287 Cardiomyopathy and Myocarditis

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DEFINITION AND CLASSIFICATION

Cardiomyopathy is disease of the heart muscle. It is estimated that cardiomyopathy accounts for 5–10% of the heart failure in the 5–6 million patients carrying that diagnosis in the United States. This term is intended to exclude cardiac dysfunction that results from other structural heart disease, such as coronary artery disease, primary valve disease, or severe hypertension; however, in general usage, the phrase *ischemic cardiomyopathy* is sometimes applied to describe diffuse dysfunction attributed to multivessel coronary artery disease, and *nonischemic cardiomyopathy* to describe cardiomyopathy from other causes. As of 2006, cardiomyopathies are defined as "a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic."[1]

The traditional classification of cardiomyopathies into a triad of dilated, restrictive, and hypertrophic was based initially on autopsy specimens and later on echocardiographic findings. Dilated and hypertrophic cardiomyopathies can be distinguished on the basis of left ventricular wall thickness and cavity dimension; however, restrictive cardiomyopathy can have variably increased wall thickness and chamber dimensions that range from reduced to slightly increased, with prominent atrial enlargement. Restrictive cardiomyopathy is now defined more on the basis of abnormal diastolic function, which is also present but initially less prominent in dilated and hypertrophic cardiomyopathy. Restrictive cardiomyopathy can overlap in presentation, gross morphology, and etiology with both hypertrophic and dilated cardiomyopathies (Table 287-1).

Expanding information renders this classification triad based on phenotype increasingly inadequate to define disease or therapy. Identification of more genetic determinants of cardiomyopathy has suggested a four-way classification scheme of etiology as primary (affecting primarily the heart) and secondary to other systemic disease. The primary causes are then divided into genetic, mixed genetic and acquired, and acquired; however, genetic information is often unavailable at the time of initial presentation, the phenotypic expression of a given mutation varies widely, and genetic predisposition influences the clinical phenotype of acquired cardiomyopathies, as well. Although the proposed genetic classification does not yet guide many current clinical strategies, it will likely become increasingly relevant as classification of disease moves beyond individual organ pathology to more integrated systems approaches.

GENERAL PRESENTATION

For all cardiomyopathies, the early symptoms often relate to exertional intolerance with breathlessness or fatigue, usually from inadequate cardiac reserve during exercise. These symptoms may initially go unnoticed or be attributed to other causes, commonly lung disease or age-dependent exercise limitation. As fluid retention leads to elevation of resting filling pressures, shortness of breath may occur during routine daily activity such as dressing and may manifest as dyspnea or cough when lying down at night. Although often considered the hallmark of congestion, peripheral edema may be absent despite severe fluid retention, particularly in younger patients in whom ascites and abdominal discomfort may dominate. The nonspecific term *congestive heart failure* describes only the resulting syndrome of fluid retention, which is common to all three types of cardiomyopathy and also to cardiac structural diseases associated with elevated filling pressures. All three types of cardiomyopathy can be associated with atrioventricular valve regurgitation, typical and atypical chest pain, atrial and ventricular tachyarrhythmias, and embolic events (Table 287-1). Initial evaluation begins with a detailed clinical history and examination, looking for clues to cardiac, extracardiac, and familial disease (Table 287-2).

GENETIC ETIOLOGIES OF CARDIOMYOPATHY

Estimates for the prevalence of genetic etiology for cardiomyopathy continue to rise, with increasing attention paid to the family history and the availability of genetic testing. Well-recognized in hypertrophic cardiomyopathy, heritability is also present in at least 30% of dilated cardiomyopathy without other clear etiology. Careful family history should elicit not only known cardiomyopathy and heart failure, but also family members who have had sudden death, often incorrectly attributed to "a massive heart attack," who have had atrial fibrillation or pacemaker implantation by middle age, or who have muscular dystrophy.

Most familial cardiomyopathies are inherited in an autosomal dominant pattern, with occasional autosomal recessive and X-linked inheritance (Table 287-3). Missense mutations with amino acid substitutions are the most common in cardiomyopathy. Expressed mutant proteins may interfere with function of the normal allele through a dominant negative mechanism. Mutations introducing a premature stop codon (nonsense) or shift in the reading frame (frameshift) may create a truncated or unstable protein the lack of which causes cardiomyopathy (haploinsufficiency). Deletions or duplications of an entire exon or gene are uncommon causes of cardiomyopathy, except for the dystrophinopathies.

Many different genes have been implicated in human cardiomyopathy (locus heterogeneity), and many mutations within those genes have been associated with disease (allelic heterogeneity). Although most identified mutations are "private" to individual families, several specific mutations are found repeatedly, either due to a founder effect or recurrent mutations at a common residue.

Genetic cardiomyopathy is characterized by age dependence and incomplete penetrance. The defining phenotype of cardiomyopathy is rarely present at birth and, in some individuals, may never manifest. Related individuals who carry the *same* mutation may differ in the severity of cardiomyopathy and associated consequences of rhythm disorders and need for transplantation, indicating the important role of other genetic, epigenetic, and environmental modifiers in disease expression. Sex appears to play a role, as penetrance and clinical severity may be greater in men for most cardiomyopathies. Clinical disease expression is generally more severe in the 3–5% of individuals who harbor two or more mutations linked to cardiomyopathy. However, the clinical course of a patient usually cannot be predicted based on which mutation is present; thus, current therapy is based on the phenotype rather than the genetic defect. Currently, the greatest utility of genetic testing for cardiomyopathy is to inform family evaluations. However, genetic testing occasionally enables the detection of a disease for which specific therapy is indicated, such as the replacements for defective metabolic enzymes in Fabry's disease and Gaucher disease.

GENES AND PATHWAYS IN CARDIOMYOPATHY

Mutations in sarcomeric genes, encoding the thick and thin myofilament proteins, are the best characterized. While the majority are associated with hypertrophic cardiomyopathy, an increasing number of sarcomeric mutations have now been implicated in dilated cardiomyopathy, and some in left ventricular noncompaction. Few mutations have been identified in excitation-contraction coupling proteins, perhaps because they are too crucial for survival to allow variation. The most commonly recognized genetic causes of dilated cardiomyopathy are structural mutations of the giant protein titin, encoded *TTN*, which maintains sarcomere structure and acts as a key signaling molecule.

As cytoskeletal proteins play crucial roles in the structure, connection, and stability of the myocyte, multiple defects in these proteins can lead to cardiomyopathy, usually with a dilated phenotype (Fig. 287-1). For example, desmin forms intermediate filaments that connect the nuclear and plasma membranes, Z-lines,

[1]From BJ Maron et al: Circulation 113:1807, 2006.