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Chapter

An Overview of the Cardiomyopathies

Ida Kåks, Marianna Leopoulou, Gustav Mattsson and Peter Magnusson

Abstract

Cardiomyopathies constitute a heterogeneous group of heart diseases. In fact, cardiomyopathies is a major cause of death either as end-stage heart failure or sudden cardiac death. Even though prognosis is, in many cases, poor there are several approaches to optimal disease management, which improves outcome and implies better quality of life including reduced risk of hospitalization. Differentiation of underlying etiology in individual cases of cardiomyopathies requires careful clinical evaluation. Echocardiography is the cornerstone in initial evaluation and follow-up but cardiac magnetic resonance provides additional value. ECG, biomarkers, detailed history taking and extracardiac features may provide clues to less common entities. While forty years ago cardiomyopathy was defined as heart muscle disease of unknown origin, the underlying pathophysiology has now been elucidated. Indeed, the last decades the genetic explanations have evolved. Advanced treatment with pacemakers, including cardiac resynchronization, implantable defibrillators, and mechanical devices in the most severe cases are nowadays available for many patients. The evidence-based pharmacological approach to heart failure provides multiple interaction of pathophysiological pathways and has improved outcome. In selected cases specific agents are indicated why differential diagnosis is crucial and the genetic link imply cascade screening. This chapter aims to present a comprehensive overview of the cardiomyopathies, categorized into: dilated-, hypertrophic-, restrictive-, arrhythmogenic and unclassified cardiomyopathy.

Keywords: arrhythmogenic cardiomyopathy, cardiomyopathy, dilated cardiomyopathy, heart failure, hypertrophic cardiomyopathy, left ventricular non-compaction, restrictive cardiomyopathy, sudden cardiac death, takotsubo cardiomyopathy

1. Introduction

The term cardiomyopathy was introduced by Brigden in 1957, to describe isolated noncoronary myocardial disease [1]. In 1980 the World Health Organization (WHO) released a document defining cardiomyopathies as "heart muscle diseases of unknown cause" [2]. Since then the understanding of these entities has grown considerably, and although some are deemed idiopathic, the underlying etiology of other cardiomyopathies have been elucidated. In 2008, the European Society of Cardiology (ESC) used the following definition of cardiomyopathy in their position statement:

"A myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality [3]."

Many cardiomyopathies are of genetic origin [4], and the inheritance pattern is most often autosomal dominant, although autosomal recessive and X-linked inheritance patterns are encountered [5]. Non-familial forms include, among others, cardiomyopathy secondary to myocarditis caused by toxic or infectious agents [3, 6].

Terminology has historically been a challenge for many of the cardiomyopathies; takotsubo cardiomyopathy has acquired at least 75 different names [7] and for hypertrophic cardiomyopathy (HCM) that number exceeds 80 [8]. The goal of this chapter is to use the most established nomenclature, while in cases when the preferred term is less clear, it will be addressed.

2. Classification

Several attempts have been made to classify the cardiomyopathies. One classification was suggested by Goodwin in 1961 [9], which described three clinical types, according to the effect the disease has on the heart's function: congestive, obstructive, and constrictive. These categories are still in use, but are now termed dilated, hypertrophic, and restrictive, respectively [10]. In the 1980 report by the WHO [2], three distinct conditions were described: dilated-, hypertrophic- and restrictive cardiomyopathy. In addition to these forms WHO included unclassified cardiomyopathy, covering the cases that did not fit in any of the other groups. Specific heart muscle disease, including, among others, conditions with infectious and metabolic etiology, was not considered to belong to the concept of cardiomyopathy. As the understanding of the pathogenesis and etiology grew, this classification was updated 15 years later - now with the addition of arrhythmogenic cardiomyopathy (ACM), at the time called arrhythmogenic right ventricular cardiomyopathy (ARVC), and the term specific cardiomyopathies replacing specific heart muscle disease [11].

In 2006 the American Heart Association (AHA) proposed a new classification, stating that the identification of several new diseases, diagnostic advancements and precise knowledge of causation called for an updated version [6]. The dilated-hypertrophic-restrictive classification, was considered limited in several regards. For example, mixing anatomical descriptions (hypertrophic and dilated) with one that is merely functional (restrictive), can result in one disease belonging in two categories. Furthermore, remodeling can cause a disease to develop from one category into another during its natural course. Instead, they propose a division of cardiomyopathies into two groups: primary and secondary. Primary cardiomyopathies include those that solely, or predominantly, affect the myocardium. Secondary cardiomyopathies replace the term specific cardiomyopathies, hence including pathology of the heart muscle caused by systemic disorders. The two groups are further divided into categories based on etiology. The AHA also includes ion channelopathies as a cardiomyopathy, contrary to former classifications.

The ESC also suggested a classification two years later, aiming for a more clinically oriented system based on morphology and function [3]. This position statement proposes five categories: dilated-, hypertrophic-, restrictive-, arrhythmogenic- and unclassified cardiomyopathy. Each category is then sub-classified as familial or non-familial (**Figure 1**). As opposed to the AHA, channelopathies and

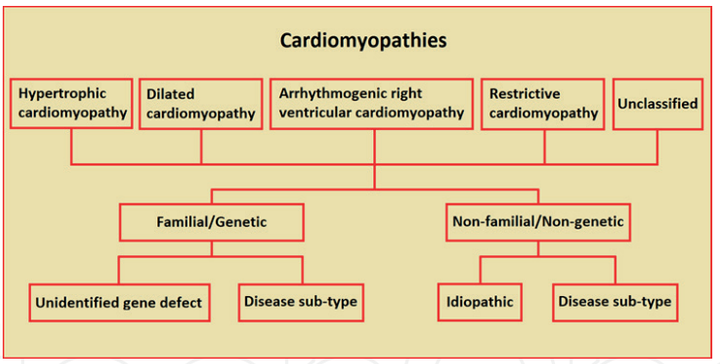

Figure 1.
Classification of cardiomyopathies as proposed by the European Society of Cardiology [3]. Cardiomyopathies are first classified according to morphology and function, then based on whether the disease is familial or non-familial, and lastly depending on either known disease causing mutation or pathophysiological mechanism. Image from Mattsson et al. [12]. Published by IntechOpen under open access https://creativecommons.org/licenses/by/3.0/.

conduction disorders were not considered cardiomyopathies. Neither in the classification system developed by the AHA nor the ESC, myocardial dysfunction caused by valvular, coronary, hypertensive or congenital heart disease, is considered as cardiomyopathy [4].

Lastly, a phenotype–genotype nomenclature, the MOGE(S) classification was suggested [4]. The letters each describe a feature of the cardiomyopathic condition where M stands for morphofunctional characteristic, O for organ involvement, G for genetic or familial inheritance pattern, and E for etiology. The S is optional, and refers to functional status.

For educative reasons, this book chapter will employ the classification suggested by the ESC.

3. Dilated cardiomyopathy

3.1 Definition

Dilated cardiomyopathy (DCM) involves a dilated left ventricle with impaired left ventricular systolic function not solely explained by abnormal loading conditions or coronary artery disease [13] (**Figure 2**). Left ventricular dilatation is defined as left ventricular end-diastolic volume or diameter that is >2 standard deviations from normal according to nomograms corrected for body surface area, age, and sex [13]. In some cases, dilatation and dysfunction of the right ventricle may occur as well [13]. It can be of genetic origin or can be attributed to non-genetic factors. To be categorized as familial, DCM has to be diagnosed in the proband and in at least on first- or second-degree relative [13].

3.2 Clinical features

DCM can lead to progressive heart failure and arrhythmias, and is associated with an increased risk of sudden cardiac death (SCD) [10]. Besides ventricular arrhythmias that may be fatal, atrioventricular block, atrial fibrillation and supraventricular tachycardia (both with and without preexcitation) may also occur [15]. Idiopathic or familial DCM is usually first diagnosed in patients between 20 and 50 years of age [16]. The most common presentation at diagnosis is related to congestive heart failure symptoms [17].

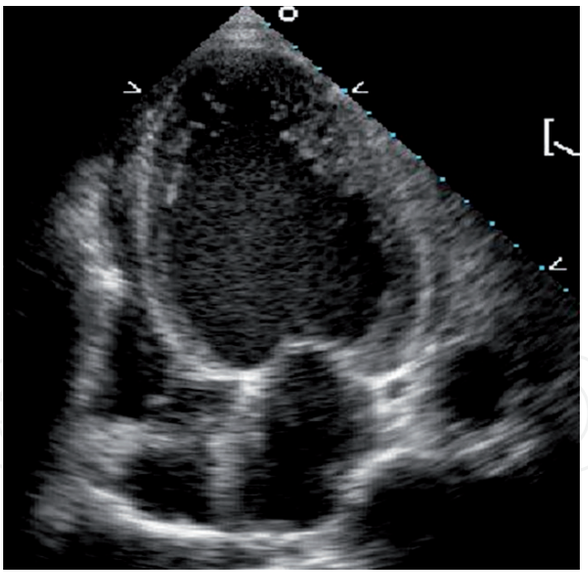

Figure 2.
Echocardiography that shows dilatation of the left ventricle and signs of diastolic dysfunction. Image adapted from Jamil et al. [14]. Published by IntechOpen under open access https://creativecommons.org/licenses/by/3.0/.

3.3 Epidemiology

DCM is the leading cause of heart transplantation and the third most common reason for heart failure [6]. The estimated prevalence is 1:2500 [6], and it more commonly affects men than women [18].

3.4 Etiology

There are several known causes for the sporadic form of DCM; toxins (for example ethanol, lead and cocaine), metabolic abnormalities (including hypothyroidism and thiamine deficiency), neuromuscular disorders (for example Duchenne muscular dystrophy) and inflammatory or infectious (viral, bacterial, fungal) conditions are all among them [16]. Chagas' disease, caused by the protozoan parasite *Trypanosoma cruzi*, is an example of an infectious disease that can lead to DCM [19]. WHO estimated that 10 million people were infected in 2009, and the cardiac form affects up to 30% [20]. Peripartum cardiomyopathy is a form of acquired DCM [15].

Approximately 20–35% of DCM cases are familial, while the most common inheritance pattern is autosomal dominant; X-linked, autosomal recessive and mitochondrial patterns occur seldom [6]. Mutations in genes coding cytoskeletal and sarcomeric proteins are the most common. Mutations in the gene coding for the protein titin is the most common, accounting for up to a quarter of known mutations [21]. Mutations in most genes result in similar phenotypes, thus broad gene panels are required. However, among patients who have atrioventricular block, mutations in the gene coding for lamin A/C (LMNA) are the most common [15]. Between 5 and 10% of patients with DCM have disease-causing LMNA mutation [18]. When no etiology is identified, DCM is categorized as idiopathic [16].

3.5 Treatment

DCM is treated similarly to other forms of heart failure with reduced ejection fraction (EF) [10]. Initial medical treatment consists of angiotensin-converting enzyme (ACE)-inhibitors or angiotensin receptor blockers (ARB), beta-blockers, and mineralocorticoid receptor antagonists (MRA). In patients who are still symptomatic

and have an EF ≤35% or, the ACE-inhibitor or ARB should be replaced by an angiotensin receptor neprilysin inhibitor. Cardiac resynchronization therapy should be considered in patients who have a QRS duration ≥150 ms, or QRS duration ≥130 ms and left bundle branch block. Ivabradine should be considered for patients in sinus rhythm with pulse above 70 beats per minute. Heart transplantation may be considered in end-stage heart failure, and left ventricular assist devices can be used a bridge to transplantation, or as a permanent treatment [22]. The sodium-glucose transporter protein 2 inhibitor dapaglifozin has been associated with a reduced cardiovascular mortality and a reduced risk of worsening heart failure in patients with heart failure with reduced EF, in both patients with diabetes type 2 [23] and non-diabetics [24].

In patients who have experienced a hemodynamically not tolerated ventricular arrhythmia, implantable cardioverter defibrillator (ICD) therapy is recommended. Furthermore, an ICD is recommended for those with symptomatic heart failure (New York Heart Association [NYHA] class II-III) with reduced EF of ≤35%, following at least three months of optimal medical therapy. These recommendations apply if the expected survival exceeds one year with good functional status. In the case of an established disease-causing LMNA mutation and clinical risk factors, an ICD should also be considered [18].

4. Hypertrophic cardiomyopathy

4.1 Definition

The ESC defines HCM as "presence of increased left ventricular wall thickness that is not solely explained by abnormal loading conditions" [25]. More precisely, a wall thickness of ≥15 mm in at least one left ventricular myocardial segment is required for the diagnosis of HCM in adults (**Figure 3**). In borderline cases with 13–14 mm, careful evaluation, including family history, is needed; if a first-degree relative had definite HCM the diagnosis is made [25]. Notably, the American guidelines from 2011 hold another position. They recognize HCM as a clinical entity "… characterized by unexplained left ventricular hypertrophy associated with nondilated ventricular chambers in the absence of another cardiac or systematic disease that itself would be capable of producing the magnitude of hypertrophy …" [26]. There are several diseases, especially in children and young adults, which mimic

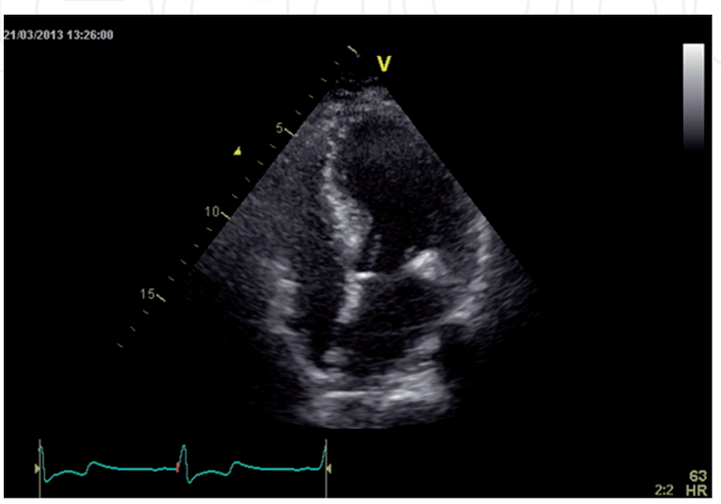

Figure 3.
Echocardiography showing septal hypertrophy in a patient with HCM. Image used with permission from the author Peter Magnusson.

hypertrophy caused by sarcomeric protein mutations. The American guidelines emphasize that these conditions, so-called phenocopies, should not be included in the term HCM [26].

In the American definition of HCM, there are other groups of diseases and conditions that present with hypertrophy, that are not included in the term HCM. These can be categorized based on cellular mechanisms, i.e. neuromuscular, mitochondrial, and metabolic disorders (glycogen storage, carnitine, lysosomal storage). Among the metabolic disorders are glycogen storage diseases such as Danon disease, Pompe disease, and Anderson-Fabry disease. Malformation syndromes are typically diagnosed in pediatric settings; LEOPARD (lentiges, ECG abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness), Noonan syndrome (facial features, short height, congenital heart disease, bleeding problems, and skeletal malformations), and others.

4.2 Clinical features

Typical symptoms include dyspnea, palpitations, syncope and chest discomfort, but many patients lack specific symptoms altogether [25]. Indeed, the majority are likely never diagnosed [27]. Chest discomfort sometimes occurs at rest or during exertion, postprandial or following alcohol consumption. It is uncommon for people with HCM to present with decompensated heart failure, but symptoms of chronic heart failure are often present. The pathology varies, from diastolic dysfunction with preserved EF to systolic left ventricular dysfunction or left ventricular outflow tract obstruction. Among those with left ventricular outflow tract obstruction, a systolic murmur can sometimes be auscultated at the left sternal edge [25].

As for syncope as a symptom of HCM, the cause can be, among others, complete heart block, sinus node dysfunction, or ventricular tachycardia [25]. Causes that are not directly related to the conduction system include left ventricular outflow obstruction, diastolic dysfunction and altered baroreflex mechanisms [28].

According to U.K. data on 357 sudden death cases in athletes the mean age was 29 years and the vast majority males (92%) [29]. Sudden arrhythmic death was the most common cause of death, and HCM accounted for 6% of all deaths. Interestingly, 40% of these athletes died during resting conditions. An Italian sample of 54 fatal cases (mean age 27 years; 76% men) revealed HCM in 9.2% [30].

4.3 Epidemiology

In adults, the prevalence of HCM is frequently reported as 1:500 [31], but a recent Icelandic study reported 1:1600 [32]. On the other hand an extremely high prevalence (about 1:200) was claimed when both phenotypes and genotypes were included based on cohorts from expert centers [33]. Moreover, misclassifications are common in HCM [34].

4.4 Etiology

HCM is often explained by a genetic disease (in approximately half of the cases); a mutation in cardiac sarcomeric protein genes, with an autosomal dominant pattern of inheritance. X-linked inheritance is less common, and autosomal recessive is the most uncommon pattern. Other genetic disorders, such as inherited neuromuscular diseases or chromosome abnormalities, are the underlying reason for 5–10% of adult cases. Non-genetic causes of HCM include amyloidosis and drug toxicity. The etiology of the remaining 25–30% is unknown [25].

4.5 Treatment

Patients with symptomatic left ventricular outflow tract obstruction should initially receive beta-blockers in the highest tolerated dose. If symptoms persist, the next step is adding disopyramide. For those who cannot tolerate beta-blockers or when they are ineffective, verapamil is an option. Loop- or thiazide diuretics may be used in low doses to improve dyspnea. For patients with a left ventricle outflow tract obstruction gradient exceeding 50 mmHg, persistent symptoms (moderate to severe) and/or repeated syncope upon exertion, despite medical therapy, invasive treatment with septal myectomy or alcohol septal ablation should be considered. For symptomatic elderly patients who are not candidates for invasive treatment, permanent pacing with short atrioventricular interval may be considered [25].

For those without left ventricle outflow tract obstruction who have symptoms of heart failure but a normal EF, beta-blockers, verapamil (or diltiazem) and careful administration of diuretics is indicated. Renin-angiotensin-aldosterone system inhibition is not extensively studied in HCM patients, but the ESC recommends the use of beta-blockers, ACE-inhibitors, ARB, MRA and diuretics for HCM patients with symptoms of heart failure and reduced EF, in line with their general recommendations for management of chronic heart failure [25].

Pacemaker therapy in bradycardia is recommended according to the general ESC guidelines [25]. When it comes to ICD treatment, patients with HCM who have not experienced ventricular fibrillation or ventricular tachycardia with hemodynamic compromise, may be candidates for ICD based on the 5-year risk, determined by the validated ESC calculator HCM Risk-SCD [18, 35].

5. Restrictive cardiomyopathy

5.1 Definition

Restrictive cardiomyopathy (RCM) is defined as the presence of restrictive filling in combination with normal or decreased diastolic ventricular volume in one or both ventricles. The systolic function is normal or only slightly impaired [11]. Different underlying causes may result in normal or increased wall thickness [36].

5.2 Clinical features

Since either one or both ventricles can be affected, both left and right ventricular failure may occur. Symptoms of right ventricular failure generally predominate (ascites, peripheral edema), but breathlessness as a symptom of left-sided heart failure occurs as well [36]. In an advanced stage of the disease all signs of heart failure, except cardiomegaly, develop [36]. Certain findings are more common with specific etiologies, such as conduction disturbances in amyloidosis [37] and sarcoidosis, and atrial fibrillation in idiopathic RCM and amyloidosis [36]. Overall, conduction disturbances as well as arrhythmias occur frequently [38]. Distinguishing RCM from constrictive pericarditis (which presents with similar findings) can be challenging, but is important due to the differences in prognosis and management [36, 39].

5.3 Epidemiology

Epidemiologic data is scarce, but RCM has been described as the least common cardiomyopathy [36].

5.4 Etiology

RCM can be idiopathic or familial. Furthermore, there are a number of different local or systemic disorders that can cause RCM [36]. Endomyocardial fibrosis is believed to be the most common cause of RCM [40]. It is endemic to parts of Africa, Asia, South and Central America, but can occur elsewhere sporadically [36]. It predominantly affects children and adolescents. The etiology is not known [40]. Other endomyocardial causes of RCM include radiation and metastatic cancers. Infiltrative diseases causing RCM include cardiac amyloidosis and sarcoidosis. Finally, RCM can develop due to storage diseases, such as hemochromatosis [36].

5.5 Treatment

Prognosis is poor, especially in children, where the 2-year survival rate is less than 50% [41]. Treatment serves to manage heart failure and, if possible, treat the underlying disease [38]. Venous congestion is treated with diuretics, used with caution as to avoid reducing filling pressures and decrease cardiac output [36]. Since atrial fibrillation can increase diastolic dysfunction, maintaining sinus rhythm is of importance and antiarrhythmic agents may be indicated [36]. Beta-blockers and calcium channel blockers are sometimes not tolerated, and should be carefully introduced if needed. Regarding ACE-inhibitors and ARB, there is not much proof of benefit and they are not always tolerated, but can be considered [38]. Due to the propensity for thrombus to form in the left atrial appendage, anticoagulation may benefit most patients [36, 38]. Selected patients may be candidates for heart transplantation or left ventricular assist device [38].

6. Arrhythmogenic cardiomyopathy

6.1 Definition

In ACM, the ventricular myocytes are replaced by fibrofatty tissue [42]. The myocardial atrophy is progressive, starting in the epicardium, it becomes transmural with time and leads to wall thinning [42]. ACM was previously known as ARVC or ARVD where the D stands for dysplasia, which it was originally characterized as [42]. With time it has become apparent that there are variants where the left ventricle is more severely involved than the right, which is the reason some have suggested an updated terminology [42]. Notwithstanding, the fibrofatty tissue replacement often occurs in a "triangle of dysplasia", involving the right ventricular inflow, outflow and apex [3]. In the 2008 classification by the ESC, the term ARVC is used. In 2019 the Heart Rhythm Society published a consensus statement on ACM, where ARVC and arrhythmogenic left ventricular cardiomyopathy were considered to be separate cardiomyopathies with specific phenotypes, under the umbrella of the term ACM [43].

In their 2008 classification, the ESC defines ARVC as dysfunction of the right ventricle, with or without left ventricular involvement, in the presence of histological evidence and/or ECG abnormalities in accordance with published criteria [3]. These include, but are not limited to, epsilon waves in leads V_1-V_3, inverted T-waves in leads V_1-V_3 or beyond in people above 14 years of age in the absence of right bundle branch block and sustained or nonsustained ventricular tachycardia of left bundle-branch morphology with superior axis [44]. The diagnostic criteria for ARVC are subdivided into major and minor criteria, where diagnosis requires two major criteria, or one major criterion in combination with two minor criteria, or

four minor criteria from different categories. The categories are global or regional dysfunction and structural alterations, tissue characterization of walls, repolarization abnormalities, depolarization or conduction abnormalities, arrhythmias, and family history [44]. Variants of the disease, such as Naxos disease and Carvajal syndrome, albeit rare, present with a specific phenotype and are considered cardiocutaneous entities; they share the presentation and risk of common ARVC [45, 46].

6.2 Clinical features

The presentation of ACM varies greatly; while some patients are asymptomatic, others suffer from supraventricular arrhythmias, ventricular tachycardia, right-heart failure [47], or even biventricular heart failure [48]. In addition to this, ACM is one of the most common causes for SCD among young people [42], and one study has reported that 10% of SCDs (in people between 1 and 65 years of age) can be attributed to ARVC [47]. A retrospective study found that among 130 patients with ARVC, overall mortality was primarily of cardiovascular origin, where heart failure accounted for two thirds of the cardiac deaths and SCD for the remaining one third [49].

6.3 Epidemiology

The prevalence of ARVC has been estimated to range between 1:1000 and 1:5000 in adults [50, 51].

6.4 Etiology

ACM is usually familial, with an autosomal dominant pattern of inheritance. The majority of patients have at least one disease-causing variant of a gene coding for a desmosomal protein [43]. The protein plakoglobin is reported to be implicated in ACM, most notably in the autosomal recessive form Naxos disease [52]. Another autosomal recessive variant of ACM is Carvajal syndrome [46].

6.5 Treatment

Competitive exercise has been shown to increase the risk of SCD in adolescents and young adults five-fold [53], and frequent exercise increases the risk of ARVC diagnosis, ventricular arrhythmias and heart failure among carriers of desmosomal mutations [54]. Consequently, it is a class I recommendation from the ECS that patients with ARVC must refrain from competitive- and endurance sports, and a class IIa recommendation that they do not participate in any athletic activities (with the possible exception of recreational low-intensity sports) [48].

Regarding medical therapy, beta-blockers should be considered in all ARVC patients, and are specifically recommended for those with recurrent ventricular tachycardia or ICD shocks (either appropriate, or inappropriate shocks due to supraventricular tachycardias). Antiarrhythmic drugs can be used to prevent ventricular arrhythmias. Amiodarone, by itself or combined with beta-blockers, has been suggested by available evidence as the most effective alternative. It has not been proven to prevent SCD [48]. Patients who develop heart failure should receive standard medical treatment [48].

There is no proof that catheter ablation prevents SCD in ARVC, but it can reduce the recurrence of ventricular tachycardia. It is recommended in patients with incessant ventricular tachycardia and those who experience frequent appropriate ICD shocks despite maximal tolerable medical therapy [48].

Preventing SCD is the most important goal of treatment [42]. The only therapy that has been proven to be life-saving is ICD, but the benefit must be weighed against the significant morbidity due to inappropriate shocks and device-related complications [42]. Indications for ICD are based on risk stratification, where patients are divided into one of three categories based on their risk factors for major arrhythmic events. As a final option, when patients suffer from severe congestive heart failure unresponsive to other treatment, or recurrent ventricular tachycardia or -fibrillation despite ablation and/or ICD therapy, heart transplantation is recommended [48].

Patients should be followed-up clinically and with ECG, echocardiography, 24-h Holter monitoring, and exercise-testing at regular intervals throughout their lives [48].

7. Unclassified cardiomyopathy

In the 2008 position statement from the ESC regarding classification of the cardiomyopathies, left ventricular non-compaction (LVNC) and takotsubo cardiomyopathy are regarded as unclassified cardiomyopathies [3]. Since this chapter is structurally based on the position statement, these two conditions will be briefly described. The group of cardiomyopathies that are deemed unclassified, however, has varied over time. In 1980, the WHO included, among others, endocardial fibroelastosis and Fiedler's myocarditis [2]. 15 years later, when the updated classification by the WHO was published, non-compaction cardiomyopathy, systolic dysfunction with minimal dilatation and mitochondrial cardiomyopathies were added to the unclassified cardiomyopathies [11, 55]. The future most certainly holds exciting advances in this field, and it is not a stretch of the imagination to think that this category will continue to evolve in the years to come.

7.1 Takotsubo cardiomyopathy

7.1.1 Definition

Takotsubo cardiomyopathy was first described in 1990. The name refers to a Japanese octopus-trap that bears likeness to the end-systolic left ventriculogram seen in the condition [56]. Sometimes referred to as transient left ventricular apical ballooning syndrome, takotsubo cardiomyopathy leads to regional systolic dysfunction of the left ventricular apex and/or mid-ventricle. For diagnosis, coronary disease should be excluded by coronary angiography [3]. Since ST-segment elevation and positive troponin is seen in more than 80% of patients [57], the diagnosis is often not considered until after coronary angiography is performed. In their 2016 position statement, the ESC refers to takotsubo as a syndrome rather than a cardiomyopathy, with the motivation that the diagnosis is based on a set of clinical observations - which is what defines a clinical syndrome. Since the patients do not appear to have a primary heart muscle disorder, no common genetic etiology has been identified, and most recover fully - takotsubo is likely different from the primary cardiomyopathies [58].

7.1.2 Clinical features

The first symptom is usually chest pain, which affects most of the patients. The condition highly resembles an acute coronary syndrome. Dyspnea is another

common presentation [57]. Although the disease is generally considered benign, more than half of patients experience some form of complication [58]. Between 4% and 20% of patients develop cardiogenic shock [58], and 1.5% go into ventricular fibrillation [57]. Most patients have clear left ventricular dysfunction when they are admitted, but in weeks the cardiac function improves drastically [57]. Left ventricular EF usually recovers within three months, while ECG and elevated BNP levels may persist for up to a year or, sometimes, become permanent [58]. However, one retrospective observational study has found that early and late mortality in takotsubo cardiomyopathy is similar to the numbers seen in acute myocardial infarction [59].

7.1.3 Epidemiology

It has been estimated that approximately 2% of ST-segment elevation myocardial infarctions are in fact takotsubo cardiomyopathy. Out of all patients, most are post-menopausal women, about 90% [57].

7.1.4 Etiology

The exact pathophysiology is unknown, although several theories have been presented. Multivessel coronary vasospasm, coronary microvascular dysfunction and elevated levels of catecholamines leading to cardiotoxicity are found among these [57]. Often, the debut is preceded by emotional or physical stress, but in a minority of patients no such stressor can be identified [57]. Because of this, the term broken heart syndrome is sometimes used for the condition [60]. However, in a small number of patients takotsubo is triggered by a positive emotional experience [61].

7.1.5 Treatment

No randomized clinical trials that can form a basis for treatment recommendations exist. The ESC Heart Failure Association has proposed a risk stratification system, including among others age, systolic blood pressure, and pulmonary congestion, to be used for choosing the appropriate approach. In patients without complications and a left ventricular EF of over 45%, early discharge from hospital may be considered. Heart failure medications, including beta-blockers, should be considered in patients with an EF between 35 and 45%, who are otherwise at low risk. According to some experts, vasoactive drugs such as ACE inhibitors, should not be given to patients with a normal cardiac output, as takotsubo may be associated with low peripheral vascular resistance [58].

Higher risk patients (risk factors include, but are not limited to, age 75 or above, EF below 35%, and systolic blood pressure less than 110 mmHg) with takotsubo cardiomyopathy should be monitored for at least 72 hours after presentation with continuous ECG. It is recommended to avoid sympathomimetic drugs. Beta-blockers may be considered in hemodynamically stable patients, and patients with tachyarrhythmias. Patients with a hemodynamically significant left ventricular outflow tract obstruction should be considered for treatment with a beta-blocker of selective alpha1-agonist. Cardiogenic shock in patients with takotsubo cardiomyopathy can be managed with temporary left ventricular assist devices and extracorporeal membrane oxygenation, or low-dose levosimendan infusion. Other inotropes are generally contraindicated, owing to the possible worsening of status and outcome due to their activation of catecholamine receptors [58].

Low risk patients should be followed-up for 3 to 6 months, with cardiac imaging and a review of the medication [58].

7.2 Left ventricular non-compaction

7.2.1 Definition

LVNC is characterized by deep intertrabecular recesses in the left ventricle [62], resulting in a "spongy" morphological appearance [6]. LNVC often leads to a thickened myocardial wall, due to thickening of the endocardial layer, but the epicardium is compacted and thin (**Figure 4**). Dilation of the left ventricle and systolic dysfunction occur in some patients [3]. In their 2008 classification, the ESC commented that it is unclear whether LVNC is a distinct cardiomyopathy or a morphology seen in several different cardiomyopathies. Echocardiographic diagnosis is based on the Jenni criteria consisting of four criteria: absence of other cardiac abnormalities, end-systolic ratio between non-compacted endocardial myocardium and compacted epicardial myocardium of >2, hyper-trabeculation localized to the apex/mid-inferior/mid-lateral areas, and color doppler with blood flow from the ventricle into deep intertrabecular recesses that do not communicate with coronary vessels [63].

7.2.2 Clinical features

The dominating clinical manifestations are heart failure, arrhythmias and embolism due to thrombi forming within the intertrabecular recesses, but the presentation varies and some patients are asymptomatic [65]. One study reports chronic atrial fibrillation in 26% of LVNC patients, and ventricular tachycardia in 41% [66]. In the same study, 50% of all deaths were SCD. Non-compaction of both ventricles has been reported [67], but since the right ventricular apex is often highly trabeculated, the distinction between normal and pathological patterns is difficult and the existence of right ventricular non-compaction is therefore disputed [65, 66].

7.2.3 Epidemiology

The prevalence is unknown, and the results of studies vary. One echocardiographic study estimated a prevalence in the general population of 0.05% [67], another prevalence estimation based on patients referred to an echocardiography laboratory was 0.014% [66].

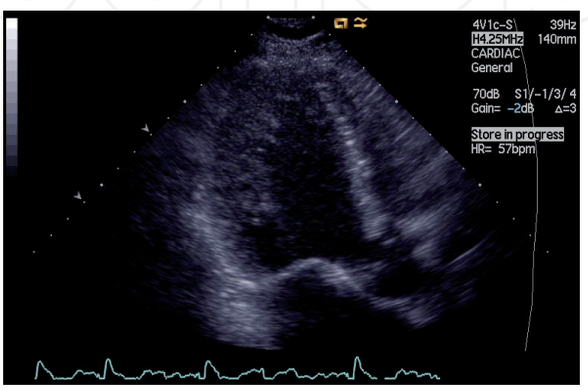

Figure 4.
A thick, non-compacted myocardium in the left ventricular wall. Transthoracic echocardiogram, during systole, apical long-axis view. Image from Mattsson et al. [64]. Published by BMC Cardiovascular Disorders under open access https://creativecommons.org/licenses/by/4.0/.

7.2.4 Etiology

LVNC is believed to occur when compaction of the myocardial fibers and meshwork is arrested during intrauterine development [62]. Normally, the intertrabecular recesses seen in LVNC are transformed to capillaries during 5 to 8 weeks of fetal development [68]. Serial echocardiographic studies where LVNC was not diagnosed in the first echocardiogram, however, suggest that it could be an acquired condition. The fact that LVNC is associated with mutations in sarcomere protein genes found in patients with both DCM and HCM, is another reason to ask the question whether LVNC could develop later in life [69].

There are descriptions of both familial and non-familial cases, and LVNC can be isolated or associated with other congenital heart anomalies [6]. The disease is classified as a primary genetic cardiomyopathy by the AHA [6]. Apart from mutations in sarcomeric proteins, LVNC can be linked to mutations in mitochondrial, Z-disc or cytoskeletal proteins [69]. The predominant mode of inheritance is autosomal dominant with incomplete penetrance, but autosomal recessive and X-linked patterns occur as well. Approximately one in four patients has a familial form [70].

7.2.5 Treatment

No specific treatment for LVNC exists [69]. Heart failure is treated with standard medical therapy. Yearly ambulatory ECGs for monitoring to assess rhythm disturbances, since these occur frequently in LVNC, should be performed [65]. In a long-term follow-up of 34 adult LVNC patients, thromboembolic complications were reported in 24%; thus the authors recommended that oral anticoagulation for all patients diagnosed with LVNC should be considered [66]. Another study found systemic embolization in 3 of their 8 patients [71]. In an article published in 2011, the authors recommend oral anticoagulation only in patients with an EF <40%, since they have never observed thromboembolic complications in a patient in sinus rhythm with a preserved EF [69]. There are no guidelines regarding anticoagulation in LVNC patients, and there is no general consensus in clinical practice [72].

8. Conclusions

The vast complexity that surrounds the diseases of the heart muscle can make the diagnosis and management of cardiomyopathy patients challenging. However, since the prevalence of heart failure and life-threatening arrhythmias is high among patients with cardiomyopathy it is crucial to correctly identify the patients and risk stratify. So far, as guidelines specific for heart muscle disease are not available for all its forms, treatment follows general guidelines for arrhythmias and heart failure. European or world-wide registries would offer most valuable insights and illuminate the future management of cardiomyopathies.

Conflict of interest

IK and ML report no conflicts of interest. GM has received speaker's fee from Alnylam, MSD, and Internetmedicin. Peter Magnusson has received speaker's fees or grants from Abbott, Alnylam, Amicus Therapeutics, AstraZeneca, Bayer, Boehringer-Ingelheim, Coala Life, Internetmedicin, Lilly, MSD, Novo Nordisk, Octopus Medical, Orion Pharma, Pfizer, Vifor Pharma, and Zoll.

Acronyms and abbreviations

ACM	arrhythmogenic cardiomyopathy
ACE	angiotensin-converting enzyme
AHA	American Heart Association
ARB	angiotensin receptor blocker
ARVC	arrhythmogenic right ventricle cardiomyopathy
DCM	dilated cardiomyopathy
EF	ejection fraction
ESC	European Society of Cardiology
HCM	hypertrophic cardiomyopathy
ICD	implantable cardioverter defibrillator
LVNC	left ventricular non-compaction
MRA	mineralocorticoid receptor antagonist
NYHA	New York Heart Association
RCM	restrictive cardiomyopathy
SCD	sudden cardiac death
WHO	World Health Organization

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