CARDIOMYOPATHIES

Definition and Description:

Cardiomyopathies are disorders of primary myocardial disease devoid of other cardiac or circulatory disease as first described by Fiedler in 1899 and so designated by Mattingly in 1950’s. The first such cardiomyopathy to be recognized was dilated cardiomyopathy; Brock and Teare in 1957 described “asymmetric hypertrophy of the heart”; and Braunwald reported the first comprehensive report of studies on “idiopathic hypertrophic subaortic stenosis” (IHSS) in 1964. In the 1970’s studies on the diastolic function of the heart led to the recognition of restrictive cardiomyopathies. The World Health Organization has officially recommended the presently used classification of cardiomyopathy as

(1) dilated,
(2) hypertrophic
(3) restrictive disease of “unknown cause”.

The term "cardiomyopathy" is now used more liberally to include myocardial disease or syndromes resulting from known causes (i.e., "ischemic cardiomyopathy” and “hibernating myocardium”).

Dilated Cardiomyopathy

Dilated cardiomyopathy is diffuse primary disease of the myocardium characterized by systolic (contractile) dysfunction of the myocardium. The essential features of this disorder is increased left ventricular (or biventricular) volumes, reduced systolic ventricular wall motion, decreased ejection fractions and absence of wall thickening (eccentric hypertrophy). Cardiac output is usually severely impaired at all levels of activity. Dilated cardiomyopathy may result from many different etiologies and the natural history and prognosis is somewhat dependent on the underlying disease treatability. A genetic link is suggested by a 20-30% incidence in first-degree relatives.
CARDIOMYOPATHIES

The clinical presentation of dilated cardiomyopathy is highly variable. Patients may present with mild to severe heart failure symptoms. Some patients may be asymptomatic until diagnosis is suggested by chest x-ray, echocardiogram or electrocardiogram. The electrocardiogram typically shows intraventricular conduction delay, left bundle branch block, left ventricular hypertrophy, atrial fibrillation, premature ventricular beats and bursts of ventricular tachycardia. The chest x-ray characteristically shows enlarged transverse cardiac dimensions from left ventricular enlargement. Atrial and ventricular arrhythmias, third and fourth heart sounds, a systolic murmur of mitral regurgitation or systemic embolism may be the initial finding leading to the diagnosis. The diagnosis of dilated cardiomyopathy is best made by demonstrating decreased systolic function as evidenced by a low ejection fraction and enlarged cardiac chambers by echocardiography. More recently recognized atypical forms of dilated cardiomyopathy include Takotsubo Syndrome, Brugada Syndrome and Arrhythmogenic Right Ventricular Dysplasia. One year mortality is 50% in NYHA Class III-IV patients in whom ejection fraction is less than 25%. Typically dilated cardiomyopathy patients manifest mitral regurgitation (from annular dilation) and develop atrial fibrillation and LBBB. Endocardial biopsy may be of some help in treatment by identifying myocardial inflammation.

Treatment is directed at:

1. myocardial inflammation,
2. the hemodynamics of cardiac dilation,
3. prevention of systemic embolization,
4. prevention and treatment of arrhythmias and
5. cardiac transplantation.

Treatment of dilated cardiomyopathy is basically the treatment of systolic left ventricular failure. ACE inhibitors (and possibly angiotensin-II receptor blockers) are the most beneficial agents that improve mortality in heart failure. Digoxin reduces hospitalizations in patients with third heart sounds, atrial
CARDIOMYOPATHIES

fibrillation and ejection fraction of less than 40%. Parenteral inotropic agents give short term improvement and provide helpful transitional therapy prior to transplantation but have been associated with an overall increase in mortality. Nitrates and hydralazine improves symptoms and mortality. Carvedilol has shown improvement in mortality if used cautiously and selected properly.

Morbidity from heart failure is high and mortality usually is due to sudden death. Mortality ranges from 5-10% per year for patients in NYHA class II to 50% for class IV. Class III-IV patients have the best chance for survival with heart transplantation (90%).

Hypertrophic Cardiomyopathy

While dilated cardiomyopathy commonly affects middle age or older patients, hypertrophic cardiomyopathy often presents as sudden death in children or young adults. Hypertrophic cardiomyopathy develops progressively during the first two decades of life in the absence of a hemodynamic stimulus. Hypertrophic cardiomyopathy is a primary myocardial disorder characterized by symmetric (concentric) or asymmetric left and/or right ventricular hypertrophy. Prior to the development of echocardiography technology, hypertrophic cardiomyopathy was recognized clinically when patients with exertional angina, dyspnea and/or syncope and an apical systolic murmur were demonstrated to have an intraventricular pressure gradient (obstructive) by cardiac catheterization. It is now recognized that hypertrophic cardiomyopathy can be nonobstructive as well as obstructive.

Cardiac hypertrophy has been recognized as a major risk factor for sudden death and heart failure. Hypertrophy commonly occurs as an adaptive response to pressure overload (afterload) producing concentric hypertrophy or to volume overload (preload) producing eccentric hypertrophy. Cardiac hypertrophy may be a compensatory response to any cardiovascular disorder, particularly hypertensive,
CARDIOMYOPATHIES

valvular and congenital heart disease. Angiotensin II, platelet-derived growth factor and norepinephrine have been identified as mediators and risk factors for hypertrophy. Therapy to prevent or reduce ventricular hypertrophy has been shown to decrease mortality risk. While in many ways the functional impact of secondary cardiac hypertrophy is similar to that of (primary, idiopathic) hypertrophic cardiomyopathy, the natural history is quite different.

In over half of the patients the disease is familially transmitted by autosomal dominance with variable expression. In 1989 Jarcho, et al. elucidated the molecular genetic basis for hypertrophic cardiomyopathy to beta-myosin heavy chain abnormality carried by chromosome 14 (band q1). More recently, mutations associated with hypertrophic obstructive cardiomyopathy have been identified on chromosome 1q3 (cardiac troponin-T abnormality), chromosome 15q2 (alpha-tropomyosin abnormality) and chromosome 11p11 (cardiac myosin protein C abnormality which is a more benign form of hypertrophic cardiomyopathy in the elderly). Molecular biologic studies suggest that the mutant genes express themselves through development of structurally abnormal, mutant myosin molecules which "poison" their sarcomeres. The principle contractile protein (myosin) is composed of one heavy and two light polypeptide chains. The heavy chain has three "domains", one with ATPase activity for energy production for contraction and the other two domains for the binding sites of actin and myosin light chains. Mutations in these three domains are not found and are believed to be lethal. Hypertrophic cardiomyopathy patients have been identified to have a total of seven different mutations in the beta cardiac myosin heavy chain gene. It is presumed that the patients with unexplained disease have unidentified gene mutations.
The histopathology of hypertrophic cardiomyopathy demonstrates the structural anomalies that result from the myosin gene mutations. Three histopathologic features have been identified:

1. Myocardial fiber disarray,
2. Loose intercellular connective tissue with fibrosis and
3. Abnormal intramural coronary arteries.

The primary pathologic feature of hypertrophic cardiomyopathy is the symmetric or asymmetric hypertrophy with normal or small cavity size. Echocardiography or autopsy show left ventricular wall thickness of 15 mm or greater. Echocardiography has demonstrated asymmetric septal hypertrophy (ASH), systolic anterior motion (SAM) of the mitral valve and sigmoid basal septal hypertrophy in some patients. Echocardiography formulas have been used to quantitate left ventricular mass, and a point system has been developed to estimate the extent of hypertrophy.

Based on the location of the abnormal hypertrophy, four patterns of intraventricular hemodynamic abnormality may occur:

1. A small early systolic pressure gradient across the aortic valve results from an accentuation of normal early systolic flow acceleration.
2. Asymmetric septal hypertrophy (ASH) of the LV outflow tract with resultant Venturi forces drawing the anterior mitral leaflet anteriorly (SAM) produces the typically obstructive gradient across the LV outflow tract.
3. Midventricular hypertrophy at the level of the papillary muscles produces midventricular systolic obstruction resulting in a high-pressure apical LV chamber.
CARDIOMYOPATHIES

(4) Hypertrophic cardiomyopathy may produce apical obliteration with increased mural tension.

Doppler echocardiography recording the maximum velocity of systolic flow gives noninvasive evidence of intraventricular pressure gradients (PG = 4V^2).

Pathologic hypertrophy and intraventricular obstruction produce clinical sequelae. High LV pressures associated with an obstructive pressure gradient result in high oxygen consumption. Abnormalities of intramyocardial coronary arteries and diminished coronary vasodilator reserve capacity result in myocardial ischemia. Impaired relaxation and increased chamber stiffness results in diastolic dysfunction. The development of atrial fibrillation often results in pulmonary edema, angina pectoris or syncope due to impaired LV filling. Mitral regurgitation occurs in near 100% of patients with an intraventricular pressure gradient further reducing cardiac output.

Most patients with hypertrophic cardiomyopathy are asymptomatic or symptoms are not recognized. Dyspnea is the most common symptom (75%) related to elevated LV end-diastolic pressure. Angina occurs in 66% of symptomatic patients due to LV outflow tract obstruction and diminished myocardial blood flow. Syncope (and presyncope) results from peripheral vasodilation and inability to increase cardiac output with exertion due to increase in LV outflow obstruction, impaired diastolic filling and disparity of myocardial oxygen supply and demand.

Physical examination findings in hypertrophic cardiomyopathy reflect the presence and severity of outflow tract obstruction and diastolic dysfunction. An increased jugular “A” wave on inspiration results from right ventricular diastolic dysfunction. A spike-and-dome carotid waveform (pulsus bisferiens) can be recorded (and palpated) as a result of midsystolic LV outflow tract obstruction. An apical sustained impulse may be displaced to the left as evidence of left ventricular hypertrophy.
CARDIOMYOPATHIES

Fourth and third heart sounds are frequently heard. The characteristic murmur of obstructive hypertrophic cardiomyopathy is an apical and left sternal border systolic murmur of LV outflow tract obstruction and mitral regurgitation. Procedures that decrease ventricular volume at end systole increase the intensity of the murmur (sudden standing, postextrasystolic beat and amyl nitrate inhalation) while increased afterload and preload reduce the murmur intensity (isometric exercise).

The EGG is usually abnormal in hypertrophic cardiomyopathy. While the electrocardiogram is not a sensitive tool to demonstrate early (mild) hypertrophy, 70% of patients with hypertrophic cardiomyopathy show ECG evidence of LVH. Pseudo-infarction patterns with abnormal Q-waves in inferior and lateral leads probably reflect septal hypertrophy. Left axis deviation, left atrial enlargement and conduction abnormalities are common.

The echocardiogram is the primary clinical tool for the diagnosis of hypertrophic cardiomyopathy. Ventricular wall thickness of 15 mm or greater is diagnostic of hypertrophy. ASH (asymmetrical septal hypertrophy) and SAM (systolic anterior motion of the anterior mitral valve leaflet) may also be demonstrated. The exclusion of aortic stenosis as a cause of LV hypertrophy can also be established. Other findings include ground-glass myocardial appearance, small ventricular cavity, hypokinetic posterior wall motion, partial midsystolic aortic valve closure, mitral regurgitation, diastolic dysfunction and left atrial enlargement.

Medical management of obstructive or nonobstructive hypertrophic cardiomyopathy is based on negative inotropic agents. For over 20 years beta-blockers were the standard of treatment, however, less than one-third of patients experience sustained improvements (those with latent or mild obstruction). Verapamil is the therapy of choice in patients with nonobstructive hypertrophic cardiomyopathy while patients with intraventricular obstruction may experience increased gradient due to vasodilation,
CARDIOMYOPATHIES

pulmonary edema and sudden death. Disopyramide, a negative inotropic antiarrhythmic agent, may
decrease obstructive pressure gradients and reduce risk of sudden death.

Surgical ventriculomyectomy has been quite effective in reducing or abolishing subaortic
pressure gradients. Success rates have exceeded 90% with both immediate and long-term benefit. This
surgery is now the procedure of choice having replaced simple myotomy. Carrying a mortality risk of up to
8%, surgery is indicated in patients remaining symptomatic on medical management. Recently,
nonsurgical ventricular septal infarction (myotomy) by alcohol injection by catheterization techniques has
been shown to be effective in obliterating outflow tract gradients.

Complications of hypertrophic cardiomyopathy pose serious risk and challenges for management.
Atrial fibrillation usually occurs in patients with massive hypertrophy, resting obstruction and left atrial
enlargement. Pulmonary edema, syncope and angina commonly result or are aggravated. Restoration of
sinus rhythm with urgent cardioversion is recommended. Beta blockers or verapamil may be helpful
acutely in slowing the ventricular response. Digoxin may risk worsening outflow obstruction due to its
inotropic effect. Disopyramide or amiodarone may be helpful in restoring and maintaining sinus rhythm.
In younger patients with obstruction, ventriculomyectomy is preferred for relief of atrial fibrillation.

Ventricular tachycardia occurs in up to 36% of patients overall and in 67% of patients with resting
obstruction and is a marker for risk of sudden death. The degree of hypertrophy appears to be directly
related to ventricular ectopy. Ventricular tachycardia is often asymptomatic; Holter monitoring shows an
incidence eight times that of patients without hypertrophy and obstruction. Salvos of ventricular beats of
three or more should be treated. Antiarrhythmic therapy (Ia, Ib, Ic or III) may abolish ventricular tachycardia
but does not prevent sudden death. Automatic implantable cardiac defibrillator (AICD) units should be
used in high risk patients experiencing a sudden death event,
CARDIOMYOPATHIES

Untreated patients with hypertrophic cardiomyopathy show a rate of deterioration of 55% or death (11%) over 4 years. A 4% annual risk of sudden death is found overall. Of higher risk profile for sudden death is the younger patient at diagnosis, history of syncope, symptomatic obstruction, family history of sudden death and asymptomatic ventricular tachycardia. The most common cause of sudden death in young athletes is hypertrophic cardiomyopathy.

Hypertensive Hypertrophic Cardiomyopathy:

Hypertensive hypertrophic cardiomyopathy is common in the elderly with African-American and female predominance (70%). Diagnosis is suggested by symptoms of dyspnea, chest pain and palpitations with a history of episodes of pulmonary edema and long-duration hypertension. Findings must be differentiated from hypertrophic obstructive cardiomyopathy. Chronic edema is unusual and suggests amyloidosis particularly when the ECG shows conduction abnormality. The pathophysiology remains uncertain, occurring rarely and not predictably related to hypertension.

Physical findings are typically a normal jugular venous pressure, a left ventricular lift, a S₄ and a systolic ejection murmur. Echocardiography classically shows left atrial enlargement, concentric left ventricular hypertrophy, systolic LV cavity obliteration and delayed mitral opening.

Treatment modalities that reduce LV mass are most effective. These include beta-blockers and nondihydropyridine calcium channel blockers. Vasodilators and inotropic agents should be avoided as left ventricular obstructive gradients may develop. Agents that should be avoided include nitrates, hydralazine, prazosin, dihydropyridines, ACEI and digoxin.

Restrictive Cardiomyopathy:

A smaller, fourth group of cardiomyopathy patients is those characterized by a primary disorder of diastolic ventricular function. Distensibility is decreased and systolic function and chamber dimensions are
CARDIOMYOPATHIES

normal. Ventricular diastolic pressures are elevated and characterized by an early diastolic dip followed by
an elevated plateau. Ventricular filling is limited to early diastole and is functionally similar to constrictive pericarditis. The most common cause of restrictive cardiomyopathy is amyloidosis. Other causes include sarcoidosis, carcinoid syndrome, scleroderma, hemochromatosis, malignacies, post-irradiation and anthracycline-induced fibrosis.

The clinical classification of restrictive cardiomyopathy includes infiltrative, noninfiltrative and storage diseases. Clinical signs and symptoms include: high systemic and pulmonary vein pressure, edema, ascites, atrial fibrillation, high degree AV or intraventricular block, ventriculoatrial regurgitation and dilated atrial chambers. Noncardiac (rectal or subcutaneous fat pad) or endocardial biopsy is often helpful in identifying the etiology. Echocardiographic findings of myocardial wall thickening with sparkling or ground glass appearance and atrial enlargement are typical. Doppler echocardiography, MRI and technetium pyrophosphate myocardial scintigraphy also contributes to the diagnosis of restrictive cardiomyopathy.

As modern technology has developed, new insights into the molecular biologic basis of the cardiomyopathies have provided a better understanding of restrictive cardiomyopathies. Amyloidosis is one of the better studied causes of restrictive cardiomyopathy. With better diagnostic techniques more specific therapy may more favorably impact the natural history of primary myocardial disease.
1. Which of the following best explains the molecular-genetic basis for hypertrophic cardiomyopathy?
   * a. Mutations of Chromosome 14 (band q 1).
   b. Increased levels of norepinephrine, angiotensin and platelet derived growth factor.
   c. Mutations of actin and myosin light chains.
   d. Mutation of myosin heavy chain ATPase domain.
   e. Mutation of myosin due to poisons and toxins.

2. Which of the following does NOT describe hypertrophic cardiomyopathy?
   a. Myocardial fiber disarray.
   b. Loose intercellular myocardial connective tissue with fibrosis.
   c. Abnormal intramural arteries.
   d. Systolic anterior mitral valve motion.
   * e. Elevated diastolic ventricular pressures with early dip followed by an elevated plateau.

3. Which of the following agents is of most value in treatment of severe obstructive hypertrophic cardiomyopathy?
   a. Propranolol
   b. Verapamil
   * c. Disopyramide
   d. Hydralazine
   e. Dobutamine