disease manifestations, which are often either poorly defined or difficult to distinguish in clinical practice. Despite

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these shortcomings, it is important to determine the underlying etiology of cardiomyopathy, both for evidenced-based clinical practice and for research purposes. This chapter offers a definition of ischemic cardiomyopathy, the most common form of heart failure, as well as describes its epidemiology, pathophysiology, diagnosis, evaluation, and treatment. It aims to facilitate for clinicians who treat patients with ischemic cardiomyopathy, researchers, and other professionals with an interest in the field and also patients and their relatives.

1.1. Definition

The term ischemic cardiomyopathy describes a state of left ventricular systolic dysfunction due to coronary artery disease [1]. However, both European and American guidelines refer to the concept of cardiomyopathy as a primary heart muscle disease rather than the acquired forms of heart disease [2, 3]. Clinically, and for definitions in numerous scientific studies, patients with heart failure attributed to ischemic etiology are labeled as having ischemic cardiomyopathy. Thus, a heart failure patient with a history of myocardial infarction and evidence of coronary artery disease from imaging tools or functional tests is said to have an ischemic etiology. In practice, the etiology in an individual patient is not always clearly discernable. Patients with heart failure and no coronary artery disease may have angina/wall motion abnormalities [4]. On the other hand, severe coronary artery disease does not necessarily imply symptoms, myocardial infarction, or heart failure [1]. Even with information from an invasive coronary angiography when evaluating heart failure, the etiology is not always unambiguous. In science, the same overlap between an ischemic cause and other contributing causes frequently occur; heart failure may be complicated by hypertension, diabetes mellitus, valvular disease, and other factors that may interplay [5]. Nevertheless, it is important to interpret subgroup analyses with this in mind as it may explain inconsistency between studies. It has been proposed that patients with single-vessel disease should be classified as having nonischemic cardiomyopathy [1]. Typically, patients with ischemic cardiomyopathy include those with reduced ejection fraction with a cutoff at 35–40%, although this is also somewhat arbitrary [1, 6]. The boundaries between ischemic, nonischemic, and mixed dilated cardiomyopathy are worth taking into account depending on the context [7].

1.2. Epidemiology

Ischemic cardiomyopathy is common, and it is increasing worldwide based on risk factors for coronary artery disease becoming more prevalent. According to the World Health Organization (WHO), ischemic heart disease is considered the most common cause of death worldwide, and cardiovascular heart disease, which is predominantly coronary artery disease, claims a global death toll of 17.7 million every year, comprising 31% of all deaths [8]. More than three quarters of cardiovascular deaths come from low- and middle-income countries [9]. Furthermore, coronary artery disease is considered the most common cause of heart failure which affects 1–2% of the general population and 10% of people aged 70 years or more [10]. The risk of having heart failure diagnosed during the remaining lifetime at an age of 55 years is higher for men (33%) than women (28%) [11]. Etiological causes of heart failure are diverse, but the ischemic component is considered to be the largest contributor. Ischemic

heart disease includes myocardial scar, stunning/hibernating myocardium, epicardial coronary artery disease, abnormal coronary microcirculation, and endothelial dysfunction [6]. The incidence of ischemic cardiomyopathy is likely to increase globally over the coming decades.

1.3. Pathophysiology

The pathophysiology consists of two major mechanisms: reversible and irreversible damage of the myocardium that results in reduced myocardial function and cardiac output, with progression into a dilated phase. This myocardial damage is typically caused mainly by atherosclerosis of coronary arteries that result in reduced perfusion of cardiac muscle tissue, which clinically presents as acute coronary syndromes: ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina pectoris. Both STEMI and NSTEMI are characterized by the presence of necrosis of the myocardium and elevated cardiac biomarkers, whereas unstable angina is characterized by myocardial ischemia without necrosis of myocardial cells; however, all forms of myocardial ischemia can cause impaired myocardial function and ischemic cardiomyopathy. Prompt revascularization restores parts of viable myocardium, whereas other parts undergo necrosis and are thus irreversibly damaged. The transient myocardial depression during acute coronary syndrome is referred as stunning. Long-lasting but potentially reversible ischemic depression is described as hibernating myocardium. Hibernation and stunning are interchangeable when it occurs from repetitive temporary ischemic triggers [12]. This is important to recognize as triggers may be managed, and successful revascularization in conjunction with an optimal pharmaceutical approach may improve ejection fraction. From this perspective ischemic cardiomyopathy is a dynamic disease. It does not necessarily lead to deterioration and clinical improvement is possible. Occlusion of a coronary artery causes a localized myocardial injury in areas of reduced perfusion, whereas global coronary artery disease may lead to diffuse myocardial injury. Both global and localized myocardial impairments constitute components of ischemic cardiomyopathy.

1.3.1. Coronary artery disease

Coronary artery disease is a consequence of atherosclerosis, which is attributed to many risk factors. Increasing age and male sex independently imply higher risk. The majority of risk factors are modifiable. In the international study INTERHEART, several risk factors for myocardial infarction were identified [13]. In this study, moderate amount of alcohol was beneficial, especially in women, but these results should be interpreted with caution:

- ApoB/ApoA1 ratio
- Smoking
- Diabetes mellitus
- Physical inactivity
- Psychosocial risk factors
- Abdominal obesity

- Hypertension
- Diet (less fruit/vegetables)

There is a strong age-related increase of atherosclerosis and myocardial infarction. Approximately 4% of the population, aged 75–84 years, suffers from symptomatic coronary disease [14]. There is a strong link between angina and risk of coronary artery disease mortality on a group level [14, 15]. Hypertension has been demonstrated to be causally linked to coronary artery disease [16]. Hypercholesterolemia is a major pathway to manifest coronary disease, and clinical events have been shown in this group in several studies over decades [16–19]. Diabetic patients have an approximately threefold risk of myocardial infarction based on increased risk of coronary artery disease [20]. Smoking is a risk factor because of its vascular damaging effects [21]. Obesity and lifestyle factors, such as physical inactivity, also constitute risk factors [22]. Family history is complex but is an independent risk factor for coronary artery disease [23]. These factors, often in combination, may lead to multivessel disease; ischemic cardiomyopathy patients have more proximal locations of stenoses, greater lumen loss lesions and thus more extensive ischemic burden, and severe clinical manifestation with reduced working capacity [24].

2. Symptoms and signs

Ischemic cardiomyopathy patients present with the same general symptoms that are common in heart failure regardless of etiology. Typical symptoms of ischemic cardiomyopathy are breathlessness, orthopnea, exercise intolerance, fatigue, ankle swelling, less typically nocturnal cough, wheezing, bloated feeling, loss of appetite, confusion, palpitations, dizziness, and syncope. Symptoms are often accompanied by signs such as elevated jugular venous pressure, hepatojugular reflux, third heart sound (gallop rhythm), and laterally apical chamber impulse. There may also be less specific signs: weight gain due to fluid retention but also weight loss and cachexia in advanced heart failure, hepatomegaly, ascites, cold extremities, oliguria, and crepitations at pulmonary auscultation [6]. The first presentation might be as acute coronary syndrome, arrhythmias (atrial/ventricular tachycardia or bradycardia), or thromboembolic complications of left ventricular thrombus/atrial fibrillation after myocardial infarction such as stroke or systemic thromboembolism. Psychiatric symptoms such as depression and anxiety are common as a consequence of the mentioned symptoms and signs [25].

2.1. NYHA functional classification

The New York Heart Association (NYHA) Functional Classification is frequently used to classify heart failure into four categories according to the severity of symptoms [26]:

- NYHA Class I: asymptomatic.

  No limitation in physical activity despite the presence of heart disease. This can be suspected only if there is a history of heart disease, which is confirmed by investigations, for example, echocardiography.

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- NYHA Class II: mild.

  Slight limitation in physical activity, more strenuous activity, causes shortness of breath, for example, walking on steep inclines or several flights of steps. Patients in this group can continue to have an almost normal lifestyle and employment.

- NYHA Class III: moderate.

  More marked limitation of activity that interferes with work. Walking on flat ground produces symptoms.

- NYHA Class IV: severe.

  Unable to carry out any physical activity without symptoms, patients are breathless at rest and mostly housebound [26].

3. Diagnosis

History taking and physical examination remain important, but laboratory tests and cardiac imaging are today a key part of diagnosis and management of ischemic cardiomyopathy.

3.1. History

Assessment of risk factors for atherosclerosis and cardiovascular disease is an important part of the history and can support clinicians by enabling the classification of patients into three categories, low-, intermediate-, and high-risk groups, and thus aid in the selection of appropriate testing and treatment to minimize risk. According to American guidelines for assessment of cardiovascular risk, global risk scores (such as the Framingham Risk Score) that use multiple traditional cardiovascular risk factors should be obtained for risk assessment in asymptomatic adults without a clinical history of cardiovascular disease. These scores are useful for combining individual risk factor measurements into a single quantitative estimate of risk that can be used to target preventive interventions [27, 28]. Framingham Risk Score is an algorithm used in assessment of 10-year cardiovascular risk and is based on data that was obtained from the Framingham Heart Study, which is a study on the residents of the city of Framingham, Massachusetts, that began in 1948 [27, 28]. The predictors used in the Framingham Heart study are age, sex, diabetes mellitus, smoking, treated and untreated systolic blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol, and body mass index (BMI) replacing lipids in a simplified model [30]. Moreover, familial history of coronary artery disease should be investigated to assess the risk of ischemic heart disease in asymptomatic individuals [27, 28]. This assessment of risk factors and classification of risk groups determine the next step of investigations and treatment; for example, low risk patients do not need further investigations for risk evaluation. On the other hand, intensive preventive interventions are already indicated in high-risk patients, and thus further testing or risk assessment would not give additional benefit [27]. Other manifestations of atherosclerosis such as stroke, carotid artery disease, and intermittent claudication are signs of increased risk for ischemic heart disease because atherosclerosis is generalized and can affect any part of the vasculature [29]. History taking should also include questions about symptoms that indicate the presence of ischemic heart disease, such as

retrosternal chest pain or discomfort that indicates angina, and this is often described as squeezing, burning pain or as a pressure, tightness, fullness, or a heavy weight in the middle of the chest that extends to the neck, left arm, jaw, and back. These symptoms can be accompanied by sweating, nausea, and vomiting [30]. Angina itself can be stable or unstable angina, and unstable angina comes in many different forms according to the American Heart Association [31]:

- Rest angina within 1 week of presentation.
- New-onset angina of the Canadian Cardiovascular Society (CCS) classification grade III or IV within 2 months of presentation.
- Angina increasing in CCS grade to at least grade III or IV.
- Variant angina.
- Non-Q-wave myocardial infarction.
- Post-myocardial infarction angina (>24 hours).

Canadian Cardiovascular Society (CCS) grading of angina pectoris is a practical way to define severity of angina by the level of physical activity needed for symptoms to arise (**Table 1**) [30].

3.2. Physical examination

Physical examination is of value in the assessment of a patient with suspected ischemic cardiomyopathy and grants important information. Heart murmurs and sounds might indicate valvular disease or other hemodynamic defects. Swelling of the ankles, an enlarged liver, crepitations on lung auscultation, and tachycardia can be signs of congestive heart failure [32]. Signs of atherosclerosis risk factors can predict the presence of coronary artery disease, for example, abdominal obesity and xanthelasma that is often associated with hyperlipidemia.

Blood pressure might be elevated, which is a risk factor for atherosclerosis and myocardial infarction, or it might be low, which could indicate hemodynamic compromise because of decreased cardiac output in severe heart failure. According to the American College of Cardiology guidelines from 2017, blood pressure is classified as normal, elevated, stage 1, or stage 2 hypertension (**Table 2**) [31].

Grade	Activity evoking angina	Limits to normal activity
I	Prolonged exertion	None
II	Walking >2 blocks	Slight
III	Walking ≤2 blocks	Marked
IV	Minimal or rest	Severe

Table 1. Canadian Cardiovascular Society grading of angina pectoris.

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Classification	Blood pressure
Normal	<120/<80 mmHg
Elevated	120–129/<80 mmHg
Hypertension stage 1	130–139 or 80–89 mmHg
Hypertension stage 2	≥140 or ≥90 mmHg

Table 2. Blood pressure classification according to ACC guidelines 2017.

3.3. Resting electrocardiography

A 12-lead electrocardiography (ECG) is simple, easily accessible, cheap, and noninvasive as well as an important tool in the management of ischemic cardiomyopathy. It is recommended that a 12-lead ECG is performed in patients with hypertension or diabetes mellitus even if no symptoms are present. Additionally, in patients without these risk factors and without symptoms, it may still be of value [27].

Myocardial ischemia may present with different changes on ECG, and these changes may appear temporarily during acute myocardial ischemia (e.g., ST-segment elevations) or remain permanently such as pathological Q-waves after a transmural infarction:

- ST-segment morphology changes [33]. ST-segment elevation occurs in acute STEMI, whereas ST-segment depression occurs in NSTEMI or unstable angina.
- T-wave morphology changes. The T-wave becomes upright and tall, *coronary T-waves*, in the first few minutes of myocardial infarction (STEMI) or may be become inverted/negative in NSTEMI and unstable angina.
- Pathological Q-waves which are negative and deep appear on ECG in transmural myocardial infarction and remain as a sign of permanent damage [33].
- Tachyarrhythmias such as ventricular tachycardia and ventricular fibrillation or bradyarrhythmia such as atrioventricular block degrees I–III.
- New left bundle branch block and less commonly right bundle branch block.

ECG abnormities may provide clues for the diagnosis of ischemic cardiomyopathy but have low specificity [34]. ECG signs can guide therapy. If atrial fibrillation is present, lifelong oral anticoagulation is warranted since all patients with ischemic cardiomyopathy and atrial fibrillation are at risk of thromboembolism. Symptomatic sinus node dysfunction or high-degree atrioventricular block can necessitate permanent pacemaker, except for intermittently during the acute phase of STEMI/NSTEMI because bradyarrhythmia is often transient following myocardial infarction. In ischemic cardiomyopathy patients with bundle branch block, typically left, cardiac resynchronization therapy (CRT) can be an option to improve symptoms of heart failure and survival. A completely normal ECG makes ischemic cardiomyopathy unlikely.

3.4. Laboratory tests

Laboratory tests can reveal and quantify many risk factors for ischemic cardiomyopathy, such as diabetes mellitus, hypercholesterolemia, renal failure, and C-reactive protein (CRP) [35].

3.4.1. Creatine kinase-MB

Creatine kinase-MB (CK-MB) is a myocardial enzyme that is elevated in blood in cardiac muscle damage and ischemia, but it is not a specific marker for myocardial ischemia and can be elevated in other conditions, for example, renal failure, rhabdomyolysis, heart failure, and hypothyroidism [36, 37].

3.4.2. Troponins

Cardiac troponins are proteins that regulate the contraction of striated muscles and include three subunits (troponin C, troponin T, and troponin I) [38]. Cardiac troponin T and troponin I are cardiac regulatory proteins that control the calcium-mediated interaction between actin and myosin [39]. Cardiac troponin C is also identified in skeletal muscles, and thus it is not specific for myocardial damage [37]. The elevation of serum levels of cardiac troponins (T, I) is used in the diagnosis of acute myocardial infarction as a biochemical marker [39, 40]. They are superior compared to CK-MB as biomarkers for detection of the myocardial damage that is associated with myocardial infarction, and moreover, while levels are affected by renal function, they still have a reliable predictive value in patients with acute coronary syndrome regardless of renal function [41]. The raised cardiac troponin in serum may not be detectable for up to 4 hours after myocardial infarction; therefore, repeated tests should be performed again, for example, after 3 and 9 hours, if troponins were not raised on admission in patients with suspected acute coronary syndrome [39, 42]. Troponin I has a high specificity for myocardial muscle injury. Troponin I has three isoforms: cardiac, skeletal slow twitch, and skeletal fast twitch [36, 37]. It does not increase in skeletal muscle diseases, after normal physical exercise or in hypothyroidism [36]. It is not detected in healthy individuals without acute coronary syndrome or another disease with damage to myocytes such as myocarditis [36, 43]. Raised cardiac troponins have an important diagnostic and prognostic value in acute coronary syndrome, caused by atherosclerosis and occlusion of coronary arteries (primary myocardial ischemia), but it can be detected in secondary myocardial ischemia associated with many other conditions such as cardiac arrhythmias, large pulmonary embolization, heart failure of other etiologies such as idiopathic dilated cardiomyopathy and hypertrophic cardiomyopathy, or after therapeutic procedures, for example, coronary intervention (angioplasty), vasospastic angina, electrophysiological ablations, or electrical cardioversions [38, 39]. Furthermore, raised cardiac troponins can be caused by nonischemic myocardial damage in conditions such as perimyocarditis, cardiac trauma, septicemia, and chemotherapy [39]. In addition, cardiac troponins are raised in patients with renal failure without acute coronary syndrome, and the exact mechanism of this increase of cardiac troponin levels is still unclear, although raised cardiac troponin I in individuals with renal failure is controversial [36, 37, 39]. It appears that elevated troponin in renal failure is not associated with myocardial infarction rather with chronic myocardial damage and depends upon the assay

technology [42]. However, cardiac troponins remain of predictive value in individuals with chest pain and suspected acute coronary syndrome despite renal failure [39]. Cardiovascular death is common in end-stage renal disease, and both increased cardiac troponin I and T predict a two- to fivefold increase in mortality in these patients [41].

3.4.3. B-type natriuretic peptide

B-Type natriuretic peptide (BNP) and its N-terminal fragment (NT-proBNP) are secreted by ventricular cardiomyocytes as a result of stress and tension in the muscle fibers of the ventricular wall and by myocardial ischemia. They have a strong prognostic and diagnostic value in patients with heart failure. Both BNP and NT-proBNP are significantly elevated in individuals with systolic or diastolic myocardial dysfunction. High levels are predictive of worse prognosis and higher risk of cardiovascular death and readmission to hospital. Furthermore, BNP and NT-proBNP levels indicate the severity of heart failure [44]. Until recently, the clinical application of BNP and NT-proBNP measurement in patients with coronary artery disease has been unclear, but many recent studies have found that both BNP and NT-proBNP levels increase in myocardial ischemia and acute coronary syndromes. This has led to the suggestion that these biomarkers can be secreted by cardiomyocytes as a direct result of myocardial ischemia regardless of ventricular wall stress [44, 45]. In support of this, it has been found that transient myocardial ischemia that occurs due to coronary interventions (stent inflation) can lead to elevation of BNP levels [46]. However, the diagnostic and prognostic value of these biomarkers in coronary artery disease remains unclear, and further investigations are needed.

3.5. Cardiac imaging

Cardiac imaging is an essential tool in understanding heart failure and guiding treatment. Historically, X-ray played a role to show pulmonary congestion and may add other clues to a dyspnea investigation. Instead, today echocardiography is the cornerstone in management of heart failure. It provides information about the morphology of all four chambers, function of wall motion and valves, ejection fraction, pulmonary artery pressure, and pericardial effusion, and is available, noninvasive, and cheap. Other imaging methods are used in the evaluation and provide incremental value, some are an essential part of clinical practice, and others are mainly used in research, but this may change in the future.

3.5.1. Transthoracic echocardiogram

Transthoracic echocardiography includes two- and three-dimensional techniques, pulsed and continuous Doppler, color Doppler, tissue Doppler imaging and contrast, and strain measurements. Assessment of ejection fraction is important as it guides therapeutic choices with regard to pharmaceutical agents and device therapy and provides information about prognosis. Therefore the method used to determine ejection fraction is crucial. According to ESC guidelines, Simpson's rule is the preferred choice. It should be obtained from the apical four-chamber view and two-chamber view but requires accurate tracing of the endocardium. Echocardiography is the most common diagnostic investigation for coronary artery disease after ECG and chest X-ray [47] and can provide detailed information about left ventricular

function, cardiac output, left ventricular ejection fraction, wall motion abnormalities in ischemic cardiomyopathy, and possible complications of acute coronary syndromes such as myocardial aneurysm [48], mitral regurgitation secondary to papillary muscle dysfunction or rupture [47, 49], intracardiac thrombus [50], ventricular free wall rupture, and pseudoaneurysm formation after myocardial infarction [47]. Transthoracic echocardiography is an important tool in the assessment of patients with acute chest pain, both for diagnosis of acute coronary syndromes and for exclusion of other causes of acute chest pain such as aortic dissection and pericardial effusion.

Echocardiogram findings in ischemic cardiomyopathy include:

- Decreased left ventricular ejection fraction, which is one of the most important predictors of mortality [51, 52].
- Left ventricular diastolic dysfunction [53]. The evaluation of left ventricular dysfunction and filling pressures is of great benefit to distinguish ischemic cardiomyopathy from other syndromes that cause dyspnea such as pulmonary diseases [54].
- Regional or diffuse wall motion abnormalities [53, 55].
- Mitral and tricuspid regurgitations [53].
- Detection of both localization and size of myocardial infarction [47].

According to 2013 ESC guidelines on the management of stable coronary artery disease, resting echocardiography should be performed in all patients with the first presentation of coronary artery disease:

- Exclusion of alternate causes of angina.
- Identification of regional wall motion abnormalities suggestive of coronary artery disease.
- Measurement of left ventricular ejection fraction for risk stratification and quantification of heart failure severity.
- Evaluation of diastolic function [54].

3.5.2. Stress echocardiography

The principle of stress echocardiography is the combination of physical (treadmill or bicycle), pharmacological (dobutamine, dipyridamole, or adenosine), or electrical stress (external pacing) with two-dimensional echocardiography [56]. The goal of this technique is the provocation of myocardial ischemia that can be detected with a two-dimensional echocardiogram. It is a noninvasive and easy test for both the patient and the physician and has accuracy in diagnosis of coronary artery disease comparable to that of radionuclide stress perfusion imaging or cardiac magnetic resonance, but it is ultimately less expensive [57].

The response of the myocardium depending on regional wall function during stress echocardiography can be classified into four patterns: normal, ischemic, necrotic, and viable [57].

- Normal response: normokinetic wall function at rest and normo- or hyperkinetic at stress.
- Ischemic response: normokinetic regional wall function at rest and hypokinesia, akinesia, or dyskinesia at stress. Stress exacerbates wall dysfunction.
- Necrotic response: an area with wall dysfunction at rest stays immobile at stress.
- Viability response: an area with dysfunction at rest responds either with recovery and improvement at stress or with improvement at an early phase of stress and thereafter impairment (biphasic response); this indicates viability despite ischemia.

A common indication for stress echocardiography is the diagnosis of coronary artery disease in the group of patients in whom exercise ECG is contraindicated, unfeasible, or not diagnostic [57, 58]. It can also be used in the assessment of viability in ischemic cardiomyopathy before revascularization. In addition, stress echocardiography can be used in the assessment of a patient with established coronary artery disease after revascularization, but also to evaluate the preoperative risk in patients with coronary artery disease and too reveal the region of ischemia in the myocardium.

3.5.3. Coronary computed tomographic angiography

Computed tomography of the coronary arteries is an accurate noninvasive diagnostic test for coronary artery disease [59]. In addition, it provides information on cardiac valves and chambers [60]. The main practical application of computed tomography angiography has been in the outpatient setting in patients with suspected coronary artery disease, but many studies now examine its application in the setting of low-risk chest pain patients in the emergency department [60]. The advantage of computed tomography angiography is its negative predictive value, while the method is lacking in positive predictive value (i.e., it is good at ruling out, but less good at confirming coronary artery disease) [60]. It should be considered in patients with lower risk of coronary artery disease as an alternative to stress testing or when results have been inconclusive [55].

3.5.4. Nuclear imaging modalities

Myocardial scintigraphy, positron emission tomography (PET), and single photon emission computed tomography (SPECT) all utilize radioactive isotopes for imaging. Scintigraphy forms two-dimensional images, while images from PET and SPECT form images in three dimensions. Scintigraphy and SPECT utilize gamma cameras to detect gamma radiation, while PET simultaneously detects two gamma rays emitted at a 180° angle to each other. Cardiac nuclear imaging at rest gives information about areas damaged by myocardial infarction and myocardial viability by mapping metabolism and perfusion. Exercise or pharmacological (usually dobutamine) stress testing provides information on the presence of angina and low perfusion in coronary arteries resulting in ischemia. Importantly, measurement of perfusion by scintigraphy is relative (not absolute) to the area with the highest perfusion. Because of this relative expression of quantification, three-vessel coronary disease with equally reduced perfusion in the whole heart might appear to be well perfused. In cases where this relative perfusion will be misleading, PET should be performed instead. The SHIFT trial viability substudy

indicated that viability or absence thereof did not identify patients with more benefit from coronary artery bypass grafting [61]. However, decision-making about revascularization based on viability using imaging could be considered in special cases. Sympathetic innervation imaging with specific tracers can be used in heart failure for risk stratification, although this is seldom used in clinical practice [62]. Stress testing is valuable in the evaluation of manifest or suspected coronary artery disease; however, it is mainly those who are unable to perform exercise testing (treadmill or bicycle) or those with defects on resting ECG that make exercise ECG difficult to interpret (pacemaker rhythm/bundle branch block) that are in need of radionuclide imaging. Scintigraphy should also be considered in patients with high pretest probability of coronary artery disease as an alternative to exercise ECG. All nuclear imaging modalities expose the patient to a small, but not negligible, amount of ionizing radiation. PET and SPECT are further limited by comparatively high cost and limited accessibility (especially of PET tracers because of short half-life time) and are not routinely used. PET can be used to measure regional myocardial blood flow, by comparing this at maximal hyperemia, and at resting flow, an estimation can be made of noninvasive fractional flow reserve. This otherwise requires an invasive coronary angiography to measure (decline in arterial pressure over a stenosis) [63].

3.5.5. Cardiac magnetic resonance tomography

The main advantage of magnetic resonance in the evaluation of ischemic cardiomyopathy is the ability to visualize scar tissue, which is nonviable and the remaining contractile myocardial tissue which is viable. In this context, there are two modalities of cardiac magnetic resonance tomography: the modality first utilizes late gadolinium enhancement in the assessment of nonviable tissue, and the second modality uses low-dose dobutamine stress magnetic resonance in the assessment of viable tissue [64]. The method assesses ventricular volumes, functions in addition to scar tissue, and is free of ionizing radiation; complications are rare and almost exclusively related to stress testing [65–67]. For patients with suspected coronary artery disease, normal cardiac magnetic resonance tomography is a predictor of good prognosis with 1-year cumulative incidence of adverse events at 1.0% (all-cause mortality, aborted sudden cardiac death, myocardial infarction), which is comparable to the population at large [67]. Moreover, magnetic resonance has been shown to both detected ischemic cardiomyopathy that was not previously suspected and conversely to find an alternate diagnosis in previously suspected coronary artery disease [65, 66].

3.5.6. Diagnostic invasive coronary angiography

Invasive coronary angiography is a procedure where a catheter is inserted into the coronary arteries, usually through the radial artery. By using radiocontrast and X-ray images, coronary vasculature can be assessed. Coronary angiography retains the advantage that if a stenosis or culprit lesion requiring intervention is found, it can be treated by balloon angioplasty and the insertion of a stent. Fractional flow reserve is a way of determining the physiological significance of a stenosis and is the ratio of blood pressure measured distally to and proximally to the stenosis; this is usually considered to be significant at 0.8 [68]. The purpose should be to either perform coronary angiography to treat confirmed coronary artery disease (percutaneous coronary

intervention) or to rule out stable coronary artery disease with noninvasive testing: Only if this has failed, a diagnostic coronary angiography should be considered [55]. Patients with severe angina (CCS 3) should perform coronary angiography, as well as patients with a clinical profile or noninvasive testing indicating high risk of cardiovascular death or myocardial infarction [55].

4. Treatment

Broadly speaking, the treatment of ischemic cardiomyopathy could be said to consist of four strategies: the primary and secondary prevention of coronary artery disease, anti-ischemic treatment such as revascularization and antiplatelet therapy, treatment of heart failure with medications or cardiac devices, and the prevention and treatment of arrhythmia and sudden cardiac death that often accompany ischemic cardiomyopathy.

4.1. Prevention of coronary artery disease

Physical activity, weight loss in patients with the metabolic syndrome or obesity, cessation of smoking, and treatment of hypertension, diabetes mellitus, and hypercholesterolemia (especially lowering of LDL) prevent progression of coronary artery disease and thus the development or worsening of ischemic cardiomyopathy [69].

4.1.1. Statins

All individuals with coronary artery disease have high risk of cardiovascular events and should be treated with statins according to the recommendations of the ESC/European Atherosclerosis Society guidelines for the management of dyslipidemia, regardless of low-density lipoprotein cholesterol (LDL-C) levels [70]. The goal of treatment is to reach LDL-C target <1.8 mmol/L and/or >50% reduction if it could not reach the target level [55]. Other medications (e.g., fibrates, resins, nicotinic acid, and ezetimibe) may reduce the LDL cholesterol level without any benefit on clinical outcomes [55].

4.2. Anti-ischemic therapy

Ischemia is by definition the root cause of ischemic cardiomyopathy; thus, targeting this pathophysiological mechanism is of great importance for prevention and treatment. Revascularization should if possible be the first line of therapy in acute coronary syndrome. Antiplatelet therapy inhibits the formation of blood clots in coronary arteries, thereby decreasing risk of myocardial infarction, while other medications increase vasodilation and coronary blood flow or decrease heart rate and myocardial oxygen demand.

4.2.1. Revascularization

In patients with ischemic cardiomyopathy, revascularization should always be considered in addition to optimal pharmacological treatment [71]. Revascularization can be performed

as open heart surgery, coronary bypass grafting, or percutaneous coronary intervention. The choice of method should be discussed with expertise in revascularization preferably including cardiothoracic surgery and anesthesiology in selected cases. In one study, all-cause mortality after 9.8 years was significantly lower in the coronary artery bypass graft group compared with patients in the medical therapy group (59 versus 66% [359 versus 398 patients]; hazard ratio 0.84; 95% confidence interval 0.73–0.97). In the STICH trial, the following variables were associated with improved outcome after coronary artery bypass grafting: 6-minute walk test more than 300 m, three-vessel disease, mitral regurgitation, and ejection fraction less than 27% [72]. Median follow-up was 56 months, and it also significantly improved health-related quality of life (at 4, 12, 24, and 36 months as assessed by the Kansas City Cardiomyopathy Questionnaire) [73]. Most studies show improvement in both survival and ejection fraction after revascularization compared to optimal pharmacological therapy alone [74–76]. It seems like viable myocardium is a predictor of improved survival [75, 76]. Unfortunately, there are no randomized controlled trials comparing percutaneous coronary intervention and coronary artery bypass grafting in ischemic cardiomyopathy. In an observational study, death rates were similar at median follow-up of 2.9 years. Patients who underwent percutaneous coronary intervention had larger risk of myocardial infarction and repeated revascularization but lower risk of stroke [77].

4.2.2. Antiplatelet and anticoagulant therapy

Antiplatelet drugs prevent occlusion by inhibiting platelet adhesion and thus the formation of thrombi in coronary vessels [78]. Acetylsalicylic acid is well studied, it exerts its effect by inhibiting cyclooxygenase (COX-1 and COX-2) enzymes and reduces cardiovascular death by 15% in high-risk patients [79]. Low-dose acetylsalicylic acid therapy is essential in secondary prevention of cardiovascular events in coronary artery disease, and its benefit in this case is clear, but it is not recommended in the primary prevention of myocardial infarction [55, 79]. The $P2Y_{12}$ receptor is a protein, which exists on the surface of platelets and plays an essential role in the aggregation process activated by adenosine diphosphate. In acute coronary syndrome, a $P2Y_{12}$ antagonists such as clopidogrel, prasugrel, or ticagrelor is recommended in addition to acetylsalicylic acid; this treatment should be continued for up to 12 months in the case of revascularization with a stent [80]. A $P2Y_{12}$ inhibitor can also be considered for secondary prevention when acetylsalicylic acid is unsuitable. In cases of primary percutaneous coronary intervention due to STEMI, dual antiplatelet therapy should be complemented with unfractionated heparin. A parenteral glycoprotein IIb/IIIa inhibitor, which inhibits platelet aggregation, may be considered as bailout therapy if thrombi or falling fractional flow reserve is seen during primary percutaneous coronary intervention [80]. In acute coronary syndrome without ST-segment elevation, a low-molecular-weight heparin, such as fondaparinux, should be administered subcutaneously [81].

4.2.3. Beta-blockers

Beta-blockers exert beneficial effects on the myocardium that decrease heart rate, contractility, atrioventricular conduction, and risk of arrhythmia. Beta-blockers reduce the risk for cardiovascular death and myocardial infarction by 30% in post-myocardial infarction patients and

are useful in the management of effort-induced angina [55, 82]. In Europe, the most widely used beta-blockers provide predominantly β_1-blockade, such as bisoprolol, metoprolol, atenolol, and nebivolol. Carvedilol, which is a nonselective β-blocker that targets the α_1-receptor, is also used, especially in advanced heart failure. By decreasing heart rate and contractility, the oxygen demand of the heart muscle decreases, thus also decreasing ischemia and ventricular arrhythmia. However, beta-blockers might worsen prognosis in the context of bradycardia or circulatory shock, because of negative inotropic effects, and should be used with caution in heart failure with decompensation.

4.2.4. Ivabradine

Ivabradine is a blocker of the *funny* channel, I_f, which is found almost exclusively in the sinus node. By selective inhibition of the sinus node, reduction of heart rate and minimization of myocardial oxygen demand can be achieved, without negative inotropic effect that could result in lowered blood pressure [55]. Ivabradine has been shown to improve heart failure outcomes both in ischemic and unspecific etiologies. It is indicated in patients with sinus rhythm above 70 beats per minute [83, 84]. The combination of atenolol with ivabradine 7.5 mg twice daily gave better heart rate control and amelioration of angina symptoms [55].

4.2.5. Vasodilators

Calcium channel blockers play a role in the management of coronary artery disease by its main effect on vessels with vasodilation and lowering of peripheral vascular resistance. Calcium channel blockers are classified into two main groups: the dihydropyridines that include amlodipine, nifedipine, felodipine, lacidipine, and lercanidipine and the non-dihydropyridines that include verapamil and diltiazem. Dihydropyridines have a greater vascular selectivity, whereas non-dihydropyridines have a property of nodal suppression and tendency of heart rate lowering, which is why the combination of beta-blockers and non-dihydropyridines (verapamil and diltiazem) must be avoided because of the risk of bradyarrhythmia or AV block [55]. By reducing heart rate and increasing dilation of coronary vessels, calcium channel blockers, like the beta-blockers, reduce the ischemic burden in coronary artery disease, although due to decreased contractility they should be avoided in heart failure [85]. Nitrates cause vasodilation of both coronary arteries and veins that gives symptomatic relief of angina due to its active component nitric oxide. There are two types of nitrates: short-acting nitrates (sublingual nitroglycerin 0.3–0.6 mg, tablet or spray form, and isosorbide dinitrate 5 mg sublingually) that is used for acute angina. Long-acting nitrates are used for angina prophylaxis: isosorbide dinitrate (oral preparation), mononitrates, and transdermal nitroglycerin patches [55].

4.3. Treatment of heart failure

Treatment of heart failure includes pharmaceutical agents, comorbidities like anemia, implantable cardioverter defibrillators, cardiac resynchronization therapy, and mechanical circulatory support and transplant.

4.3.1. Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers

Renin-angiotensin-aldosterone system (RAAS) inhibition that is achieved by either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers is an essential component of heart failure management. Both European and American guidelines for the management of heart failure recommend inhibition of the renin-angiotensin system for patients with chronic heart failure to reduce mortality and morbidity [86]. ARNi is a combination of an angiotensin receptor blocker and an inhibitor of neprilysin, which is an enzyme that breaks down vasoactive peptides such as natriuretic peptides, adrenomedullin, and bradykinin and as a result brings about vasodilation. The first approved ARNi product was valsartan/sacubitril. ARNi should not be administered together with angiotensin-converting enzyme inhibitor, which has to be withdrawn [86].

4.3.2. Beta-blockers

Both in coronary artery disease and in heart failure, beta-blockers are a crucial part of therapy. Beta-blockers are useful independent of blood pressure levels in patients with heart failure and improve survival. Bisoprolol was shown to reduce mortality of patients with heart failure in the CIBIS-II trial [87]. The CIBIS-III trial showed non-inferiority for titration of bisoprolol before enalapril as compared to the reverse order [88]. Considering the beneficial and well-documented effect of beta-blockers in coronary artery disease, in ischemic cardiomyopathy, titration of beta-blockers first should be considered in hemodynamically stable patients. Metoprolol is also beneficial in heart failure and was in the MERIT-HF trial shown to improve survival by both preventing worsening of heart failure and decreasing risk of sudden cardiac death [89]. In the US Carvedilol HF trial, decreased risk of death was seen for carvedilol as well [90].

4.3.3. Selective aldosterone receptor antagonists

The selective aldosterone receptor antagonist group includes spironolactone and eplerenone. This class of medication exerts pharmacological effect by blocking the aldosterone receptor; therefore, sodium reabsorption and diuresis are decreased, while potassium retention is increased. Consequently, they cause water loss and lower blood pressure. Spironolactone has been shown to decrease morbidity and mortality in symptomatic heart failure but is associated with antiandrogen side effects such as gynecomastia and disadvantageous mineral corticoid steroid effects [91]. Eplerenone has milder side effects and has shown at least similar beneficial effect on prognosis [92]. In symptomatic heart failure, a selective aldosterone receptor antagonist should be administered in addition to baseline therapy, if tolerated by the patient [6].

4.3.4. Digoxin

Digoxin, first isolated from the digitalis plant, has inotropic properties; it increases contractility and decreases heart rate. It is most commonly used in rate control of atrial fibrillation preferably in addition to beta-blockers. The role of digitalis in the treatment of patients with chronic heart failure is controversial, and its long-term effect on mortality remains unclear. Studies indicate that digoxin decreases the frequency of hospitalization and relives symptoms

of heart failure, but it has no effect on survival or mortality in individuals receiving angiotensin-converting enzyme inhibitors and diuretics [93].

4.3.5. Loop diuretics

By far the most commonly used loop diuretic is furosemide; alternative substances are bumetanide and torsemide. Blockage of sodium-potassium-chloride cotransporters results in increased excretion of sodium, chloride, and potassium and thereby increased diuresis [94]. This decreases the congestion induced by heart failure and therefore it can be useful for symptomatic relief. High doses of loop diuretics have been linked to increased mortality; however, it is the patients with most severe heart failure and congestion that receive the highest doses. For stable patients enteral administration is used, while in cases of worsened heart failure with congestion, intravenous therapy is recommended [94].

4.3.6. Levosimendan

Levosimendan is an inodilator, with both vasodilator and positive inotropic properties. It increases calcium sensitization of troponin C and thus increases cardiac contractility [95]. It can be indicated in acutely decompensated patients with chronic heart failure due to systolic dysfunction of the left ventricle [95, 96]. Levosimendan is well tolerated in general but might have adverse effects such as hypotension, tachycardia, atrial fibrillation, hypokalemia, and headache [95]. Levosimendan has an active metabolite (OR-1896); due to this, effects such as improved hemodynamics and contractility can last for over 1 week. Infusions are administered intermittently. Levosimendan infusions reduce symptoms, hospitalizations, and short-term mortality [95].

4.3.7. Management of anemia

Anemia can mimic symptoms of heart failure such as dyspnea and tiredness. It also worsens prognosis and symptoms in heart failure. In the RED-HF trial darbepoetin alfa, an agent that binds to the erythropoietin receptor and thus stimulates formation of red blood cells did not decrease cardiovascular mortality in anemic heart failure patients; in fact it increased the risk of stroke [97]. Intravenous iron on the other hand has been shown to decrease symptoms and improve quality of life, and enteral iron substitution is associated with gastrointestinal side effects that might be exacerbated in heart failure where gastrointestinal swelling and malabsorption are common [98]. Anemia might worsen ischemia in coronary artery disease, the underlying cause of ischemic cardiomyopathy, and thus extra care is warranted in this group of patients.

4.3.8. Implantable cardioverter defibrillators

Implantable cardioverter defibrillators (ICDs) effectively not only abort ventricular arrhythmias by either antitachycardia pacing or cardioversion but also provide protection against bradycardia. In heart failure, a major cause of death is due to sudden arrhythmic events. Notably, the proportion of sudden cardiac death is higher in patients with NYHA II than NYHA III. Therefore, even patients with mild heart failure symptoms need to be considered for an ICD as primary

prevention. Antiarrhythmic drugs, including amiodarone, might reduce the risk of tachyarrhythmia, but they do not reduce overall mortality and may even increase it. In survivors of cardiac arrest, ICD is recommended as secondary prevention. Patients who have documented ventricular tachycardia with hemodynamic compromise have a secondary prevention indication for ICD for protection from sudden cardiac death [99–102]. Primary prevention indication for ICD should be considered in patients who never experienced a ventricular arrhythmia, with ejection fraction below 35% despite at least 3 months of optimal pharmacological therapy, NYHA functional classes II–III, and at least an estimated survival above 1 year. Two randomized controlled trials showed no benefit in patients who had an ICD the first 40 days after myocardial infarction [103, 104]. If the patient is considered at high risk, during this period a wearable defibrillator is an option [105, 106]. Before offering the patient an ICD, the physician should integrate information about comorbidity and life expectancy; if it is estimated to be less than 1 year including patients with NYHA IV despite pharmacological optimization, ICD is not indicated, but the patient may be reevaluated if improvement occurs. For the group of patients with mild heart failure (NYHA II), an ICD saves one life per year for every 50 patients. Ischemic cardiomyopathy patients have higher risk of sudden death, and the benefit in that group is believed to be higher [107]. In elective replacement of an ischemic cardiomyopathy device, careful judgment is warranted including reevaluation of risk [108–112]. Subcutaneous ICD (S-ICD) is an alternative in selected cases where risk of infection is high or vascular access is difficult and when there is no need of pacing or expected need of antitachycardia pacing. In general 20% of ICD leads fail over a period of 10 years; therefore, S-ICD may be more advantageous in cases of long life expectancy [113, 114].

4.3.9. Cardiac resynchronization therapy

Cardiac resynchronization therapy (CRT), which can be used either with a pacemaker (CRT-P) or with an ICD (CRT-D), reduces morbidity and mortality and improves health-related quality of life in selected patients who fulfill certain criteria [115]. The principle of these devices is to use a pacing system that is biventricular to decrease dyssynchrony and thus heart failure, in patients with heart failure, reduced ejection fraction, and a bundle branch block [116].

According to ESC guidelines from 2013 regarding the indications of CRT in patients with heart failure and sinus rhythm:

- Left bundle branch block with QRS duration >150 ms. CRT is recommended in chronic heart failure patients with left ventricular ejection fraction ≤35% who remain in NYHA functional classes II, III, and ambulatory IV despite adequate medical treatment (recommendation class I, level of evidence A).
- Left bundle branch block with QRS duration 120–150 ms. CRT is recommended in chronic heart failure patients with left ventricular ejection fraction ≤35% who remain in NYHA functional classes II, III, and ambulatory IV despite adequate medical treatment (recommendation class I, level of evidence B).
- Non-left bundle branch block with QRS duration >150 ms. CRT should be considered in chronic heart failure patients with left ventricular ejection fraction ≤35% who remain in

NYHA functional classes II, III, and ambulatory IV despite adequate medical treatment (recommendation class IIa, level of evidence B).

- Non-left bundle branch block with QRS duration 120–150 ms. CRT may be considered in chronic heart failure patients with left ventricular ejection fraction ≤35% who remain in NYHA functional classes II, III, and ambulatory IV despite adequate medical treatment (recommendation class IIb, level of evidence B).
- CRT in patients with chronic heart failure with QRS duration <120 ms is not recommended (recommendation class III, level of evidence B) [117].

In clinical practice it has been revealed that CRT in patients with severe heart failure has positive effects on symptoms and exercise tolerance. Furthermore, it improved quality of life and minimized the need for rehospitalization. However, some patients are nonresponders and receive little or no benefit from CRT. The level of ejection fraction in the trials varies: RAFT and MADIT-CRT used 30% as a cutoff [118, 119]. REVERSE used 40% and BLOCK-HF 50% [118, 120–122]. The QRS width is important in selecting patients. None of the landmark trial selected patients based on sex, QRS morphology, or ischemic vs. nonischemic subgroups. It is not clear if CRT itself reduces the need for ICD or if the improvement of heart failure may expose the patient to a longer period of risk for sudden death. Imaging tests with regard to dyssynchrony are not part of guidelines in selecting patients for CRT [123]. When there is an extensive myocardial scar, the improvement in ejection fraction will be less, and the optimal placement of the left ventricular lead will be more difficult to gain acceptable pacing thresholds without phrenic nerve stimulation.

4.3.10. Mechanical circulatory support and transplant

In patients who do not stabilize with optimal pharmacological therapy, the need for further therapeutic options including mechanical assists should be addressed. In cardiogenic shock, extracorporeal support like Impella™ can be used for temporary bridging. When long-term mechanical assist is indicated, left ventricular assist device can be used for recovery or more often as destination therapy if transplant is not possible. In the meantime, extracorporeal membrane oxygenation (ECMO) may be used to support patients with heart failure (left or biventricular failure) until a decision about a permanent solution is taken. In a randomized trial on high-risk percutaneous coronary intervention in patients with impaired left ventricular function, the 30-day cumulative incidence of major adverse events was not different for patients with intra-aortic balloon pump as compared to left ventricular assist device [124]. Due to lack of heart donors, the left ventricular assist device as a destination therapy has been advocated. The survival rates after 3 years in those receiving the latest continuous flow devices are at least as good as in transplanted patients, but long-term survival is unknown [125].

5. Conclusions

Ischemic cardiomyopathy, which is commonly encountered as an underlying cause of heart failure, warrants qualified management to improve survival. This includes thorough evaluation

and optimal pharmaceutical treatment, device therapy with cardiac resynchronization therapy with/without an implantable cardioverter defibrillator, and mechanical support as bridging or destination therapy in end-stage disease. From a general perspective, it is crucial to reduce risk factors for coronary artery disease to prevent ischemic cardiomyopathy.

Author details

Burhan Sheikh Alkar[1], Gustav Mattsson[1]* and Peter Magnusson[1,2]

*Address all correspondence to: gustav.mattsson@regiongavleborg.se

1 Centre for Research and Development, Uppsala University, Gävle, Sweden

2 Cardiology Research Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

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