Clinical Features. **The central abnormality in HCM is reduced stroke volume due to impaired diastolic filling.** This is a consequence of a reduced chamber size, as well as the reduced compliance of the massively hypertrophied left ventricle. In addition, approximately 25% of patients with HCM have dynamic obstruction to the left ventricular outflow. The compromised cardiac output in conjunction with a secondary increase in pulmonary venous pressure explains the exertional dyspnea seen in these patients. Auscultation discloses a harsh systolic ejection murmur, caused by the ventricular outflow obstruction as the anterior mitral leaflet moves toward the ventricular septum during systole. Because of the massive hypertrophy, high left ventricular chamber pressure, and frequently thick-walled intramural arteries, focal myocardial ischemia commonly results, even in the absence of concomitant coronary artery disease. Major clinical problems in HCM are atrial fibrillation, mural thrombus formation leading to embolization and possible stroke, intractable cardiac failure, ventricular arrhythmias, and, not infrequently, sudden death, especially with certain specific mutations. Indeed, HCM is one of the most common causes of sudden, otherwise unexplained death in young athletes.

The natural history of HCM is highly variable. Most patients can be helped by pharmacologic intervention (e.g., β-adrenergic blockade) to decrease heart rate and contractility. Some benefit can also be gained by reducing the septal myocardial mass, thus relieving the outflow tract obstruction. This can be achieved either by surgical excision of muscle or by carefully controlled septal infarction through a catheter-based infusion of alcohol.

Restrictive Cardiomyopathy

Restrictive cardiomyopathy is characterized by a primary decrease in ventricular compliance, resulting in impaired ventricular filling during diastole. Because the contractile (systolic) function of the left ventricle is usually unaffected, the functional abnormality can be confused with that of constrictive pericarditis or HCM. Restrictive cardiomyopathy can be idiopathic or associated with distinct diseases or processes that affect the myocardium, principally radiation fibrosis, amyloidosis, sarcoidosis, metastatic tumors, or the deposition of metabolites that accumulate due to inborn errors of metabolism.

The morphologic features are not distinctive. The ventricles are of approximately normal size or slightly enlarged, the cavities are not dilated, and the myocardium is firm and noncompliant. Biatrial dilation is commonly observed. Microscopically, there may be only patchy or diffuse interstitial fibrosis, which can vary from minimal to extensive. Endomyocardial biopsy can often reveal a specific etiology. An important specific subgroup is amyloidosis (described later).

Several other restrictive conditions merit brief mention.

- *Endomyocardial fibrosis* is principally a disease of children and young adults in Africa and other tropical areas, characterized by fibrosis of the ventricular endocardium and subendocardium that extends from the apex upward, often involving the tricuspid and mitral valves. The fibrous tissue markedly diminishes the volume and compliance of affected chambers and so causes a restrictive functional defect. Ventricular mural thrombi sometimes develop, and indeed the endocardial fibrosis may result from thrombus organization. The etiology is unknown.
- *Loeffler endomyocarditis* also results in endomyocardial fibrosis, typically with large mural thrombi, with an overall morphology similar to the tropical disease. However, in addition to the cardiac changes, there is often a peripheral eosinophilia and eosinophilic infiltrates in multiple organs, including the heart. The release of toxic products of eosinophils, especially major basic protein, is postulated to initiate endomyocardial necrosis, followed by scarring of the necrotic area, layering of the endocardium by thrombus, and finally organization of the thrombus. Many patients with Loeffler endomyocarditis have a myeloproliferative disorder associated with chromosomal rearrangements involving either the platelet-derived growth factor receptor (PDGFR)-α or -β genes (Chapter 13). These rearrangements produce fusion genes that encode constitutively active PDGFR tyrosine kinases. Treatment of such patients with the tyrosine kinase inhibitor imatinib has resulted in hematologic remissions associated with reversal of the endomyocarditis, which is otherwise often rapidly fatal.
- *Endocardial fibroelastosis* is an uncommon heart disease characterized by fibroelastic thickening that typically involves the left ventricular endocardium. It is most common in the first 2 years of life; in a third of cases, it is accompanied by aortic valve obstruction or other congenital cardiac anomalies. Endocardial fibroelastosis may actually represent a common morphologic endpoint of several different insults including viral infections (e.g., intrauterine exposure to mumps) or mutations in the gene for tafazzin, which affects mitochondrial inner membrane integrity. Diffuse involvement may be responsible for rapid and progressive cardiac decompensation and death.

Myocarditis

Myocarditis is a diverse group of pathologic entities in which infectious microorganisms and/or a primary inflammatory process cause myocardial injury. Myocarditis should be distinguished from conditions such as ischemic heart disease, where myocardial inflammation is secondary to other causes.

Pathogenesis. In the United States, *viral infections* are the most common cause of myocarditis. *Coxsackie viruses A* and *B* and other enteroviruses probably account for most of the cases. Other less common etiologic agents include cytomegalovirus, HIV, and influenza (Table 12-13). In some (but not all) cases, the responsible virus can be ascertained by serologic studies or by identifying viral nucleic acid sequences in myocardial biopsies. Depending on the pathogen and the host, viruses can potentially cause myocardial injury either as a direct cytopathic effect, or by eliciting a destructive immune response. Inflammatory cytokines produced in response to myocardial injury can also cause *myocardial dysfunction* that is out of proportion to the degree of actual myocyte damage.