Cardiomyopathy: A Review

G Vijayaraghavan

Director, Clinical Services, Kerala Institute of Medical Sciences, Trivandrum 695029, Kerala.

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Hypertrophy, dilatation and fibrosis of myocardium are common squeal of congenital, valvular, hypertensive or ischemic heart disease. When these myocardial changes occur as a primary phenomenon, it is called cardiomyopathy. Cardiomyopathy is defined as 'heart muscle disease of unknown cause'. World Health Organization and International Society and Federation of Cardiology have classified cardiomyopathy as dilated, hypertrophic and restrictive forms (Table 1). They included arrythmogenic right ventricular cardiomyopathy and unclassified forms also as primary cardiomyopathy. There is a long list of myocardial diseases where the heart muscle is involved secondary to valvular, vascular, hypertensive, inflammatory or infiltrative diseases. They may be termed specific secondary cardiomyopathies.

DILATED CARDIOMYOPATHY (DCM)

This is the most common variety of primary cardiomyopathy and forms about 25% of all patients presenting with cardiac failure. Earlier it was called congestive cardiomyopathy, as the common presenting feature was cardiac failure. It was noticed that most forms of cardiomyopathies could ultimately present with cardiac failure and hence, the term congestive cardiomyopathy is inappropriate. DCM is characterized by cardiac enlargement and systolic dysfunction of one or both ventricles. The main features are increasing systolic and diastolic ventricular volumes with decreasing left ventricular ejection fraction below 40%. In many patients ventricular dilatation and reduced ejection fraction could be detected many years before the development of cardiac failure.

Etiology

DCM represents the final common pathway produced by a variety of toxic, metabolic, immunological, familial and infectious mechanisms damaging the heart muscle (Table 2). Damage secondary to viral myocarditis or alcohol, produces hemodynamic and pathological changes identical to primary dilated cardiomyopathy. It is observed that about 15% of patients with viral myocarditis may progress to DCM, as shown by inflammatory cells seen in endomyocardial biopsy studies. In 20% of patients, a first-degree relative may show subclinical involvement of the ventricles. They may subsequently develop frank congestive cardiac failure. Most familial cases show an autosomal dominant transmission. However, the disease is genetically heterogeneous and autosomal recessive and X-linked inheritance has also been found. Genetic markers like angiotensin converting enzyme DD genotype are increasingly found in DCM patients. Anthracyclines like adriamycin may produce cardiomyopathy which could be differentiated from DCM only by electron microscopic studies.

Table 1 : Classification of Cardiomyopathies. (World Health Organization and International Society and Federation of Cardiology, 1966)

- A. Functional classification
  - 1. Dilated cardiomyopathy
  - 2. Hypertrophic cardiomyopathy
  - 3. Restrictive cardiomyopathy
  - 4. Arrhythmogenic right ventricular cardiomyopathy
  - 5. Unclassified cardiomyopathy
- B. Specific cardiomyopathies
  - 1. Ischemic cardiomyopathy
  - 2. Valvular cardiomyopathy
  - 3. Hypertensive cardiomyopathy
  - 4. Inflammatory
    - a. Idiopathic
    - b. Autoimmune
    - c. Infectious
  - 5. Metabolic cardiomyopathy
    - a. Endocrine
    - b. Familial storage diseases and infiltrations
    - c. Deficiency
    - d. Amyloid
  - 6. General systemic disease
    - a. Connective tissue disorders
    - b. Infiltrations and granulomas
  - 7. Muscular dystrophies
  - 8. Neuromuscular disorders
  - 9. Sensitivity and toxic reactions
  - 10. Peripartum cardiomyopathy

Clinical features

Symptoms of left ventricular failure dominate the clinical picture. Clinical presentation is variable, as most cases remain asymptomatic for years. Fatigue and weakness due to diminished cardiac output is often the presenting symptom. Many patients present with sudden onset of dyspnea during an episode of chest

infection. Chest pain when present should alert the physician towards the possibility of underlying coronary artery disease. Chest pain due to pulmonary embolism or abdominal pain of enlarged liver may occur during late stage of the disease.

Clinical examination will show dyspnea and persistent tachycardia. Chyene-Stokes breathing indicates poor prognosis. Pulse pressure is low and during late stages of the disease, hands and feet may appear cold and clammy. Significant elevation of jugular venous pressure with prominent a and v waves may be seen. Large v waves due to tricuspid regurgitation indicate an ominous prognosis. Dependant edema and ascites are features of right-sided involvement. Moderate to large cardiomegaly with signs of biventricular enlargement and palpable shock of third heart sound will be present. Auscultation will reveal soft first heart sound, loud diastolic gallop and soft pansystolic murmur of mitral regurgitation. Pulmonary congestion produces bibasal rales over lung fields. Right heart failure is diagnosed by the presence of tender hepatomegaly, ascites and dependant edema.

Investigations

There are no specific electrocardiographic changes. One may find atrial and ventricular arrhythmias, poor progression of r waves in right chest leads, pathologic q waves, and ST or T wave abnormalities. Ventricular arrhythmias indicates poor prognosis.

Echo Doppler studies are very useful for diagnosis and follow up of these patients. There will be dilatation of all four cardiac chambers with global hypokinesia and reduced left ventricular ejection fraction. Left ventricular thrombi are common in patients with markedly dilated left ventricle and poor ejection fraction. Variable degree of mitral and tricuspid regurgitation will be seen. Pulmonary hypertension when seen is mild to moderate. Thallium 201 myocardial perfusion imaging will help to differentiate DCM from ischemic left ventricular failure. Cardiac catheterization is indicated to identify patients with treatable etiology. Left and right ventricular end-diastolic pressure will be elevated. Mild to moderate pulmonary hypertension will be seen. Global hypokinesia and reduced ejection fraction will be seen on ventriculography. All patients with chest pain suggestive of ischemia should undergo selective coronary angiography. Endomyocardial biopsy is required to rule out active myocarditis or when infiltrative diseases like sarcoidosis or hemochromatosis is suspected.

Management

Management is mostly directed against control of cardiac failure. Patients and their family need counseling regarding the need for lifelong treatment and the various modalities of treatment available. All attempts should be made to identify treatable conditions like coronary artery disease, active myocarditis, hemochromatosis, or other infiltrative diseases. Many patients present for the first time with complications like chest infection or cardiac arrhythmias, which should be treated aggressively. Bed rest may be required during severe cardiac failure. But graded activities should be advised under strict medical supervision. Judicious use of angiotensin converting enzyme inhibitors, diuretics, vasodilators like long-acting nitrates, spironolactone and digoxin will help these patients to lead a useful life for many years. Those with persistent tachycardia will be helped by carefully titrated doses of beta-blockers like carvedilol. Patients with very large left ventricle and those with intracardiac thrombi are kept on long-term oral anticoagulants. Ventricular arrhythmias should be treated aggressively. Implantation of automatic cardioverter defibrillators has increased the longevity of these patients. Patients with very large left ventricle and mitral regurgitation may get temporary respite with mitral valve replacement and reduction of left ventricular size by excision of posterior part of left ventricle between the two papillary muscles. However, most of these patients will ultimately require cardiac transplantation.

Table 2 : Secondary Causes of Dilated Cardiomyopathy

1.	**Associated with other heart diseases**	
	Ischemic heart disease	
	Hypertensive heart disease	
	Valvular heart disease	
	Chronic tachyarrhythmias.	
2	Toxic myocardial damage	
	Ethenol	
	Anthracyclines like doxorubicin	
	Cobalt	
3)	Metabolic diseases	
	a. Nutritional deficiencies like thiamine, carnitine	
	b. Endocrine disorders like thyrotoxicosis, hypothyroidism, pheochromocytoma, diabetes mellitus	
4.	Infections	
	a. Viral (coxsackie virus, cytomegalovirus, HIV)	
	b. Rickettsial	
	c. Bacterial	
	d. Parasitic (toxoplasmosis, trichinosis, Chagas' disease)	
5.	Systemic disorders	
	Systemic lupus erythematosus	Rheumatoid arthritis
	Polyarteritis nodosa	Kawasaki disease
	Amyloidosis	Hypereosinophilic syndrome

Myocardial Diseases Presenting as Dilated Cardiomyopathy

Peripartum cardiomyopathy

Postpartum or peripartum cardiomyopathy is systolic dysfunction and cardiac failure during the last trimester of pregnancy or within 6 months of delivery. It is common in women above 30 years, who are obese and multiparous. It is presumed to be due to viral myocarditis or an autoimmune mechanism. Cardiac failure with higher incidence of thromboembolism is characteristic. Patients with persistent cardiomegaly have bad prognosis. There is high incidence of recurrent cardiac failure during subsequent pregnancies. Patients have to be managed on the same lines as in dilated cardiomyopathy. They have to be counseled to avoid future pregnancy.

Alcohol-associated cardiomyopathy

Acute or chronic consumption of excessive quantities of alcohol is associated with myocardial damage. Both alcohol and its metabolite, acetaldehyde damages the cellular calcium transport functions, mitochondrial function, lipid metabolism, protein synthesis, and myofibrillar ATPase. Microscopic examination of the heart will show edema of the vasculature and mitochondria.

The disease often affects men who consume large quantity (more than half pint of hard liquor) of whiskey, wine or beer for more than ten years. Atrial arrhythmias are common. Clinical picture is indistinguishable from primary dilated cardiomyopathy. Sudden onset of atrial arrhythmias especially atrial fibrillation seen after single large bout of alcoholism is called holiday heart syndrome. Arrhythmia is short lived and disappears on abstinence of alcohol or on treatment with beta-blockers.

Viral myocarditis

More than 20 viruses are known to produce an inflammatory disease of myocardium, an acute dilated cardiomyopathy-like syndrome, following a documented viral infection. Cardiomegaly, sinus tachycardia, arrhythmias, cardiac failure or low output syndrome indicates myocardial involvement. Chest pain due to pericardial involvement or segmental myocardial necrosis presenting like acute myocardial infarction is also observed. Radiography may show cardiomegaly with cardiac failure. Electrocardiographic changes are nonspecific. Echocardiography shows dilatation of all cardiac chambers with impaired ventricular function. Endomyocardial biopsy is often diagnostic. Myocardial necrosis with mononuclear cell infiltration is characteristic of the disease. Treatment of cardiac failure and cardiac arrhythmias often helps these patients to recover from the illness. ACE inhibitors like captopril and vasodilators are helpful. Use of immunosuppressive agents is controversial. Gamma globulins have been used in some patients with benefit.

Other causes of myocarditis

Bacterial infections with *Diphtheria*, *Legionella*, *Salmonella*, *Borrelia* and *Mycoplasma* can all produce myocarditis. Similarly *Trypanosoma cruzi* produces Chaga's disease presenting with dilated myopathy and chronic congestive heart failure.

HYPERTROPHIC CARDIOMYOPATHY (HCM)

Left ventricular hypertrophy is the adaptive response of the heart to chronic pressure or volume overload. When concentric or regional hypertrophy of the left ventricle is seen without any pressure or volume overload one has to suspect a primary heart muscle disease. Hypertrophic cardiomyopathy is a genetically transmitted primary cardiomyopathy characterized by hypertrophy of the left ventricle. Hypertrophy may be restricted to the interventricular septum, which along with systolic anterior movement of the mitral valve can produce dynamic obstruction to the left ventricular outflow tract. The wide spectrum of its pathologic and clinical presentation has given it names like, hypertrophic obstructive cardiomyopathy (HOCM), idiopathic hypertrophic subaortic stenosis (IHSS), etc. Prevalence is about 0.2 percent in the general population. In many individuals it may go undetected, as the symptoms may be absent or mild and the diagnosis is made only on routine echocardiography or still later, on autopsy examination.

Pathology

The disease is diagnosed when left ventricular hypertrophy without cavity dilatation is seen in the absence of any cardiac or systemic disease. In some patients hypertrophy may also affect the right ventricle. Characteristically hypertrophy involves the interventricular septum and anterolateral wall, sparing the posterior free-wall of the left ventricle. Marked hypertrophy of ventricular septum, along with anterior displacement of mitral apparatus and systolic anterior movement of the anterior mitral leaflet, produces left ventricular outflow obstruction during mid and late systole. There is heterogeneity in involvement of various parts of the ventricle, and in many, only localized mild hypertrophy of one small region alone is present. Microscopically there is gross disorganization of muscle bundles resulting in a 'whorled pattern'. Within the cells, there is myofiber disarray and disorganization of myofibrillar architecture. Sometimes, the differentiation from the physiological hypertrophy of the 'athlete heart' may be difficult, even after detailed Doppler studies. Degree of hypertrophy is dynamic, appearing any time after birth but often after adolescence. A variant with predominant involvement of the left ventricular apex is common in Japan. Small left ventricular cavity with mild hypertrophy is the presenting feature in the elderly. Morphological features similar to HCM may be seen in infants born to diabetic mothers and in patients with Friedreich ataxia, Noonan's syndrome, hyperparathyroidism, pheochromocytoma and multiple neurofibromatosis.

Etiology

The disease may occur in familial or sporadic form. Genetic defects affect multiple loci, which do not explain the clinical variability. It is transmitted as an autosomal dominant trait with disease loci in one of eight different chromosomes. Morphological evidence of the disease is seen in 25% of asymptomatic first-degree relatives of patients with HCM.

Pathophysiology

The main pathophysiological feature is diastolic dysfunction of the hypertrophied left ventricle. Impaired relaxation and distensibility results in rising filling pressure, and pulmonary venous pressure. Systolic function is normal, often with increased ejection fraction. Left ventricular outflow may be narrowed in late systole in some due to systolic anterior movement of the anterior mitral leaflet coming close to the bulging hypertrophied interventricular septum. This will produce a dynamic systolic gradient, varying from beat to beat and worsened by positive inotropic agents like isoprenaline and abolished by negative inotropic agents like propranolol. Increased oxygen demand of the hypertrophied ventricle with outflow gradient, elevated filling pressure, and compression of intramyocardial coronary vessels may produce ischemia in many patients.

Clinical features

Many patients are totally asymptomatic and the disease is detected during routine echocardiography or autopsy following sudden death. Syncope and sudden death following competitive sports warrants early diagnosis of this condition in suspected families. Many have only mild symptoms with resting or post-exercise electrocardiographic changes. There is a direct relationship between the extent of hypertrophy and incidence of sudden death. Presyncope and syncope identifies patients who are prone to sudden death. The late stage of the disease is characterized by incapacitating symptoms like angina, dyspnea and recurrent syncope.

The disease is diagnosed often in middle-aged men. Most common presentation is with dyspnea due to diastolic failure of

the left ventricle. Paroxysmal nocturnal dyspnea and congestive heart failure may follow over a period of time. Progressive heart failure can lead on to left ventricular dilatation when the classical pathological features may be altered. Chest pain similar to classical angina pectoris may occur. When this is the dominant symptom in elderly patients, associated coronary artery disease should be ruled out. Syncope is the result of sudden reduction of cardiac output by arrhythmias or outflow obstruction or both and indicates grave prognosis. Many patients complain of paroxysmal palpitations due to ventricular arrhythmias requiring urgent investigation and management.

Physical examination may not reveal any abnormality except brisk pulse and apical 4th heart sound. However, in the classical form with left ventricular outflow obstruction, one may find bifid peripheral pulse with brisk upstroke, ill-sustained peak and a secondary shoulder. The brisk pulse may be collapsing in character. Jugular venous pulse may show prominent 'a' waves. Cardiomegaly is absent or mild. Apex beat is forcible with distinct systolic and diastolic impulse. This double apical impulse is due to forceful atrial contraction producing late diastolic left ventricular filling with loud 4th heart sound. A harsh late systolic murmur may be heard over the apex, left sternal border and aortic area. This is due to dynamic left ventricular outflow obstruction. Length and intensity of the murmur increases on standing, Valsalva maneuver, exercise or after vasodilators and decreases on squatting, isometric handgrip or after vasoconstrictors like phenylephrine and after beta blockade. These maneuvers help to differentiate HCM from valvar and discrete subvalvar aortic stenosis. Rarely pansystolic murmur of mitral regurgitation may be audible over apex and axilla.

Investigations

The electrocardiogram is abnormal in 85% of patients. Left ventricular hypertrophy with the tallest R waves in mid precordial leads with ST depression and T inversion are characteristic. Pathological q waves in the inferior and / or anterior leads are seen in 50% of patients. Giant T inversion in mid-precordial leads is characteristic of apical form of HCM. Cardiac arrhythmias should be searched using periodic ambulatory Holter monitoring.

Echocardiography is diagnostic and should be done for diagnosis and follow up of patients and to screen their asymptomatic relatives. The diagnostic feature is left ventricular hypertrophy predominantly affecting the septum and anterolateral wall. Septum at end-diastole is 1.3 times or more thick than the posterior wall (asymmetric septal hypertrophy – ASH). Interventricular septum measures 15 to 30 mm or more and appears bright and speckled, an appearance not seen in other conditions. Patients with marked septal thickness have high incidence of sudden death. Systolic obstruction to the left ventricular outflow is a variable feature produced by the bulge of hypertrophied septum and systolic anterior movement (SAM) of the anterior mitral leaflet. The latter in turn produces variable degree of mitral regurgitation. Slow motion analysis of systolic frames will show the sequence of ejection jet across left ventricular outflow, followed by obstruction with systolic gradient and mitral regurgitation. The left ventricular cavity is small with reduced septal motion. Mitral E-F slope will be reduced. Hypertrophy and systolic obliteration of the left ventricular apex is characteristic of the apical variety where the cavity may appear spade-like. All segments of the left ventricle and the right ventricular free-wall should be examined carefully for signs of hypertrophy. Impaired left ventricular diastolic function can be monitored using Doppler techniques. Cardiac catheterization is indicated only when associated coronary artery disease is suspected or interventional procedures are anticipated. The ventricular cavity is small with exaggerated ejection fraction and virtual obliteration of left ventricular cavity at end-systole. A dynamic subaortic late systolic gradient is recorded in many patients.

Management

All family members should be examined and detailed echo Doppler studies done. Genetic counseling is very important to alert the family about occurrence of HCM in asymptomatic relatives. Patients should be told to avoid strenuous and competitive exercise. All symptomatic patients should be put on beta-blockers which will relieve angina, dyspnea and prevent presyncopal attacks. Beta-blockers reduce contractility, systolic gradient and oxygen demand of the myocardium. Reduction of heart rate improves diastolic filling. Other drugs like verapamil and disopyramide, which alters calcium kinetics, are also effective in improving diastolic function and reducing systolic gradient. Aggressive antiarrhythmic therapy is required if resting or ambulatory ECG monitoring reveals cardiac arrhythmias. Many patients may benefit from dual chamber pacing or implantation of automatic cardioverter defibrillator. Septal ablation by selective injection of ethyl alcohol into the first septal branch of the left anterior descending coronary artery may produce infarction of the obstructing segment of ventricular septum and relieve outflow obstruction. Similar results may be obtained by surgical septal myectomy. When patients develop congestive heart failure, conventional therapy using digitalis and diuretics may benefit them. Unfortunately in spite of the best management strategy one may not substantially reduce the incidence of sudden death in these patients.

RESTRICTIVE CARDIOMYOPATHY

Idiopathic restrictive cardiomyopathy is a rare form of heart muscle disease where the primary abnormality is restriction to ventricular filling due to infiltrative disease of myocardium or endomyocardial fibrosis. Tropical endomyocardial fibrosis is commonly seen in Kerala State in South India, Nigeria and Uganda in Central Africa and Brazil in South America. These countries close to the equator are endemic for worm infestation and many parasitic infestations like malaria and filariasis. Similarities in the histopathological changes of this disease and endomyocardial fibrosis seen in eosinophilic heart disease have been observed by many workers. Worm infestation producing eosinophilia and eosinophilic toxins damaging the subendocardial myocardium may trigger fibrosis. However, no conclusive proof is available to us regarding the etiology of this rare disease. Fibrosis involves the inflow tract of one or both ventricles, resulting in diastolic failure. Fibrosis may extend to papillary muscles and produce atrioventricular valve regurgitation. When it involves predominantly the left side of the heart, it presents with mitral regurgitation and severe pulmonary hypertension. Dominant right-sided involvement is characterized by aneurismal dilatation

of right atrium and severe right heart failure. Endocardial fibrosis prevents significant dilatation of ventricles.

Left ventricular endomyocardial fibrosis

The disease is insidious in onset and often affects children and adolescents. Patients with left ventricular endomyocardial fibrosis present with dyspnea and palpitation. Clinically the features are similar to rheumatic mitral regurgitation. Mild to moderate cardiomegaly, loud apical third heart sound and pansystolic mitral regurgitation murmur with late systolic decrescendo, is characteristic of this disease. Pulmonary hypertension and left heart failure are out of proportion to the degree of mitral regurgitation. Electrocardiogram may show left ventricular hypertrophy. Myocardial calcification seen in plain x-ray films or on fluoroscopy is characteristic. Echocardiography delineates areas of endocardial fibrosis and distortion of the mitral apparatus. Left atrium is enlarged and signs of pulmonary hypertension may be evident. Cardiac catheterization will show markedly elevated left ventricular end-diastolic pressure. These patients develop severe congestive heart failure, intraventricular thrombi and often die of systemic embolism and low output stage.

Right ventricular endomyocardial fibrosis

The right ventricular disease presents with fatigue, dyspnea and abdominal distension. About a fourth of the patients are in atrial fibrillation at the time of presentation. In spite of marked elevation of jugular venous pressure and severe ascites, dependant edema is rare. Marked cardiomegaly extending to both sides of the chest is mainly due to the dilated right atrium. Loud third heart sound, and soft tricuspid regurgitation murmur may be audible. The massive ascites is very characteristic and the ascitic fluid shows high protein content and many round cells. Electrocardiogram may show qr pattern in the right precordial leads due to dilated right atrium. Massive cardiomegaly seen in chest skiagram is mainly due to the dilated right atrium. Echocardiogram is diagnostic. Aneurismal right atrium with small right ventricle showing apical fibrosis and cavity obliteration is characteristic. Dynamic intracavitary echoes and massive right atrial thrombi are common in late stage of the disease. Doppler studies will show low-pressure tricuspid regurgitation. The high systemic venous pressure may produce late diastolic flow into the pulmonary artery. Cardiac catheterization shows marked elevation of right ventricular diastolic pressure. These tracings show an early diastolic dip followed by elevated mid and late diastolic pressure producing a plateau. Right atrial a waves are large and may force open the pulmonary valve, producing diastolic pulmonary flow as seen in Doppler studies.

The clinical picture may sometimes resemble Ebstein's anomaly or constrictive pericarditis. But routine investigations can easily identify patients with right ventricular endomyocardial fibrosis. Infiltrative diseases like amyloidosis, sarcoidosis, Gaucher's disease and Hurler's disease, affect the myocardium restricting the diastolic filling. They may easily be diagnosed by biopsy studies.

Treatment

Disease is slowly progressive and we do not have any treatment to arrest the progress of the disease. Congestive failure should be treated on conventional lines. Anticoagulants may be used in patients with normal liver function. Surgical endocardiectomy with valve replacement helps patients with significant atrioventricular valve regurgitation. It has been observed that with the decreasing incidence of worm infestation and improvements in nutrition there is significant decrease in the incidence of this disease.

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

This is a rare form of right ventricular dysplasia characterized by loss of muscle with total or partial replacement by adipose and fibrous tissue. Reentrant ventricular tachycardia and sudden death are common in this condition. Patients presents with palpitation and syncopal attacks. Clinical examination will not reveal any abnormal findings. Electrocardiogram may show T inversion in right chest leads. Echocardiogram will reveal dilated poorly contracting right ventricle. Therapy with sotalol or amiodarone is effective in controlling arrhythmias. Drug resistant ventricular arrhythmias may need treatment by radiofrequency ablation of the arrythmogenic focus or implantation of automatic cardioverter defibrillator.

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