Chapter

Cardiomyopathy Etiologies, Symptoms and Management

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Abstract

Cardiomyopathy can be defined as a structural and functional myocardial disorder that is commonly genetic rather than due to coronary artery, valvular or congenital heart disease. It can be subcategorized into dilated, hypertrophic, restrictive, unclassified, and arrhythmogenic right ventricular cardiomyopathy/dysplasia. They can be further subdivided into primary and secondary cardiomyopathy. Primary includes genetics (HOCM, ARVC/D), mixed (DCM, RCM) or acquired (stress-induced, myocarditis) causes; while secondary cardiomyopathy is derived from the involvement of other organ systems. Cardiomyopathies can be identified by echocardiogram to display the anatomic and functional changes related to each subtype including systolic or diastolic dysfunction. In certain instances, cardiac-MRI or CT are used to further elucidate its specific characteristics such as fatty infiltration and focal hypertrophy. Treatment is very diverse and catered to each individual case. This will all be further elaborated on in the following chapter.

Keywords: cardiomyopathy, heart diseases, systolic dysfunction, diastolic dysfunction

1. Introduction

Cardiomyopathies are a heterogeneous group of diseases of the myocardium that are associated with mechanical and/or electrical dysfunction. They generally exhibit inappropriate ventricular hypertrophy or dilation and have multiple etiologies, which are often genetic [1]. They can be further subdivided into primary and secondary cardiomyopathy. Primary includes genetics, acquired or mixed causes; while secondary cardiomyopathy is derived from the involvement of other organ systems. Cardiomyopathies can be identified by echocardiogram to display the anatomic and functional changes related to each subtype including systolic or diastolic dysfunction. In certain instances, cardiac-Magnetic resonance imaging or Computer tomography scans are used to further elucidate its specific characteristics such as fatty infiltration and focal hypertrophy. Treatment is very diverse and catered to each individual case. This will all be further elaborated on in the following chapter.

I. Primary & Secondary Cardiomyopathy:

Cardiomyopathies can be characterized into two different groups, primary and secondary. Primary cardiomyopathies are defined by primary involvement of the heart while secondary cardiomyopathies are consequences of other medical disease states such as endocrine diseases or drug induced. Primary cardiomyopathies can be further divided by their causes. These include cardiomyopathies of genetic, acquired, or mixed origin [1].

Genetic sources of primary cardiomyopathy include hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), mitochondrial myopathies and ion channel disorders. Mixed causes of primary cardiomyopathy can include dilated cardiomyopathy (DCM) and restrictive cardiomyopathy (RCM). Finally, the acquired causes of primary cardiomyopathy include a wide variety of diseases, such as myocarditis, peripartum cardiomyopathy, stress-induced cardiomyopathy (Takotsubo) and tachycardia-induced cardiomyopathy. These are all summarized in **Table 1**.

II. Systolic and Diastolic Dysfunction

Systolic dysfunction is defined as a decrease in the contractility of the heart [2]. Contractility can be reduced throughout the left ventricle (LV), as seen in DCM, or only in a portion of the LV, as seen in stress-induced cardiomyopathy. Systolic dysfunction is also classically seen following myocardial ischemia. Initially, cardiac output is maintained through compensatory mechanisms which include an increased preload in order to improve contractility (Frank-Starling relationship) and enlargement of the LV to increase the stroke volume. However, these mechanisms ultimately fail and lead to the clinical manifestations of heart failure. Systolic dysfunction can be evaluated through echocardiogram (echo) and is characterized by a decreased left ventricular ejection fraction (LVEF) and increased end diastolic volume (EDV).

Diastolic dysfunction is characterized by abnormal myocardial filling and relaxation with concurrent elevated filling pressures. It can occur in combination with systolic dysfunction or it can be an isolated phenomenon. Its main features are due to impairment of active relaxation and/or passive compliance during LV diastole. This takes place during both isovolumetric relaxation and early rapid filling. Diastolic dysfunction is a common characteristic of both HCM and RCM and can sometimes be seen in patients with DCM. It is also found secondary to myocardial hypertrophy presenting with decreased compliance. An echo study is done to identify diastolic dysfunction where a normal LVEF and EDV are seen, however occasionally systolic function may be impaired. These two markers are one way to differentiate diastolic from systolic dysfunction, both of which lead to a common clinical endpoint of heart failure symptoms.

Primary Cardiomyopathy
Genetic Causes: Hypertrophic Cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy/dysplasia, mitochondrial myopathies and ion channel disorders
Acquired Causes: Myocarditis, Peripartum cardiomyopathy, stress-induced cardiomyopathy and tachycardia-induced cardiomyopathy
Mixed Causes: Dilated cardiomyopathy and Restrictive cardiomyopathy
Secondary Cardiomyopathy
Toxin induced, medication induced, Endocrine disorders, autoimmune/collagen diseases, nutritional deficiencies.

Table 1.
Primary and secondary causes of cardiomyopathy.

IIIA. Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) manifests as global dilation of one or both ventricles leading to systolic dysfunction. Left ventricular ejection fraction is ≤40% and affected patients can develop symptomatic heart failure (HF). DCM causes around 10,000 deaths and 46,000 hospitalizations in the United States each year. Idiopathic DCM is the leading indication for heart transplantation [3]. Affected patients are generally between 20 and 60 years of age [4]. Symptoms vary, but most patients present with HF symptoms of progressive dyspnea with exertion, peripheral edema, orthopnea, and/or paroxysmal nocturnal dyspnea. Conduction disturbances, cardiomegaly, thromboembolic disease, and sudden death can also be observed [5, 6].

There are many causes of DCM including idiopathic, stress-induced, myocarditis, infiltrative disease (amyloidosis, sarcoidosis, hemochromatosis), peripartum cardiomyopathy, tachycardia-mediated, infections, drugs (alcohol, cocaine, anthracyclines) [7], as well as others illustrated in the **Table 2**.

DCM is frequently idiopathic, indicated after exclusion of both primary and secondary causes of cardiac disease except genetic causes. Familial disease is seen in about 50% of patients with idiopathic DCM. The disease is generally inherited in autosomal dominant fashion but also other forms of inheritance (autosomal recessive, X-linked, and mitochondrial). Mutations in more than 30 genes were identified in the past 20 years. Sarcomere genes are responsible for about 30% of familial DCM cases. These include mutations in genes for beta myosin heavy chain (MYH7), cardiac troponin T (TNNT2), titin (TTN), alpha-tropomyosin (TPM1), and cardiac troponin C (TNNC1) [8].

IIIB. Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a disease of the heart muscle that is mainly due to genetic mutations in sarcomere genes, the contractile component of the heart. The prevalence of HCM is about 0.5% in adults and typically has an autosomal dominant transmission pattern [9]. HCM is defined by left ventricular hypertrophy (LVH), which manifests with a multitude of different clinical features. The location and amount of hypertrophy will determine the clinical presentation

Infectious diseases: adenovirus, HIV, influenza virus, coxsackie virus, streptococci-rheumatic fever, diphtheria, typhoid fever
Deposition diseases: amyloidosis, hemochromatosis
Medications: antiretroviral drugs (didanosine, zidovudine, zalcitabine), chemotherapeutic agents (cyclophosphamide, anthracyclines, trastuzumab), chloroquine, hydroxychloroquine, phenothiazines, clozapine
Toxins: ethanol, amphetamines, cocaine, lead, mercury, lithium, carbon monoxide
Nutritional deficiencies: niacin, selenium, thiamine, carnitine
Electrolyte and renal abnormalities: hypophosphatemia, uremia, hypocalcemia
Autoimmune/inflammatory: rheumatoid arthritis, systemic lupus erythematosis, scleroderma, dermatomyositis, sarcoidosis, giant cell arteritis, kawasaki disease
Endocrinologic disorders: growth hormone and thyroid hormone excess/deficiency, diabetes mellitus, pheochromocytoma, cushing's syndrome
Genetic: duchenne's muscular dystrophy, familial and sporadic genetic cardiomyopathies, friedreich's ataxia, myotonic dystrophy, arrhythmogenic right ventricular cardiomyopathy
Other: tachycardia, peripartum cardiomyopathy, hypothermia, heat stroke, sleep apnea

Table 2.
Etiologies of dilated cardiomyopathy.

which can include left ventricular outflow tract (LVOT) obstruction, myocardial ischemia, diastolic dysfunction and mitral regurgitation.

HCM presents with a huge spectrum of signs and symptoms; patients can be asymptomatic or present with symptoms of chest pain, arrhythmias, or those related to HF [10]. Many patients are diagnosed with HCM incidentally during a routine doctor visit by identification of an abnormal ECG or murmur and through family screening protocols. Otherwise, patients can present with many different symptoms including dyspnea on exertion, fatigue, chest pain, palpitations, and presyncope or syncope commonly after exertion.

The most common presenting symptom is HF seen clinically as dyspnea on exertion. This is found in approximately 90% of symptomatic patients and can result from diastolic dysfunction caused by hypertrophy, impaired LV emptying from the LVOT obstruction, and mitral regurgitation. Concurrent systolic dysfunction is also seen in very extensive disease due to adverse LV remodeling [11].

Another common symptom is angina, both typical (following exertion) and atypical, which is frequently worsened after heavy meals. The pathophysiology behind this chest pain in HCM can be broken down into two categories: increased myocardial oxygen demand and decreased myocardial blood flow. HCM increases oxygen demand in several ways including increased muscle mass, myocardial hypertrophy and disarray, and increased diastolic pressures due to LVOT obstruction. Causes of decreased myocardial blood flow in HCM is due to decreased ability of coronary arterioles to vasodilate and myocardial fibrosis.

Arrhythmias are also a major complication of HCM as they can lead to sudden cardiac death (SCD) [12]. Both supraventricular and ventricular arrhythmias are found which can lead to palpitations, dyspnea, presyncope, syncope, and SCD. Of the supraventricular arrhythmias, atrial fibrillation (AF) is the most common [12].

Syncope occurs in around 15–25% of patients with HCM and is caused by a variety of mechanisms which ultimately lead to decreased cardiac output. Some of these include AF, LVOT obstruction and conduction abnormalities such as atrioventricular nodal block. Syncope not due to vasovagal or cardiogenic causes is an increased risk for SCD, especially when occurring in young patients. Predictors of SCD includes experiencing at least one syncopal episode include a family history of SCD from HCM, massive LVH, unexplained syncope, LV apical aneurysm, HCM with LV systolic dysfunction [13, 14].

Just as there are a variety of clinical symptoms, the physical exam of a patient with HCM can range from normal to several nonspecific findings. These findings include a systolic crescendo-decrescendo murmur that is similar to the murmur seen with aortic stenosis, a fourth heart sound. Physical exam findings are mainly caused by LVOT obstruction thus if there is minimal or no obstruction, the physical exam will commonly be normal. Other physical exam findings are not specific to HCM and can be seen with other heart diseases. They are listed in the following **Table 3**.

Paradoxical Split of S2
Brisk and Bifid Carotid Pulse
Prominent a wave seen in neck veins
Diffuse, forceful LV apical impulse
Systolic thrill
Parasternal lift

Table 3.
Physical exam findings in hypertrophic cardiomyopathy.

The histology of HCM is unique, showing myocyte hypertrophy and myofibrillar disarray with interstitial fibrosis. Coronary arterioles with decreased luminal cross-sectional area can also be seen. These arterioles have reduced ability to vasodilate leading to decreased myocardial blood flow during periods of stress [15].

IIIC. Restrictive Cardiomyopathy

Restrictive cardiomyopathy (RCM) presents as non-dilated ventricles and diastolic dysfunction. It causes a ventricular filling defect, leading to elevated pressure and biatrial enlargement. Systolic function is generally normal unless RCM becomes more severe.

RCM is significantly less common universally than both DCM and HCM. However, mortality from RCM is high in Africa, South and Central America, and Asia. This is due to a higher incidence of endomyocardial fibrosis, which is one of the major causes of RCM.

There are several causes of RCM including infiltrative, familial non-infiltrative, storage diseases, other disorders (scleroderma, endomyocardial fibrosis, diabetic cardiomyopathy), secondary causes, and idiopathic RCM [16]. The various etiologies are demonstrated in **Table 4**.

RCM presents as pulmonary and systemic congestion with peripheral edema, dyspnea, palpitations, weakness, and inadequate cardiac output with exercise. Severe RCM can have elevated central venous pressure, ascites, and hepatosplenomegaly [17]. In addition, autonomic dysfunction leading to arrhythmias can occur. During auscultation, a third heart sound can be heard. Jugular venous pressure (JVP) is often elevated with a prominent y descent. Kussmaul's sign with an increase in JVP with inspiration may be observed. These two JVP signs are seen in constrictive pericarditis as well.

IIID. Arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is defined by right ventricular (RV) origin arrhythmias and structural abnormalities. The myocardium is scarred and replaced with fibrous or fibro-fatty tissue. Scarring can occur first regionally and then become global leading to RV dilation, RV dysfunction, and wall motion abnormalities. Demonstration of biventricular myocardial injury is illustrated through the use of autopsy investigations, genotype and phenotype correlation studies and cardiac MRI. However, these diagnostic tools show an equal or increased extent of left ventricular severity when compared to the right ventricular involvement. This development has led to a new understanding of arrhythmogenic cardiomyopathy(ACM) [18]. ACM/ARVC is generally inherited in an autosomal dominant fashion. However, autosomal recessive inheritance has also been noted as in the cardiocutaneous syndrome, Naxos disease [19]. Patients can

Infiltrative disorders: amyloidosis, Gaucher disease, sarcoidosis, fatty infiltration, and Hurler syndrome
Familial: familial cardiomyopathy with unknown gene, sarcomeric protein mutations (troponin I, essential light chain of myosin), familial amyloidosis, pseudoxanthoma elasticum, and desminopathy, hemochromatosis, Fabry disease, glycogen storage disease
Storage diseases: Fabry disease, hemochromatosis, and glycogen storage disease.
Other disorders: scleroderma, diabetic cardiomyopathy, endomyocardial fibrosis (caused by hypereosinophilic syndrome, drugs, or idiopathic), chemotherapy, radiation, metastatic cancers, and carcinoid heart disease.
Secondary causes: hypertension, dilated cardiomyopathy, or ischemic heart disease
Idiopathic RCM

Table 4.
Etiologies of restrictive cardiomyopathy.

present with palpitations, dizziness, syncope, atypical chest pain, and dyspnea, but many are asymptomatic. The most common arrhythmia of ARVC is monomorphic ventricular tachycardia with a left bundle branch block. SCD can be the initial presentation of ARVC [20].

IIIE. Stress-Induced cardiomyopathy

Stress-induced cardiomyopathy, also known as takotsubo cardiomyopathy or broken heart syndrome, is characterized as brief systolic dysfunction in the absence of coronary artery disease that is usually brought on by stress. The systolic dysfunction is focal and mainly limited to the cardiac apex which is in contrast to DCM where we see global systolic dysfunction.

Patient presentation is similar to that of a patient with ST-elevation myocardial infarction (STEMI). It is more common in elderly women. About 1–2 percent of patients that are troponin positive with a suspected STEMI are diagnosed with stress-induced cardiomyopathy [21]. As in a STEMI, the most common presenting symptom is substernal chest pain with or without dyspnea. The pathophysiology of this disease is not very well understood but it is thought to be in part due to catecholamine excess thus cocaine-related ACS should be ruled out.

IIIF. Cirrhotic cardiomyopathy

Cirrhosis which leads to systolic and/or diastolic myocardial dysfunction independent of alcohol consumption has been termed cirrhotic cardiomyopathy. The pathophysiology of this disease is not well established. Patients may have normal or increased cardiac output at rest but the myocardium inadequately responds when placed under stress. ECG findings can include QT interval prolongation and mechanical and electrical desynchrony. Structurally, the LV is normal, but the left atrium is generally dilated. Treatment is mostly supportive but the orthotropic liver transplantation has been shown to improve patient's condition [22].

IV. Diagnosis:

Diagnosis of the various cardiomyopathies are done by clinical presentation (chest pain, fatigue, dyspnea, syncope, etc.), physical exam, diagnostic tools (12-lead ECG, chest radiograph, echocardiography, cardiac MRI, doppler ultrasound), genetic testing, endomyocardial biopsy, and/or plasma BNP. Systolic dysfunction is observed in DCM and stress-induced cardiomyopathy as decreased LVEF and increased EDV on echo. Diastolic dysfunction is observed in HCM and RCM and can sometimes occur in DCM. An echo of diastolic dysfunction demonstrates normal LVEF and EDV.

Dilated cardiomyopathy demonstrates systolic dysfunction, ventricular dilation, myocyte hypertrophy and fibrosis, and possible conduction system involvement. Familial DCM is diagnosed when idiopathic DCM is seen in two or more close relatives. A three to four generation family history and clinical screening (history, exam, electrocardiogram, echocardiogram) of first-degree relatives is done when a new diagnosis is made to identify asymptomatic/undetected disease. Genetic testing is also done for known familial DCM and nonfamilial without an obvious alternative cause. Screening for specific mutations does not necessarily determine therapy, but certain genes are related to clinical characteristics. This may affect family counseling, screening, and influence of primary prevention or pre-symptomatic therapy [23].

Hypertrophic cardiomyopathy should be suspected if there is a positive family history of the disease, clinical symptoms, an abnormal 12-lead ECG, or if a systolic ejection murmur is heard. In addition, increased LV wall thickness (≥15 mm) seen anywhere in the LV wall without any identifiable cause such as valvular disease or hypertension is suggestive of the HCM [24]. Other findings are not required to make a diagnosis of HCM but may include a hyperdynamic LV or systolic anterior motion of the mitral valve seen on echo.

Restrictive cardiomyopathy is diagnosed as non-dilated, non-hypertrophied ventricles with biatrial enlargement seen on echo. Abnormal ventricular filling is visualized with Doppler imaging. Although RCM is generally characterized as non-hypertrophied, the LV may have increased wall thickness if due to infiltrative or storage disease. Echo, cardiac MRI, and endomyocardial biopsy can all be used to differentiate various types of RCM. Chest radiograph can demonstrate cardiomegaly with atrial enlargement, pulmonary venous congestion, and pleural effusions.

RCM appears similar to constrictive pericarditis with impaired ventricular filling but is distinguished by echo, MRI, CT, and endomyocardial biopsy. A patient history can also differentiate the two since possible causes of constrictive pericarditis include different causes such as tuberculosis, malignancy, connective tissue disease. Plasma BNP indicates LV wall stretching and helps separate RCM from constrictive pericarditis. Levels of ≥400 pg./mL indicate RCM due to the limited wall stretch in constrictive pericarditis from very stiff and thickened endocardium [25].

Arrhythmogenic right ventricular cardiomyopathy echo shows dilation of the RV and its outflow tract, aneurysm, akinesis, and dyskinesis. Genetic testing is recommended (DSC2, DSP, DSG2, JUP, TMEM43, and PKP2).

In order to identify stress-induced cardiomyopathy, it is very important to take a thorough history as a physical stress or emotional trigger may sometimes be identified and can help lead to the diagnosis. Stress induced cardiomyopathy should be considered when a patient presents with signs and symptoms of acute coronary syndrome along with an abnormal ECG that are out of proportion to elevations in cardiac biomarkers [26]. The diagnostic criteria consist of four required findings: transient LV systolic dysfunction that is typically regional and contains more than one epicardial coronary distribution, no obstructive coronary disease in the area of the wall motion abnormality, new ECG abnormalities including ST-elevation and/or T wave inversion or moderately elevated cardiac troponin and lastly no pheochromocytoma or myocarditis present [27]. Apical ballooning is also commonly seen as a result of wall akinesia. Therefore, in order to diagnose stress induced cardiomyopathy, the patient must undergo an ECG, coronary angiography and an echo in order to assess LV systolic function.

V. Management:

Management of the cardiomyopathies are generally directed towards relieving symptoms, slowing progression of the disease, and preventing SCD. The specific therapy depends on whether the patient is suffering from systolic dysfunction, diastolic dysfunction, fluid overload and/or arrhythmias.

Patients with HF with reduced ejection fraction, like DCM, are managed with beta blockers(BBs), nondihydropyridine calcium channel blocker (ndCCB), angiotensin converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARBs), pacemakers, and implantable cardioverter-defibrillators (ICD) for arrhythmias [28].

HCM and RCM present mainly with diastolic dysfunction. Therefore, treatment is aimed at lowering heart rate to increase diastolic filling time and decreasing venous pressure [28]. Loop diuretics are used to relieve congestion, but careful monitoring is needed to prevent hypoperfusion. In HCM they are generally avoided since it can worsen the LVOT obstruction. In both HCM and RCM, BBs and CCBs can improve the patient's diastolic dysfunction by decreasing heart rate and increasing filling time. For HCM, they are generally only given when a patient is symptomatic.

For patients with HCM, if symptoms continue despite adequate medical management, dual therapy with another negative inotrope is recommended. This can include beta blocker + disopyramide, nondihydropyridine calcium channel blocker + disopyramide, or beta blocker + nondihydropyridine calcium channel blocker. If

patients still have refractory symptoms and have a LVOT gradient of ≥50 mmHg then septal reduction therapy can be considered [29].

In addition, patients with RCM can benefit from ACEi/ARBs, which might reduce myocardial stiffness. Dual chamber pacemaker is used with advanced AV block, anticoagulants are used for patients with atrial fibrillation, and cardiac transplantation is indicated for patients with intractable heart failure [28].

Patients suffering from ARVC should minimize their strenuous physical activity since there is a significant association between exercise and ARVC. Beta blockers are recommended for patients with clinical symptoms but not asymptomatic patients with a positive genotype. ICDs are indicated for patients who were previously resuscitated from SCD and those with sustained ventricular arrhythmias. If beta blockers and ICDs are not helpful, antiarrhythmic drugs or radiofrequency ablation can serve as adjunct therapy. Management of patients with RV dysfunction is similar to other patients with HF with reduced ejection fraction (ACEi, ARBs, mineralocorticoid receptor antagonist, diuretics, and BBs).

Stress-induced cardiomyopathy is a transient disorder that will likely resolve within a couple of weeks and thus its mainstay in management is supportive. However, the mortality rate is about 3–4 percent. During the acute onset and following stabilization, heart failure management is started following current guidelines. Anticoagulation is also provided similarly to patients that are post-myocardial infarction [30].

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The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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