Table 12-11 Cardiomyopathy and Indirect Myocardial Dysfunction: Functional Patterns and Causes

Functional Pattern	Left Ventricular Ejection Fraction*	Mechanisms of Heart Failure	Causes of Phenotype	Indirect Myocardial Dysfunction (Mimicking Cardiomyopathy)
Dilated	<40%	Impairment of contractility (systolic dysfunction)	Genetic; alcohol; peripartum; myocarditis; hemochromatosis; chronic anemia; doxorubicin (Adriamycin) toxicity; sarcoidosis; idiopathic	Ischemic heart disease; valvular heart disease; hypertensive heart disease; congenital heart disease
Hypertrophic	50% to 80%	Impairment of compliance (diastolic dysfunction)	Genetic; Friedreich ataxia; storage diseases; infants of diabetic mother	Hypertensive heart disease; aortic stenosis
Restrictive	45% to 90%	Impairment of compliance (diastolic dysfunction)	Amyloidosis; radiation-induced fibrosis; idiopathic	Pericardial constriction

*Normal, approximately 50% to 65%.

Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is characterized morphologically and functionally by progressive cardiac dilation and contractile (systolic) dysfunction, usually with concomitant hypertrophy. Many cases are familial, but the DCM phenotype can result from diverse causes, both primary and secondary.

Table 12-12 Conditions Associated with Heart Muscle Diseases

Cardiac Infections
Viruses
Chlamydia
Rickettsia
Bacteria
Fungi
Protozoa
Toxins
Alcohol
Cobalt
Catecholamines
Carbon monoxide
Lithium
Hydrocarbons
Arsenic
Cyclophosphamide
Doxorubicin (Adriamycin) and daunorubicin
Metabolic
Hyperthyroidism
Hypothyroidism
Hyperkalemia
Hypokalemia
Nutritional deficiency (protein, thiamine, other avitaminoses)
Hemochromatosis
Neuromuscular Disease
Friedreich ataxia
Muscular dystrophy
Congenital atrophies
Storage Disorders and Other Depositions
Hunter-Hurler syndrome
Glycogen storage disease
Fabry disease
Amyloidosis
Infiltrative
Leukemia
Carcinomatosis
Sarcoidosis
Radiation-induced fibrosis
Immunologic
Myocarditis (several forms)
Posttransplant rejection

Pathogenesis. By the time of diagnosis, DCM has typically progressed to end-stage disease; the heart is dilated and poorly contractile. Unfortunately, at that point, even an exhaustive evaluation frequently fails to suggest a specific etiology. Increasingly, familial (genetic) forms of DCM are recognized, but the final pathology can also result from various acquired myocardial insults; as this implies, several different pathways can lead to DCM (Fig. 12-31).

- *Genetic Influences.* DCM is familial in at least 30% to 50% of cases, in which it is caused by mutations in a diverse group of more than 20 genes encoding proteins involved in the cytoskeleton, sarcolemma, and nuclear envelope (laminin A/C). In particular, mutations in *TTN*, a gene that encodes titin (so-called because it is the largest protein expressed in humans), may account for approximately 20% of all cases of DCM (Fig. 12-30).

  In the genetic forms of DCM, autosomal dominant inheritance is the predominant pattern; X-linked, autosomal recessive, and mitochondrial inheritance are less common. In some families there are deletions in mitochondrial genes that result in defects in oxidative phosphorylation; in others there are mutations in genes encoding enzymes involved in β-oxidation of fatty acids. Mitochondrial defects typically manifest in the pediatric population, while X-linked DCM typically presents after puberty and into early adulthood. X-linked cardiomyopathy can also be associated with mutations affecting the membrane-associated dystrophin protein that couples cytoskeleton to the extracellular matrix; recall that dystrophin is mutated in the most common skeletal myopathies (i.e., Duchenne and Becker muscular dystrophies; Chapter 27). Some patients and families with dystrophin gene mutations have DCM as the primary clinical feature. Interestingly, and probably resulting from the common developmental origin of contractile myocytes and conduction elements, congenital abnormalities of conduction may also be associated with DCM.
- *Myocarditis.* Sequential endomyocardial biopsies have documented progression from myocarditis to DCM. In other studies, the detection of the genetic fingerprints of coxsackie B and other viruses within myocardium of patients with DCM suggests that viral myocarditis can be causal (see later discussion).
- *Alcohol and other toxins. Alcohol abuse* is strongly associated with the development of DCM, raising the