59

Myocarditis

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Key Points

- Viruses are the most common cause of myocarditis in economically advanced countries.
- Enteroviruses and adenoviruses are the most common etiologic agents.
- Viral myocarditis is a triphasic process. Phase 1 is the period of active viral replication in the myocardium during which the symptoms of myocardial damage range from none to cardiogenic shock. If the disease process continues, it enters phase 2, which is characterized by autoimmunity triggered by viral and myocardial proteins. Heart failure often appears for the first time in phase 2. Phase 3, dilated cardiomyopathy, is the end result in some patients. Diagnostic procedures and treatment should be tailored to the phase of disease.
- Viral myocarditis is a significant cause of dilated cardiomyopathy, as proved by the frequent presence of viral genomic material in the myocardium, and by improvement in ventricular function by immunomodulatory therapy.
- Myocarditis of any etiology usually presents with heart failure, but the second most common presentation is ventricular arrhythmia. As a result, myocarditis is one of the most common causes of sudden death in young people and others without preexisting structural heart disease.
- Myocarditis can be definitively diagnosed by endomyocardial biopsy. However, it is clear that existing criteria for the histologic diagnosis need to be refined, and that a variety of molecular markers in the myocardium and the circulation can be used to establish the diagnosis.
- Treatment of myocarditis has been generally disappointing. Accurate staging of the disease will undoubtedly improve treatment in the future. It is clear that immunosuppression and immunomodulation are effective in some patients, especially during phase 2, but may not be as useful in phases 1 and 3. Since myocarditis is often self-limited, bridging and recovery therapy with circulatory assistance may be effective. Prevention by immunization or receptor blocking strategies is under development.
- Giant cell myocarditis is an unusually fulminant form of the disease that progresses rapidly to heart failure or sudden death. Rapid onset of disease in young people, especially those with other autoimmune manifestations, accompanied by heart failure or ventricular arrhythmias, suggests giant cell myocarditis.
- Peripartum cardiomyopathy in economically developed countries is usually the result of myocarditis.

The difficulty of diagnosing and treating myocarditis was recognized by Senac[1] in 1772: "The inflammation of the heart is difficult to diagnose and when we have diagnosed it, can we then treat it better?" After Sobernheim[2] in 1837 defined myocarditis as any inflammation or degeneration of the heart, the term *myocarditis* was used for nonvalvular myocardial diseases, including ischemic and hypertensive cardiomyopathies. Nearly a century later, White[3] suggested that the term *myocarditis* be restricted to "true inflammation of the myocardium." The last half-century has seen the development of endomyocardial biopsy techniques, histologic criteria, and serologic methods to diagnose myocarditis. As our knowledge of the immunopathologic mechanisms evolves, new therapeutic strategies are developing.

The World Health Organization/International Society and Federation of Cardiology Task Force on Cardiomyopathies[4] classified cardiomyopathies whenever possible by etiologic/pathogenetic factors. This classification recognizes chronic viral, postinfectious autoimmune, and primary autoimmune forms of dilated cardiomyopathy (DCM). The classification states that "myocarditis is diagnosed by established histological, immunological and immunohistochemical criteria." The Dallas criteria[5] provide consensus-derived histologic criteria: "an inflammatory infiltrate of the myocardium with necrosis and/or degeneration of adjacent myocytes not typical of ischemic damage associated with coronary artery disease." However, many have speculated that less pronounced histologic abnormalities may be present and that additional molecular, immunologic, and immunohistochemical diagnostic criteria can be used productively.[6–11] Myocarditis, irrespective of the etiopathologic factors, remains an

inflammatory cardiomyopathy associated with cardiac dysfunction.

Etiology and Epidemiology

A wide variety of infectious and noninfectious causes are associated with myocarditis (Tables 59.1 to 59.3). Several epidemiologic observations linking these agents with myocarditis have been corroborated by serologic, polymerase chain reaction (PCR), or in situ hybridization methods. The incidence of infectious myocarditis in the general population is largely unknown. In a prospective study[12] over several years, in a predefined subpopulation, an incidence of 0.02% was found. These cases were confirmed by myocardial enzyme leak and characteristic electrocardiographic (ECG) changes.[12] The ECG abnormalities suggesting asymptomatic myocardial involvement, in the absence of enzyme release, have been noted in 1.2% of military conscripts during the course of other acute infectious diseases.[13] During an epidemic of influenza A, the incidence rose to 7.7%.[14] In a prospective trial of 2310 consecutive patients admitted to a large infectious disease hospital in Sweden, 8% showed ECG abnormalities suggestive of myocarditis.[15] Approximately 5% of a virus-infected population may experience symptoms or findings suggestive of cardiac involvement. The incidence of myocarditis associated with nonviral infections is even more difficult to estimate. Although the list of possible etiologic agents is large, the enteroviruses, specifically coxsackievirus B, over decades have been the most commonly identified etiologic agents of inflammatory cardiomyopathy. Among healthy active adults, at least 50% have detectable serum antibodies indicating prior infection with coxsackievirus B.[16,17] The World Health Organization has surveyed viral infections related to cardiovascular disease globally. In a 10-year period from 1975 to 1985, coxsackievirus B had the highest incidence of cardiovascular disease (34.6 cases per 1000 population), followed by influenza B (17.4 cases), influenza A (11.7 cases), coxsackievirus A (9.1 cases), and cytomegalovirus (CMV) (8.0 cases).[18]

The predominance of enteroviruses among myocarditis-associated agents has been substantiated by several laboratory and clinical studies.[19–21] Using serologic methods, Vikerfors and associates[19] reported that nearly 50% of consecutively studied myocarditis patients had enterovirus immunoglobulin IgM. Frisk and coworkers[20] found a similar incidence of coxsackievirus B IgM antibodies by reverse

TABLE 59.1. Common etiologies of myocarditis

Infections	*Hypersensitivity reactions to drugs*
Adenovirus	Hydrochlorothiazide
Coxsackievirus	Methyldopa
Cytomegalovirus	Penicillins
Epstein-Barr virus	Sulfadiazine
Herpes simplex virus	Sulfamethoxazole
Influenza virus	
Borrelia (Lyme disease)	*Systemic diseases*
Parvovirus (B19)	Crohn's disease
Respiratory syncytial virus	Kawaski disease
	Sarcoidosis
Drugs	Systemic lupus erythematosus
Amphetamines	Ulcerative colitis
Anthracyclines [especially	Cardiac rejection
doxorubicin (Adriamycin)]	Giant cell myocarditis
Catecholamines	Peripartum myocarditis
Cocaine	
Cyclophosphamide	
Interleukin-2	
Smallpox vaccine	

TABLE 59.2. Uncommon infectious etiologies of myocarditis

Viral
Arbo virus (dengue fever, yellow fever)
Arena virus (Lassa fever)
Corona virus
Echo virus
Encephalomyocarditis virus
Hepatitis B
Herpes virus
Influenza virus
Junin virus
Mumps virus
Polio virus
Rabies virus
Respiratory syncytial virus
Rubella virus
Rubeola virus
Vaccinia virus
Varicella-zoster virus
Variola virus

Bacterial
Brucella
Campylobacter jejuni
Chlamydia psittaci
Chlamydia trachomatis
Clostridia
Corynebacterium diphtheriae
Francisella tularensis
Gonococcus
Haemophilus
Legionella
Listeria
Meningococcus
Mycobacteria (tuberculosis, avium-intracellulare, leprae)
Mycoplasma
Pneumococcus
Salmonella
Staphylococcus
Streptococcus
Tropheryma whippelii (Whipple's disease)

Fungal
Actinomyces
Aspergillus
Blastomyces
Candida
Coccidioides
Cryptococcus
Fusarium oxysporum
Histoplasma
Mucor
Nocardia
Sporothrix

Rickettsial
Coxiella burnetti (Q fever)
Rickettsia typhi (typhus)
Rickettsia rickettsii (Rocky Mountain spotted fever)
Rickettsia tsutsugamushi (scrub typhus)

Spirochetal
Leptospira
Treponema pallidum (syphilis)

Helminthic
Cysticercus
Echinococcus
Schistosoma
Toxocara (visceral larva migrans)
Trichinella

Protozoal
Entamoeba
Leishmania

TABLE 59.3. Uncommon noninfectious causes of myocarditis

Drugs	**Toxins**
Toxic myocarditis	Arsenic
Amphetamines	Carbon monoxide
Arsenic	Copper
Chloroquine	Kerosene
Emetine	Iron
5-fluorouracil	Lead
Interferon-α	Mercury
Lithium	Phosphorus
Paracetamol	Scorpion stings
Thyroid hormone	Snake venom
	Spider bites
Hypersensitivity myocarditis	Wasp stings
Acetazolamide	
Allopurinol	**Systemic Diseases**
Amphotericin B	Arteritis (giant cell, Takayasu's)
Carbamazepine	β-thalassemia major
Cephalothin	Churg-Strauss vasculitis
Chlorthalidone	Cryoglobulinemia
Clozapine	Dermatomyositis
Colchicine	Diabetes mellitus
Diclofenac	Hashimoto's thyroiditis
Ephedrine	Mixed connective tissue disease
Diphenhydramine	Myasthenia gravis
Furosemide	Periarteritis nodosa
Indomethacin	Pernicious anemia
Isoniazid	Pheochromocytoma
Methylenedioxyamphetamine	Polymyositis
Lidocaine	Rheumatoid arthritis
Methysergide	Scleroderma
OctreoScan	Sjögren's syndrome
Montelukast	Thymoma
Oxyphenbutazone	Wegener's granulomatosis
Para-aminosalicyclic acid	
Phonindione	**Other**
Phenylbutazone	Eosinophilic myocarditis
Phenytoin	Generic
Procainamide	Granulomatous myocarditis
Pyribenzamine	Head trauma
Ranitidine	Hypothermia
Reserpine	Hyperpyrexia
Spironolactone	Ionizing radiation
Tetanus vaccine	Mononuclear myocarditis
Smallpox vaccine	
Streptomycin	
Tetracycline	
Trimethoprim	

radio immunoassay. Other agents such as adenoviruses, Epstein-Barr virus, *Mycoplasma*, and *Chlamydia* have also been associated with myocarditis. Martin and colleagues[21] demonstrated specific viral genome sequences in endomyocardial biopsies in 26 of 38 children (68%) with acute myocarditis: adenovirus in 15 patients, enterovirus in eight, herpes simplex in two, and CMV in one patient. The control group did not demonstrate any viral genome sequences.

Just as the incidence of specific viral infections varies over time, so should the relative proportion of agents responsible for myocarditis. In a recent study, Bowles and colleagues[22] supported the observation by Martin and coworkers[21] that adenovirus is the most common agent associated with myocarditis in children, but they also found that adenoviruses predominated over enteroviruses in adults. Figure 59.1 shows the dominant role of adenoviruses and enteroviruses in myocarditis. Note that parvovirus was detected in young people. Parvovirus B-19 has recently been identified as a cause of myocarditis and, in some regions, it has been found in adults as well as children.[23–27] These differences between previous and newer studies are due, at least in part, to geographical and temporal variation in the incidence of specific viral infections.

Cytomegalovirus is a recognized cause of acute infectious myocarditis, although it is rare in healthy individuals.[28,29] Maisch and associates[30] demonstrated, using in situ hybridization techniques, CMV-specific nucleotide sequences in 15% of patients with acute myopericarditis. Certainly in transplant recipients, CMV infection is fairly common and has been reported to affect the transplanted heart.[31,32] Hepatitis C virus infection is frequently noted in patients with DCM,[33] and hepatitis C virus RNA has also been recovered from lymphocytes infiltrating the myocardium in chronic active myocarditis.[34] Matsumori and colleagues[35,36] found a high incidence of hepatitis C viral genomic material in a wide variety of cardiac disorders in Japan.

Bacterial Myocarditis

Myocarditis is a well-recognized complication of *Corynebacterium diphtheriae* infection, although this is now rare in the Western world.[37] Myocardial dysfunction is also seen in association with *Salmonella* septicemia, although it is rarely clinically severe.[38,39] Myocardial dysfunction is primarily related to the toxemia of the severe infection, which is also observed in meningococcal and nonrheumatic streptococcal infections.

Perhaps the best-recognized bacterial agent thought to be responsible for myocarditis is the β-hemolytic streptococcus

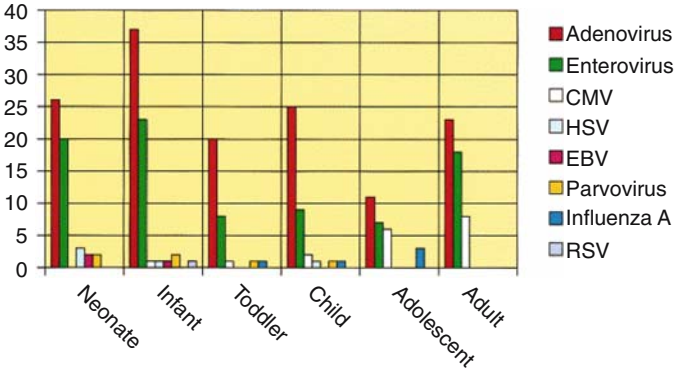

FIGURE 59.1. Incidence of detection of specific viral genomic material in human cardiac tissue by polymerase chain reaction (PCR).

that causes rheumatic fever. Fortunately, rheumatic fever is seen in the Western world with only a low frequency of sporadic cases in regional clusters. The incidence in the United States is less than 2 per 100,000, but in the developing world, rheumatic heart disease continues to be the leading cause of cardiac hospitalization in the 5- to 25-year-old age group.[40] Although the inflammatory component of rheumatic carditis is largely restricted to the valves, it has been believed to cause myocardial dysfunction.

Myocarditis is a well-documented complication of *Borrelia burgdorferi* infection (Lyme disease) and is reported in up to 8% of cases. Cardiac involvement is often characterized by the development of atrioventricular (AV) block and rarely progresses to left ventricular dysfunction and cardiomegaly.[41] *Mycoplasma pneumoniae* infection has also been associated with myocarditis. Lewes and coworkers[42] demonstrated asymptomatic myocardial involvement as documented by ECG changes in a third of the cases with acute *Mycoplasma* infection. Six percent of military conscripts with clinical myocarditis were found to have active *M. pneumoniae* infection.[43] *Chlamydia* infections have also been associated with myocarditis, especially among small children, often having fatal outcomes.[44] *C. pneumoniae* infection has also been noted in a few cases of mild myocarditis[45] and has been found with respiratory infection associated with myocarditis, resulting in sudden death in a young athlete.[46] *Chlamydia psittaci* infection may be associated with myocarditis in 5% to 15% of those affected, usually with minimal clinical signs or symptoms.[44] Pericarditis is more frequent and likely to cause cardiac morbidity with ornithosis.[47]

Other Causative Infectious Agents

Rickettsial infections, like Rocky Mountain spotted fever and scrub typhus, are frequently accompanied by myocardial involvement, although vasculitis is more prominent with these infections.[48] Q fever may also be associated with myocarditis.[49] *Trypanosoma cruzi* is a well-recognized cause of myocarditis and cardiomyopathy in South America (Chagas' disease).[50] *Toxoplasma gondii* poses a significant problem among cardiac transplant recipients because a large number of the recipients lack antibodies against this agent, which may cause myocarditis.[51] Toxoplasmosis also poses a major threat to patients with AIDS. Myocarditis has frequently been seen in human immunodeficiency virus (HIV)-infected populations with or without concomitant *Toxoplasma* infection.[52,53] In two autopsy studies of patients with AIDS, myocarditis was found in almost half of the cases; in another study, 54% of 102 prospectively studied patients with AIDS had echocardiographic evidence of myocardial dysfunction.[54,55] Myocarditis may also occur in patients with AIDS as a result of T-cell restitution after antiviral therapy.[56]

Myocarditis can also be seen with parasitic infections such as *Trichinella spiralis*, which has an affinity for striated muscle, including the heart.[57]

Other Noninfectious Causes

Noninfectious causes of myocarditis include drug-induced hypersensitivity,[58–89] direct toxicity of specific pharmaceutical agents,[77,90–92] and systemic collagen vascular disorders.[93–100] Eosinophilic myocarditis[101–104] and giant cell myocarditis (GCM)[105–111] are distinct forms of inflammatory myocarditis of uncertain etiology.

Microorganisms are rarely isolated or demonstrated in heart muscle; hence, identification of a specific infectious etiologic agent depends on recognition of its systemic manifestations. Once specific noninfectious and nonviral infectious agents are excluded, myocarditis is often assumed to be of viral etiology. Although definitive serologic evidence of viral infection can be obtained in many patients, it is absent in the majority of patients with presumed myocarditis. A significant number of cases of myocarditis is due to autoimmune phenomena either induced by a viral infection or resulting from systemic autoimmune disease. Since the establishment of definitive etiologic diagnoses is ambiguous, the terms *viral myocarditis*, *idiopathic myocarditis*, *lymphocytic myocarditis*, *autoimmune myocarditis*, and *interstitial myocarditis* are frequently used interchangeably.

Pathophysiology of Viral Myocarditis

The pathophysiologic mechanisms of myocarditis in humans are not fully understood. Clearly, multiple mechanisms exist, including direct infection by viruses, bacteria, and other organisms; noninfectious causes, such as toxins and drug hypersensitivity; and parainfectious etiologies, resulting from the immune response to infection. Most cases of overt heart failure due to myocarditis in North America, Europe, and Japan are thought to arise from the latter type of mechanism, during and after viral infection of the heart. A triphasic disease process is observed[112,113] (Fig. 59.2A). In the first phase, active viral infection of the myocardium results in a variable

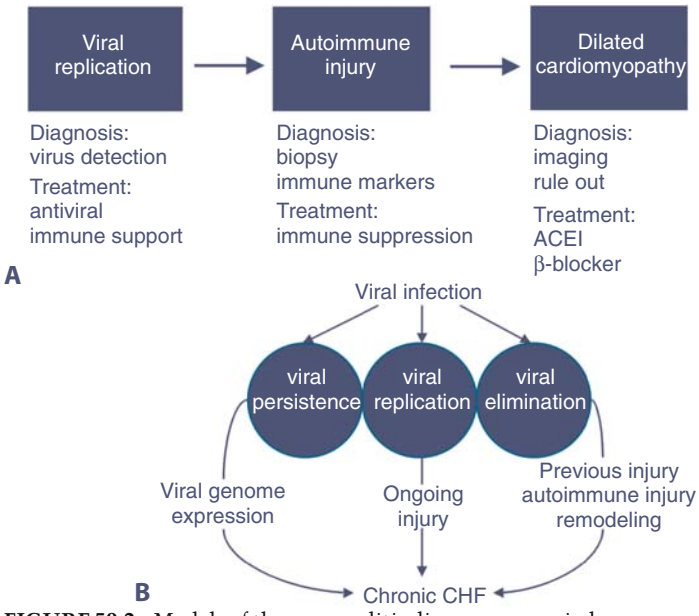

FIGURE 59.2. Models of the myocarditis disease process in humans. (A) Myocarditis in humans has three distinct phases that are diagnosed and treated differently. (B) Viruses cause myocardial injury and functional impairment, leading to heart failure, through a variety of mechanisms.

extent of muscle damage, which often may not be clinically apparent. Phase 2 develops in an unknown proportion of infected individuals after partial or complete resolution of active infection and is characterized by further myocardial damage, both by ongoing immune activation and by newly developed autoimmune activity. A small proportion of patients develops dilated cardiomyopathy, the third phase of disease, resulting from the cumulative damage caused by infection, immunity, and autoimmunity. During this phase, a considerable body of evidence suggests that the immune and autoimmune processes persist, in part as a result of viral persistence.[114] Figure 59.2B depicts the three roles virus may play in bringing about dilatation and chronic heart failure. After the initial injury that occurs during active viral replication, latent, nonreplicating viruses can still alter myocyte function through viral genomic expression.[115] Even if the virus is completely eliminated and the immune response ceases, through the various mechanisms of adverse remodeling, the cardiomyopathy may progress inexorably.

Animal Models

The most widely accepted models for the study of human myocarditis are those of enteroviral myocarditis induced by coxsackievirus B3 (CVB3) and the encephalomyocarditis virus.[116] Induction of chronic murine myocarditis by CVB3 requires the virus to have a cardiovirulence capacity and murine strains of certain genetic background.[117,118] Infection of syngeneic weanling mice with CVB3 results in brief cardiac infection lasting about a week, beyond which the virus cannot be cultured. However, viral RNA persists for several months after the initial infection.[119,120] Several mechanisms have been hypothesized to explain the initiation of chronic inflammatory response in myocytes by the viral infection:

1. Dysregulatory processes that stimulate inflammation and result in myocyte destruction may be provoked by persistent infection of the cell by the replicating virus or even remnant virions.[121]
2. The virus-induced myocyte injury releases or exposes hitherto hidden or cryptic antigens to immune cells, leading to autoimmune effector molecule synthesis and maintained inflammatory response.[122,123]
3. The CVB3 virion or other viral proteins share epitopes with internal or plasma membrane proteins of normal cells (molecular mimicry) and stimulate immune responses that participate in autoimmune reactions.[124]

These three mechanisms are not mutually exclusive and all may be simultaneously operative. The CVB3 and CVB4 share epitopes with human cardiac myocyte sarcolemmal proteins,[125,126] human and mouse cardiac myosins,[127,128] streptococcal M protein,[127] adenine nucleotide translocator protein,[129] and other proteins on normal mouse myocytes and fibroblasts.[130] A large number of target epitopes have been proposed, including the β-adrenergic receptor,[131] laminin,[132] branched chain ketoacid dehydrogenase,[133] and heat shock protein 60.[134] Although antibodies to these antigens are frequently identified in association with myocarditis, the clinical significance and causal relationship are yet unresolved.

Cytotoxic lymphocytes (CTLs) from mice with CVB3-induced myocarditis possess the ability in vitro to recognize and kill neonatal myocytes, fibroblasts, and endothelial cells infected with the same strain of the virus,[135] suggesting that the recognition of a novel tissue antigen is induced by the infection. Cross-reactive, concurrent recognition of unrelated cardiac epitopes also occurs because CTLs also lyse uninfected myocytes in vitro.[136] The production of perforin, a pore-forming protein, has been proposed as one of the mechanisms for the cytolysis induced by lymphocytes. Perforins, when inserted into myocyte membrane, induce a lethal augmentation in cell permeability that results in cellular edema and death.[137] Perforin-independent mechanisms have also been proposed, including a Fas (CD95/Apol)–based inositol-1,4,5-triphosphate–mediated cytolysis that can be demonstrated in perforin-deficient gene-knockout mice.[138] Coxsackievirus-infected mice also develop additional immune sensitization to cardiac heavy chain myosin, possibly owing to the release of the sequestered myosin antigens from the virus-damaged cells. Immunization of mice with the heavy chain myosin and an adjuvant produces a histomorphologically similar picture to CVB3-induced myocarditis. Adoptive transfer of splenocytes can also produce experimental autoimmune myocarditis after myocardial infarction in syngeneic rats. The sensitized lymphocytes when transferred to normal rats cause cardiac-specific cellular infiltration with accompanying myocyte necrosis.[139] The genetic susceptibility, kinetics, and cellular composition of the infiltrates in these models are similar and suggest the role of endogenous antigens as an epitope for the inflammatory response.[140]

Role of Cellular Immunity

The pathways and cellular participants in the immunopathogenesis of experimental viral myocarditis are well recognized. The replicating viral particles can be readily identified in cardiac myocytes within a few hours of inoculation of CVB3 into mice.[141,142] The viral particles reach a numerical peak in 3 to 4 days, and usually at 7 to 10 days, they are no longer detectable.[143] The inflammatory infiltrate is detectable by day 5 and reaches a plateau by days 7 to 10. The early inflammatory infiltrate consists of lymphocytes, macrophages, neutrophils, natural killer cells, and the associated cytokines and humoral effectors.[144–146] The natural killer cells are the first to appear and are detected in the activated state in 3 to 4 days. These cells are capable of lysing virus-infected cells in vitro.[145] The T lymphocytes and macrophages follow the natural killer cells in the temporal sequence and become the predominant cells infiltrating the myocardium in 7 to 10 days. Although CVB3 replicates readily in myocytes in vitro, the cells are resistant to lysis in comparison with other cultured cell lines. Direct myocytolysis appears to play a minimal role in cell lines derived from normal mice.[147]

The immunodeficient severe combined immunodeficiency (SCID) mouse model has provided valuable insight into the early immune activity in response to the viral infection. The SCID mice lack mature T- and B-lymphocyte function and develop extensive myocardial necrosis with pleomorphic infiltrates, rapid viral proliferation, and profound virus-associated myocytolysis when inoculated with CVB3.[148] The macrophage and natural killer cell activity is

unaffected in the SCID mouse model and may participate in the myocytolytic activity, although direct viral myocytolysis predominates. Pharmacologically immunosuppressed mice demonstrate similar characteristics, with higher viral loads, delayed clearance, and extensive myocyte necrosis, although direct viral myocytolysis is not frequent in immunocompetent mice.[143,147,149–151] Even noncardiovirulent strains may have sufficient time to replicate and transform into quasi-cardiovirulent species in the absence of a functional antiviral immune response, which can then result in fatal myocarditis.[152] This may also explain the clinical observation that many severe and fatal cases of myocarditis develop in young children with immature and incompletely developed immune systems.[153]

Virus-specific CTLs play a major role in the inflammatory response to viral infection of the myocytc.[143,151] The inflammatory response can be diminished significantly by T-lymphocyte depletion with either antithymocyte globulin or thymectomy and irradiation.[142,154] The CTLs must recognize the foreign antigen in association with the syngeneic major histocompatibility complex (MHC) class I antigen that is found on immune-derived cells. The CVB3-infected cells can readily express MHC class I antigens.[155] The MHC class I molecules provide peptide-binding sites that evoke effector responses on recognition of the foreign peptide by the antigen-specific receptors of the T lymphocyte.[156] However, T-lymphocyte depletion and specific immunosuppression using cyclosporine have varying effects, depending on the murine model, the virus, and the time of therapy, and are not uniformly beneficial.[157–159] The virus can no longer be cultured from cells after 7 to 10 days; however, areas of inflammatory infiltrate and myocyte necrosis do demonstrate persistence of viral RNA, and the virus-specific CTLs may continue to see these as immunologic targets and, hence, perpetuate the myocyte damage.[160]

The infected myocyte can still remain a target for the CTLs, even if the viral antigens are cleared, owing to expression of "neoantigens" either induced by the virus or unsequestered due to the injury.[161,162] Even nonviral antigens on infected myocytes can react with CTLs, such as those induced by actinomycin D,[162] and new glycoproteins have been identified on the surface of CVB3-infected cells that can be recognized by CTLs from other syngeneic-infected mice.[163] Recent observations suggest that co-stimulatory molecules B7-1, B7-2, and CD-40 may be expressed on myocytes in patients with myocarditis and may make the myocytes into antigen-presenting cells for CTLs and natural killer cells, thereby playing an important role in the direct myocardial damage by these lytic cells.[164]

Role of Humoral Immunity

Another mechanism for ongoing myocyte damage is the antibody-mediated autoimmune response. Since the majority of the proteins identified as cardiac autoantigens are intracellular, it is unclear how these antibodies could harm normal intact myocytes. Several mechanisms are proposed. One suggests that after the antibody response is initiated, the circulating antibodies to intracellular antigens cross-react with the native membrane cardiac tissue proteins. Thus, after a small number of myocytes are damaged by the viral infection and release intracellular antigens, the resulting antibody response may affect normal myocytes, leading to global myocardial dysfunction. This hypothesis is supported by the demonstration of a number of cross-reacting antibodies.[125–134] Also, the antibodies against the intracellular mitochondrial adenine nucleotide transferase protein cross-react with the myocyte sarcolemmal calcium ion channel protein, and binding of these channels can physiologically alter the metabolism and contractile function of the myocyte.[165]

Another theory holds that CTLs and antibodies target uninfected myocytes by recognition of self-antigens that were previously sequestered from immune surveillance. The processing and presentation of the self-immunogenic peptides complexed with the MHC is a prerequisite for this hypothesis. Normal human cardiac myocytes do not express detectable levels of MHC class II antigens, and their constitutive expression of MHC class I molecules remains controversial.[166] A significant increase in the expression of MHC class I and class II antigens by the myocytes has been demonstrated in association with myocardial inflammation, such as that seen with viral myocarditis or transplant rejection.[167–169] The increased MHC expression has also been demonstrated in endomyocardial biopsy specimens from patients with idiopathic DCM and myocarditis,[170–172] and immune regulatory dysfunction may have a genetic predisposition.[173] There is also evidence for aberrant expression of intracellular antigens, such as adenine nucleotide translocator (ANT) and branched-chain α-keto acid dehydrogenase (BCKD), on the surface of the myocytes.[172]

The formation of antiidiotypic antibodies is an additional mechanism of immune regulation in which an antibody is formed to the idiotypic determinants (antigen recognition site) of the primary antibody. The antiidiotypic antibody may cross-react with unoccupied viral receptor sites on uninfected myocytes. This phenomenon has been reported with the reovirus, polyomavirus, and coxsackievirus B models of myocarditis.[174–176] The passive transfer of antiidiotypic B cells from a CVB3 myocarditic mouse to a syngeneic mouse can cause nonviral myocarditis.[177]

Role of Cytokines

The presence of a complex, cytokine-rich microenvironment is suggested by the heterogeneous inflammatory cell populations in the hearts of infected mice. The cytokines perform myriad immunomodulatory functions, including regulation of antibody production, preservation of self-tolerance,[178,179] conscription of ancillary cells in the inflammatory milieu,[180,181] and maintenance of clonal expansion of CTLs.[182,183] Certain cytokines regulate the collagenogenic and collagenolytic activity of fibroblasts.[184] Although mounting evidence supports the negative inotropic effects or the blunting of catecholamine response in myocytes exposed to various cytokines, there is no direct evidence to suggest that the cytokines are directly responsible for myocytolysis.[185] In an in vitro model, Barry[185] demonstrated that high concentrations of interleukin (IL)-1, tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), and IL-4 have no effect on myocyte survival over 24 hours, whereas the CTLs from a mixed lymphocyte reaction cause virtually 100% killing.

Gulick and colleagues[186] demonstrated that cultured neonatal myocytes, when exposed to macrophage-derived IL-1 and TNF-α, have reduced levels of cyclic adenosine monophosphate and have a reduced inotropic response to catecholamines. The mechanism for decreased responsiveness to catecholamines is believed to be modulated by increases in nitric oxide production mediated by increased inducible nitric oxide synthase (iNOS) activity, and the blunting of the catecholamine response can be inhibited by the L-arginine analogue N^G-monomethyl-l-arginine (l-NMMA).[187] The decreased contractile response of cardiac myocytes to β-adrenergic agonists following induction of iNOS also requires the presence of insulin and the co-induction of enzymes responsible for the production of tetrahydrobiopterin, a cofactor for nitric oxide synthase.[188] The role of iNOS remains controversial because increased expression of iNOS mRNA and that of other proinflammatory cytokines is evident and is associated with contractile dysfunction.[189] There is evidence to support the idea that iNOS induction is crucial for the host response to CVB3 infection, and iNOS-deficient mice have significantly increased viral loads with extensive myocardial damage.[190] Inhibition of iNOS through suppression of nuclear factor (NF)-κB induction has recently been shown to prevent encephalomyocarditis virus myocarditis.[191]

Other investigators have suggested that inflammatory cytokines may have direct negative inotropic effects, independent of the responsiveness to the β-adrenergic agonists. High doses of IL-2 during chemotherapy have been reported to result in depression of myocardial function.[89] Exposure of cardiac myocytes to endotoxin results in increased nitric oxide production and direct depression of contractility owing to increased levels of cyclic guanosine monophosphate.[192] Further, TNF-α may induce direct negative inotropic effects by decreasing the Ca^{2+} transient, with no change in the l-type Ca^{2+} current and independent of nitric oxide synthesis.[193] Although the extent to which cytokines cause direct negative inotropic effects or attenuation of endogenous β-adrenergic agonist activity remains unclear, they do produce myocyte dysfunction and cardiac decompensation. Transgenic mice with overexpression of TNF-α develop biventricular dilatation and cardiac failure, resulting in premature death. Pathologic specimens from these mice reveal globular dilated hearts and transmural myocarditis with myocyte apoptosis.[194]

Increased levels of intracellular adhesion molecule (ICAM-1), IL-1α, IL-1β, TNF-α, and macrophage-stimulating factor have been demonstrated in patients with myocarditis and idiopathic DCM.[195,196] Furthermore, the susceptibility of mice in the CVB3 myocarditis model can be increased by pretreatment with these cytokines.[197] Transforming growth factor-β is identifiable by immunohistochemistry in the prenecrotic regions of infiltrates in the murine myocardium and decreases when the macrophages and fibroblasts migrate to the necrotic foci. These growth factors may be responsible for recruitment of the immunologic effectors and may directly affect cardiac function.[198] An intriguing feature of cytokine activity remains their possible role in the secondary development of myocyte hypertrophy and interstitial fibrosis, characteristic of dilated cardiomyopathy.[199] Among animals with different forms of viral myocarditis associated with similar intensity of initial myocyte necrosis, only those animals with persistent inflammation develop interstitial fibrosis, reflected by fibroblast proliferation and an increase in the extracellular matrix. Myocardial fibrosis correlates well with the presence of T lymphocytes and macrophages, which in their activated state release fibrogenic cytokines such as fibroblast growth factor and transforming growth factor-β.[200]

Matrix metalloproteinases (MMPs), and their inhibitors, are thought to play a critical role in the process of myocardial remodeling. Some of the cytokines elaborated during the course of viral myocarditis, such as TNF-α, disturb the balance between MMPs and their inhibitors by increasing MMP, leading to failure of collagen cross-linking and worsened ventricular function (Fig. 59.3).[201] This pathophysiology may present opportunities for prevention of the development of dilated cardiomyopathy resulting from myocarditis.

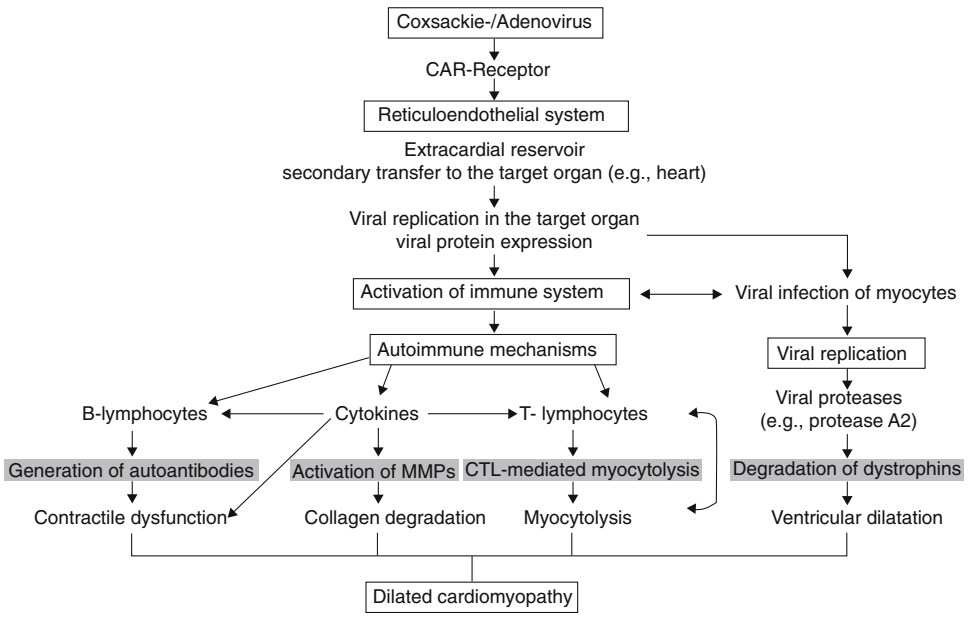

FIGURE 59.3. Detailed pathophysiologic mechanisms of myocarditis in humans.

Significance of Animal Models

Lymphocytic myocarditis models in animals have conclusively demonstrated the association of viral infection and myocarditis. This association clearly exists in humans, but the proportion of cases that can be accounted for by viral infection is not known. The myocardial damage in murine models of viral myocarditis occurs in two distinct phases: an early phase of direct viral cytotoxicity in which virus-specific T-lymphocyte– and antibody-mediated cytotoxicity predominate; and a late or chronic phase in which the persistent viral genome, reactive CTLs, autoantibodies, cytokines, and microvascular damage mediate myocyte damage and dysfunction. The hypothetical mechanisms of virus-induced autoimmune heart disease are presented in Figures 59.2 to 59.4.

The recognition that immune responses to specific viruses are consequential in the development of myocyte injury has led to exhaustive research to exploit the possibility of designing immunomodulatory and antiviral therapies. The pretreatment of mice with inactivated virus vaccine prevents the manifestations of encephalomyocarditis virus myocarditis.[202] The administration of antiviral therapies reduces the viral load and attenuates the histologic findings of myocarditis.[203,204] The antiviral response can be augmented by IFN-α or the exogenous administration of IL-6.[205,206] Recombinant murine IFN-γ has also been demonstrated to improve the prognosis of acute murine myocarditis caused by encephalomyocarditis virus by suppressing replication.[207]

The murine model has also been the subject of intensive study with clinically applied immunosuppressants, such as corticosteroids,[208] nonsteroidal antiinflammatory agents,[209,210] and cyclophosphamide,[211] all of which have demonstrated deleterious effects when given in the acute viremic phase. Cyclosporine, when administered in the early viremic phase, worsens myocardial injury but, in the late immune phase, has a beneficial effect.[157,158,212] Similar results have been reported with tacrolimus,[213] and survival improves significantly when immunosuppressants such as cyclosporine, azathioprine, and 15-deoxyspergualin are used in adjunct to immunomodulators, such as IFN-α.[214] Antibodies to TNF-α have been demonstrated to improve survival and reduce myocardial injury.[215] Cytokine inhibitors have had promising results in animal models, but human clinical trials have been inconsistent. Vesnarinone, a phosphodiesterase III inhibitor, has demonstrated beneficial hemodynamic effects and inhibits the production of TNF-α and favorably modulates induction of iNOS.[216] Amlodipine has also been shown to increase survival of mice with viral myocarditis by inhibiting expression of iNOS and production of nitric oxide in vivo and in vitro.[217]

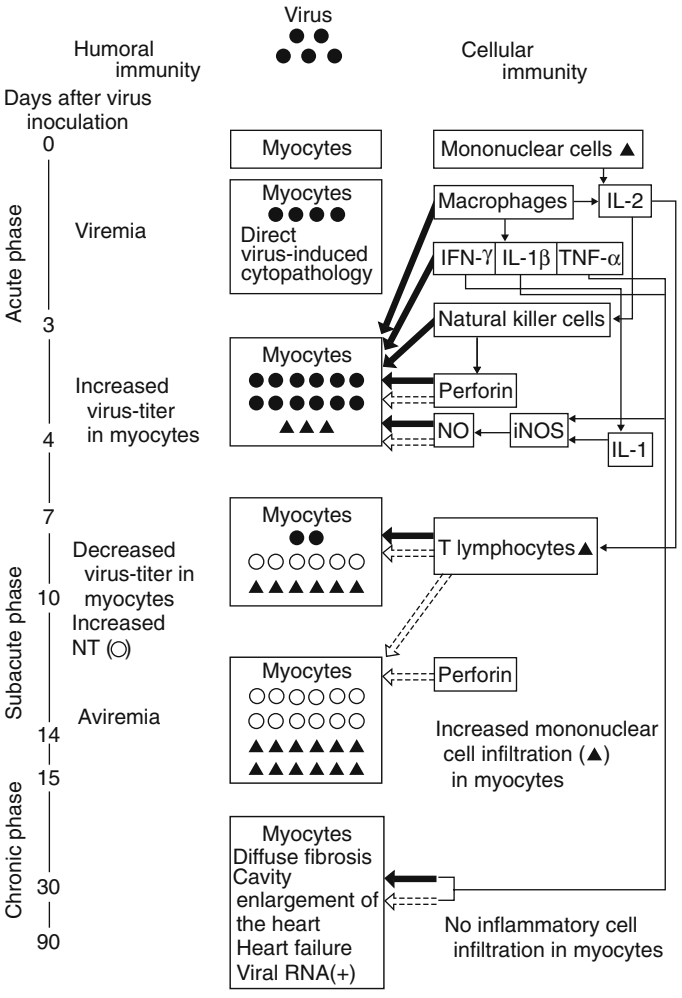

FIGURE 59.4. Multiple mechanisms of injury in murine viral myocarditis.

Clinical Features and Approach to Diagnosis

Clinical Presentation

The diversity of immunopathogenetic mechanisms and variability in the severity of observed disease in the murine model are only a preview to the potpourri of clinical manifestations of myocarditis in humans. The presentation of unexplained progressive cardiac dysfunction or ventricular arrhythmias should lead to the suspicion of myocarditis, especially when routine cardiac diagnostic studies do not reveal an etiology. The history of an antecedent viral infection or prodrome is often sought but seldom reported and rarely confirmed by convalescent serologies. The presence of mild elevation of creatine kinase MB isoenzyme (CK-MB) or troponin, leukocytosis, or ECG changes may further underscore the possibility of myocarditis.

Most patients with myocarditis likely remain asymptomatic and never seek medical attention. The high frequency of exposure to cardiotropic viruses and the observation of a fairly high incidence of ECG abnormalities in apparently healthy individuals support this speculation.[9] The incidence of myocarditis in an autopsy series following traumatic deaths in previously healthy individuals has been reported at 2.2%.[218] Others have reported incidences ranging from 0.11% to as high as 5% in unselected autopsy series.[219,220] These studies may suggest that at any given time, a significant percentage of the asymptomatic general population has myocarditis.

The most common presentation of myocarditis is an acute febrile syndrome associated with pericardial and sys-

temic complaints. Cardiotropic viruses may cause pericardial inflammation, and patients often present with a syndrome of myopericarditis. Chest pain is the most common symptom and is secondary to pericarditis or myocardial injury.[221] A rather dramatic presentation of myocarditis is one indistinguishable from an acute myocardial infarction, complete with chest pain, ECG features suggesting acute ischemic injury, enzymatic evidence of myocardial damage, and echocardiographic or ventriculographic regional wall motion abnormalities, but on endomyocardial biopsy myocarditis is confirmed.[222–224] Most patients presenting with this acute syndrome completely recover, although there are isolated instances where progressive myocyte loss and cardiac failure or sudden arrhythmic death is reported.[225] The segmental wall motion abnormalities result from virus-mediated injury, although local coronary arteritis and vasospasm have been suggested as possible culprits.[226,227]

Symptoms of right and left ventricular failure and even cardiogenic shock are frequently found in patients with biopsy-proven myocarditis, since it is these symptoms that lead to medical attention. However, the true incidence of heart failure in patients with myocarditis is probably much lower. In patients presenting with recent-onset heart failure and biopsy-proven myocarditis, 50% to 60% have had an antecedent flu-like illness.[225]

Neonatal myocarditis is often a fulminant syndrome consisting of fever, tachycardia, tachypnea, cyanosis, and rapid progression to circulatory collapse.[228] Mortality rates are the highest in this subpopulation, approaching 50%. Children are known to present with syncope due to heart block.[229] Other atrial arrhythmias described with myocarditis include sinoatrial block, atrial standstill, AV block, intraatrial conduction abnormalities, atrial tachycardia, flutter, and fibrillation.[230–235] Histologic evidence of possible myocarditis has been described in up to two thirds of patients with lone atrial fibrillation.[236] Complete heart block has also been described in certain viral infections, such as Epstein-Barr virus or mumps, and also with rickettsiae.[237–239] Myocarditis may also manifest as myocardial thickening and fibrosis presenting as diastolic dysfunction or restrictive cardiomyopathy, and asymmetric septal thickening resembling hypertrophic cardiomyopathy.[240–242] Lieberman and coworkers[243] proposed a clinicopathologic description of myocarditis based on the initial manifestations, endomyocardial biopsy, and recovery (fulminant, acute, chronic active, or chronic persistent myocarditis).

Ventricular Arrhythmias

Ventricular arrhythmias are frequently encountered in patients with myocarditis, ranging from innocuous premature ventricular contractions to malignant and incessant ventricular tachycardia, and myocarditis is often incriminated in otherwise unexplained ventricular arrhythmias and sudden death.[10,244–269] Myocarditis has been documented as a cause of ventricular repolarization abnormalities in athletes with or without arrhythmias.[247,248] Ventricular arrhythmias may also be precursors to sudden cardiac death in young athletes with occult myocarditis.[249] In autopsy series, myocarditis accounts for 10% to 25% of sudden deaths in young, healthy people.[250,252,266,267] In a population-based retrospective study from Turin, Italy, an incidence of only 0.53% was reported among 17,162 autopsies performed over three decades,[253] but the application of standardized systematic histologic examination and criteria tends to give a higher incidence, in the range of 5%, among autopsies performed at a general hospital.[254] Wesslen and associates[255] reported signs of active, healing, or healed myocarditis in 12 of 16 cases of sudden death in young Swedes. Among high-performance athletes, sudden death due to undiagnosed myocarditis often stirs media attention.[256] Myocarditis has also been anecdotally implicated in sudden infant death syndrome.[257] Ventricular arrhythmias are frequently the initial and most prominent presentation of giant cell myocarditis.[107–110,251,270]

Ventricular arrhythmias and sudden death are common in all forms of myocardial failure, but specific immune-mediator–induced effects on myocyte electrophysiology could also account for a portion of these arrhythmias. Binah[271] summarized a number of the mechanisms recognized by work in his laboratory and in others. As noted above, perforin elaborated by CTLs is capable of forming membrane channels that pass charged ions, resulting in action potential shortening and diastolic oscillations.[272] In addition, Fas ligand can lengthen the action potential and induce afterpotentials, in part through inhibiting I_{to} and augmenting I_{CaL}.[273]

Physical Examination

The physical findings in acute myocarditis are dependent on the extent of myocardial or pericardial involvement, inciting agent (cardiotropic virus), and other factors. Fever occurs occasionally, and in the Myocarditis Treatment Trial (MTT),[274] it was noted in 18% of patients with myocarditis. Sinus tachycardia may frequently accompany the febrile state but is often out of proportion to the fever and is more likely adrenergically mediated, owing to the hemodynamic alterations of the failing heart. Significant ventricular dysfunction may also be associated with hypotension, gallops, murmurs of regurgitation, rales, jugular venous distention, hepatomegaly, ascites, pleural effusions, and peripheral edema. Pericardial involvement may result in a friction rub. The physical findings are not specific for myocarditis.

Laboratory Findings

Patients with myocarditis frequently have serologic evidence of an inflammatory state with elevation of nonspecific markers of inflammation, such as erythrocyte sedimentation rate, C-reactive protein, and leukocyte counts. A fourfold increase in virus-specific IgG titers in the convalescent period is considered reliable evidence of recent infection and is found in 20% of patients with myocarditis.[275,276] In the MTT, more than half of the patients with biopsy-proven myocarditis had an elevated sedimentation rate.[274] Other markers noted to be elevated in myocarditis include TNF-α, ICAM-1, vascular cell adhesion molecule-1, interleukins, and soluble Fas.[195,196,277,278] Unfortunately, these markers are not specific for myocarditis.

Myocarditis, although associated with myocyte damage and necrosis, results in CK-MB elevation in only 12% of

patients with biopsy-proven myocarditis.[279] More recently, Lauer and colleagues[280] reported on CK-MB elevation in only one of five patients with histologic evidence of myocarditis, but cardiac troponin T (cTnT), which is extremely specific for myocardial damage, was elevated in all five. Additionally, cTnT was elevated in 28 patients, of whom 26 had immunohistologic evidence of myocarditis. Thus, cTnT elevation appears to be highly predictive for myocarditis.[280] In an analysis of stored sera on 88 patients from the MTT,[276] cardiac troponin I (cTnI) was elevated in 34% of patients (18 of 53) with myocarditis, compared with 11% (4 of 35) without myocarditis. In contrast, CK-MB values were elevated in only 5.7% of patients (3 of 53) with myocarditis. Further, the cTnI elevations correlated with less than 1 month's duration of heart failure symptoms.[276]

Antibodies to cardiac antigens can be detected in the serum of patients with myocarditis.[126,281,282] Anti-α-myosin IgG antibodies may have promise as a diagnostic tool, and, along with other antibodies, probably play a functional role.[283,284] The clinical efficacy of IgG immunoadsorption[285,286] in DCM supports this notion (see also Fig. 59.6).

Electrocardiography, Echocardiography Cardiac Scintigraphy, and Cardiovascular Magnetic Resonance

Historically, acute myocarditis was diagnosed with the constellation of clinical symptoms, physical signs, and ECG abnormalities. Although no particular feature on the electrocardiogram is pathognomonic of acute myocarditis, sinus tachycardia, repolarization abnormalities, conduction abnormalities, and arrhythmias are common findings. In a series of 45 patients with biopsy-proven myocarditis, Morgera and associates[287] noted an abnormal QRS duration in 45%; abnormal Q waves in 18%; left bundle branch block (LBBB) and right bundle branch block (RBBB) patterns in 18% and 13%, respectively; ST elevation in 16%; T-wave inversions in 16%; and advanced AV block in 16%. In patients presenting earlier in the course of the disease, with symptoms of less than 1 month's duration, 31% had advanced AV block and 47% had ST elevation with T-wave inversions. The latter finding has been noted to portend a poorer prognosis. Other predictors of poor outcome include LBBB, RBBB, and other conduction abnormalities, which seem to suggest active, severe, and extensive myocarditis.[288] Patients may present with sustained ventricular tachycardia, and continuous ECG monitoring of patients with myocarditis often reveals complex ventricular ectopy and nonsustained ventricular tachycardia.[245,289]

Echocardiography is useful in assessing the extent of left ventricular systolic dysfunction, which may range from mild segmental hypokinesis to severe global hypokinesis or akinesis associated with severe congestive heart failure (CHF).[290] Patients presenting with chest pain or arrhythmias without CHF often have normal echocardiograms. The ventricular dimensions may remain normal or may be only mildly enlarged. There may be an increase in left ventricular sphericity and right ventricular elongation and an increase in wall thickness and left ventricular mass with the interstitial edema and compensatory hypertrophy.[241,291] Restrictive filling patterns in the left ventricle identifying diastolic dysfunction have been reported consistently in biopsy-proven myocarditis.[241] Mural thrombi in diffusely hypokinetic ventricles have been reported frequently.[292] Hyperrefractile myocardium and other qualitative and quantitative analyses of myocardial texture have been described to assess the degree of active myocardial inflammation.[293] Pericardial effusion is a helpful echocardiographic finding, reported in 10% of patients with myocarditis, though hemodynamic compromise with cardiac tamponade is infrequent.[293] Urhausen and associates[294] recently demonstrated that cardiac tissue velocity imaging by ultrasound is more sensitive than magnetic resonance imaging (MRI) in some cases in detecting myocarditis with subtle ventricular functional impairment. Imaging of leukocyte-mediated inflammation through ultrasound fracture of phagocytosed microbubbles shows promise as a means for detecting many forms of myocardial inflammation, although the method remains to be fully evaluated in humans.[295]

Cardiac scintigraphy has been proposed as a convenient, noninvasive test with high sensitivity to diagnose active myocarditis. Gallium-67 imaging, which identifies areas of increased inflammation, has been studied in clinical settings and noted to have sensitivity and specificity of 83% and 86%, respectively, with a negative predictive value of 98% for the diagnosis of myocarditis.[296] Indium-111 antimyosin monoclonal antibodies have been extensively studied to identify areas of myocyte damage in acute myocarditis.[297,298] This technique has extremely high sensitivity and often detects myocarditis that, on endomyocardial biopsy, is not seen by routine histologic assessment but is detected by immunohistochemistry.[299] Dec and coworkers[300] studied 74 patients with DCM with radiolabeled antimyosin antibody and endomyocardial biopsy. Thirty-nine patients had abnormal antimyosin scans, but only 11 of 39 had evidence of myocarditis (predictive value of 33%). However, functional improvement was more likely in antimyosin scan–positive patients irrespective of the biopsy. The left ventricular ejection fraction (LVEF) improved significantly in both concordant-positive (scan and biopsy both positive) and discordant-positive (scan positive, biopsy negative) patients, but it did not markedly improve in the negative scan and negative biopsy subset. The investigators proposed that discordant-positive scans represented patients with myocarditis in whom there may have been a sampling error on biopsy, hence the reason for missing the diagnosis.[300] Anastasiou-Nana's group[301] in Athens reported that a combination of minimal or no left ventricular dilatation and a positive indium-111 antimyosin monoclonal antibody scan is highly specific for myocarditis. Other nuclear techniques, such as technetium-99m (^{99m}Tc)-MIBI single photon emission computed tomography (SPECT) imaging,[302] may also be useful in detecting myocarditis.

Contrast media–enhanced cardiovascular MRI in patients with myocarditis has also been demonstrated to be an excellent tool in visualizing the location, activity, and extent of inflammation.[303] Early in myocarditis (day 2), the enhancement on MRI signals is accentuated and focal, whereas later (day 84), this seems to be attenuated and more diffuse.[304] Furthermore, the severity of change correlates with prognosis.[305] Myocardial phosphorus-31 magnetic resonance spectroscopy has been utilized in assessing abnormalities in

cardiac high-energy phosphate metabolism in patients with DCM and allograft rejection, but its role in the diagnosis of active myocarditis remains to be elucidated.[306]

Endomyocardial Biopsy and Cardiac Catheterization

The antemortem diagnosis of myocarditis was made feasible by the development of the endomyocardial biopsy technique. Myocardial samples could be obtained via a transvascular approach with minimal discomfort to the patient and a low complication rate. Whereas other approaches for acquiring myocardial tissue included percutaneous biopsy and mediastinotomy,[307,308] these were fraught with complications, precluding their acceptance into clinical practice. The safe and successful transvascular endomyocardial biopsy first described by Sakakibara and Konno[309] was readily accepted for surveillance of cardiac allograft rejection in transplant recipients. The use of endomyocardial biopsy for the diagnosis and management of myocarditis was first reported in 1980.[310] Subsequently, many reports[170,225,243,258–264,269,311–329] documented myocarditis in patients presenting with unexplained heart failure or ventricular arrhythmias (Table 59.4). However, there was considerable incongruity in the diagnostic criteria used in these largely anecdotal reports. The Dallas criteria were developed in preparation for a large, randomized, multicenter clinical trial of immunosuppressive therapy in myocarditis.[330] These criteria define *active* myocarditis (see also Fig. 59.7A) as "an inflammatory infiltrate of the myocardium with necrosis and/or degeneration of adjacent myocytes not typical of ischemic damage associated with coronary artery disease." Furthermore, other causes of inflammation (e.g., connective tissue disorders, infection, drugs) should be excluded.[5,330] The Dallas criteria also defined *borderline* myocarditis as an inflammatory infiltrate that is sparse and lacks myocyte injury, and often (67%) on repeat biopsy, borderline myocarditis will histologically progress to active myocarditis.[331]

A limitation of endomyocardial biopsy is possible sampling error. The inflammation in myocarditis may be patchy or focal, unlike allograft rejection, which is a relatively diffuse process. Although obtaining four samples from the right ventricular septum provides a high sensitivity for detection of allograft rejection in transplant recipients,[332] this may not hold true for myocarditis. In an autopsy study of the right ventricular biopsy technique (10 samples taken from the apical septum), only six of 11 patients dying of myocarditis were correctly identified. Left ventricular biopsy missed the diagnosis in eight of 11.[333] In another study using the standard four to six samples, the sensitivity of right ventricular endomyocardial biopsy was reported at 50%.[334] Dec and colleagues[331] reported that employing repeat left and right ventricular biopsies in patients with suspected myocarditis with an initial negative biopsy increases the yield by 15%. Because an ideal study to evaluate sampling error has not been done, the true yield is unknown, but clearly a negative biopsy does not exclude active myocarditis. In the MTT, only 9% of patients screened had histologic evidence of myocarditis. The European Study of Epidemiology and Treatment of Cardiac Inflammatory Disease (ESETCID)[7] demonstrated a 20% incidence of biopsy-proven myocarditis by expanding the Dallas criteria with the use of newer techniques of PCR and in situ hybridization. As discussed earlier,[6–11] there is a need for validation of new histologic and nonhistologic criteria for diagnosis of this disease to improve upon the Dallas histologic criteria.

TABLE 59.4. Myocarditis by biopsy

Investigators	*Year*	*Biopsies (n)*	*Myocarditis n (%)*
In unexplained heart failure			
Mason et al.[310]	1980	400	7 (2)
Baandrup and Olsen[329]	1981	201	8 (4)
Fenoglio et al.[312]	1983	135	34 (25)
Rose et al.[313]	1984	76	0 (0)
Daly et al.[314]	1984	69	12 (17)
Parillo et al.[315]	1984	74	19 (26)
Regitz et al.[316]	1985	150	41 (27)
Cassling et al.[317]	1985	80	6 (7)
Salvi et al.[318]	1985	74	13 (18)
Dec et al.[319]	1985	27	18 (67)
Mortensen et al.[320]	1985	65	12 (18)
Hammond et al.[170]	1987	79	14 (18)
Meany et al.[321]	1987	123	40 (32)
Chow et al.[322]	1988	90	4 (4)
Maisch et al.[323]	1988	123	10 (8)
Hobbs et al.[324]	1989	148	31 (21)
Popma et al.[325]	1989	61	8 (13)
Vasiljevic et al.[326]	1990	85	10 (12)
Lieberman et al.[243]	1991	348	60 (17)
Herskowitz et al.[225]	1993	534	38 (26)
Kuhl et al.[327]	1996	170	9 (5)
Arbustini et al.[328]	1997	601	26 (4)
Frustaci el al.[10]	2003	478	80 (16)
*In unexplained ventricular arrhythmias and sudden death**			
Strain et al.[258]	1983	18	3 (17)
Sugrue et al.[259]	1984	12	1 (8)
Take et al.[269]	1985	241*	21 (9)
Phillips et al.[250]	1986	19	8 (42)
Hosenpud et al.[260]	1986	12	4 (33)
Yoshizato et al.[261]	1990	8	2 (25)
Sekiguchi et al.[262]	1992	43	9 (21)
Wiles et al.[263]	1992	33	3 (9)
Thongtang et al.[264]	1993	53	18 (36)
Frustaci et al.[265]	1994	17	7 (41)
Frustaci et al.[10]	2003	136	28 (21)
Doolan et al.[266]	2004	193*	23 (12)
Eckart et al.[267]	2004	126*	13 (10)

* Autopsy studies included.

Coronary arteriography is usually normal, although in animal models, coronary vasculitis has been reported. The one major exception is Kawasaki disease, in which coronary artery aneurysms are frequently seen in association with myocarditis.[335] Ventriculograms may demonstrate global or regional ventricular dysfunction, associated valvular regurgitation, and mural thrombi.[336] Localized ventricular aneurysms with normal global systolic function have also been reported.[337]

The hemodynamic profiles of patients with acute myocarditis are representative of the extent of myocardial and pericardial involvement. In patients with significant ventricular dysfunction, elevated filling pressures with depressed cardiac output and stroke work indices are seen. A restrictive hemodynamic profile can be seen and must be differentiated from that seen with postviral constrictive pericarditis.

Natural History of Myocarditis

The true natural history of myocarditis is largely unknown because the great majority of cases is perhaps subclinical and resolves without any significant residual cardiac dysfunction. Clinically apparent myocardial dysfunction as seen with acute coxsackievirus B infections also resolves without any adverse sequelae in most cases. It has been estimated that only 12% of patients with clinically suspected acute myocarditis will proceed to develop DCM,[338] but the true incidence is unknown. The murine myocarditis models frequently develop a pathologic process indistinguishable from that of the human form of idiopathic DCM.

The direct link among viral infection, myocarditis, and DCM has not been conclusively proven. Isolation of infectious virus from the heart has been achieved in only a few cases of acute fulminant myocarditis in neonates and infants.[21,339] Given the hypothesis that DCM may develop after viral infection has been eradicated, the presence of virus in the myocardium is neither sufficient nor necessary to link virally mediated myocarditis with DCM. The indirect evidence of viral etiology of DCM relies on (1) progression of viral myocarditis to DCM in experimental animal models, (2) apparent progression of myocarditis in some patients to DCM, (3) increased enteroviral antibody titers in patients with DCM, (4) presence of viral genomic material in the myocardial tissue of patients with DCM, and (5) improvement of ventricular function in subjects with DCM receiving immunomodulatory treatments. The major limitations are as follows: the relevance of disease in mice to humans is suspect, most cases of DCM are not preceded by documented myocarditis, and epidemiologic serologic evidence is incomplete. Whereas coxsackievirus B IgM antibodies are detected with greater frequency in patients with DCM than in normal controls, the frequency is similar to matched community controls and household contacts.[287,340] Enteroviral genomic sequences are detected in the myocardium of 8% to 70% of patients with active myocarditis and in 0% to 45% of patients with DCM, but in data derived from most published studies, the average detection frequencies are 25% for active myocarditis, 15% for DCM, and not significantly different from 15% among healthy controls.[288,341] In a meta-analysis of the association of enteroviruses with human heart disease, Baboonian and Treasure[342] concluded that although the causative role of enteroviruses in acute myocarditis, particularly in children, was supported by an overall odds ratio of 4.4 [confidence interval (CI), 2.4 to 8.2], and the association of DCM was suggested by an overall odds ratio of 3.8 (CI, 2.1 to 4.6), six of 17 studies did not demonstrate an increased presence of viral remnants. The same investigators demonstrated more recently that PCR positivity is not found in minimally affected first-degree relatives of patients with familial DCM,[343] suggesting that in this group, genetic predisposition to viral myocarditis does not underlie the inherited predisposition to development of DCM. In recent studies, other investigators have found strong evidence for a viral link,[344] while others have found no viral vestiges in the myocardium of patients with end-stage heart failure.[345,346] Regional variation in the etiology of DCM may be responsible in part for the reported differences in PCR positivity.

Responsiveness of patients with DCM to immunomodulatory interventions provides an interesting line of evidence supporting a viral/immune etiology of DCM. One would expect immune suppression to be an effective treatment in DCM if postviral and other forms of autoimmunity play a causative role in the disease. Efficacy of such interventions has been reported in carefully selected patients.[285,286,347–349]

Although the link between myocarditis and DCM is unclear, certain prognostic factors are identifiable. The presence of an abnormal QRS complex on ECG correlates with more severe left ventricular damage and is an independent predictor of survival. Left atrial enlargement, atrial fibrillation, and LBBB are also associated with increased mortality.[287] Higher baseline LVEF is positively associated with survival, whereas intensity of conventional therapy at baseline is negatively associated with survival.[274] The presence of right ventricular dysfunction, as evidenced by abnormal right ventricular systolic shortening on echocardiography, was shown to be the most important predictor of death or need for cardiac transplantation in a group of 23 patients with biopsy-proven myocarditis who were followed long-term.[291] In addition, a net increase in LVEF (between initial and final ejection fraction) was associated with improved survival, whereas baseline ejection fraction was not predictive of outcome. The presence and degree of left ventricular regional wall motion abnormalities did not affect the clinical course.[291]

Light microscopic findings on biopsy have not been found to predict outcome in myocarditis. However, the extent of myocardial inflammation was a predictor of outcome after surgical ventricular remodeling for heart failure.[350] Higher baseline serum antibodies to cardiac IgG by indirect immunofluorescence was associated with a better LVEF and a smaller left ventricular end-diastolic dimension.[274]

Treatment

General Supportive Measures

General supportive measures for patients with myocarditis include a low-sodium diet, discontinuation of ethanol, and fluid restriction, especially in the presence of heart failure. Patients with myopericarditis may need analgesics for pain control. Recommendations for the limitation of physical activity are based on the murine model of CVB3 myocarditis, in which forced exercise during the acute phase of illness was associated with higher titers of infectious virus, increased inflammatory and necrotic lesions, and mortality.[339,351,352] Ibuprofen, indomethacin, and salicylates administered to mice after inoculation with CVB3 also resulted in increased viral titers, increased histologic severity of myocarditis, and increased mortality.[209] This led to the suggestion that even nonsteroidal antiinflammatory drugs should be avoided in

patients with active acute myocarditis. The American College of Cardiology Task Force on myopericardial diseases recommends a convalescent period of approximately 6 months after the onset of clinical manifestations before a return to competitive sports.[353]

Conventional Therapy

The management of patients with presumed or confirmed myocarditis is primarily directed toward treatment of CHF, arrhythmias, and symptoms from pericardial disease. Diuretics, vasodilators, and digoxin should be administered to patients with mild-to-moderate systolic dysfunction. Inotropic therapy and mechanical support with intraaortic balloon pump or ventricular-assist devices may be required for patients in refractory cardiogenic shock. Cardiac transplantation is reserved for those patients who do not improve despite the measures described previously.

Although there are multiple studies on the use of angiotensin-converting enzyme inhibitors (ACEIs) in heart failure,[354] the utility of ACEIs in myocarditis has been studied only in the murine model. Early treatment with captopril in a CVB3 myocarditis model resulted in less inflammatory infiltrate, myocardial necrosis, and calcification. Heart weight, heart/body weight ratio, and liver congestion diminished. Even with delayed therapy, a reduction in left ventricular mass and liver congestion was evident.[355] The ACEIs exert a potent vasodilator response, improve pump function, prevent ventricular remodeling, and may have antiarrhythmic properties. Hence, all patients with systolic dysfunction, including those with myocarditis, should be placed on maximally tolerated doses of ACEIs.

The use of beta-blockers in patients with mild-to-moderate heart failure due to DCM has been reported to be beneficial,[356] but once again, no trials in humans with myocarditis have been performed. Metoprolol-treated mice in an acute CVB3 murine myocarditis model have increased viral replication, myocyte necrosis, and 30-day mortality rates.[355] Carteolol, a nonselective beta-blocker, has been studied in a chronic myocarditis model and found to have beneficial effects with improved histologic scores, reduced heart weight and volume, and liver congestion.[357] It appears that in the acute setting, beta-blockers should be avoided, and in the chronic heart failure stage, the nonselective beta-blockers may be beneficial.

Antiarrhythmic therapy may be needed for control of ventricular and supraventricular dysrhythmias. Although the data from clinical trials of antiarrhythmic therapy in heart failure have not shown a primary mortality benefit, patients with active myocarditis were excluded in these trials. Since immunosuppression is probably not helpful in myocarditis[274] and no other specific therapy is available, one might consider treating the arrhythmias in the usual fashion, but there appears to be a rationale for making the diagnosis of myocarditis in patients who do not have profound ventricular dysfunction along with their arrhythmia. First, the majority of patients with myocarditis have a spontaneous resolution. Second, current antiarrhythmic therapy of ventricular tachyarrhythmias is exacting, involving electrophysiologic studies and use of potentially toxic drugs or implantable defibrillators. The benefit of making the diagnosis of myocarditis is that the patient may require only short-term protection while the underlying process resolves, which can be provided by using amiodarone or other antiarrhythmic drugs under inpatient monitoring. If myocarditis resolves, antiarrhythmic therapy can be withdrawn. Patients whose arrhythmias fail to improve despite histologic resolution of myocarditis, or who survived cardiac arrest, may be candidates for aggressive electrophysiologic approaches and implantable defibrillators.[244] Temporary and permanent pacemakers may be required in patients presenting with conduction system abnormalities.

Immunosuppressive and Immunomodulatory Therapy

Clinical trials of immunosuppressive therapy were first reported in children with clinical evidence of myocarditis, prior to the introduction of endomyocardial biopsy. In two series, in a total of eight children presenting with acute onset of severe CHF, rapid improvement and survival were noted with adrenocorticotropic hormone or hydrocortisone treatment.[358,359] Mason and associates[310] reported 10 patients with biopsy-proven myocarditis, half of whom improved with azathioprine and prednisone. Gagliardi and coworkers[360] followed 20 children with biopsy-proven myocarditis who were treated with cyclosporine and prednisone. At 1 year, 10 of 20 patients still had histologic evidence of myocarditis. No patient died or required transplantation. However, there was no control group. The data supporting an immunologic basis of myocarditis resulted in multiple treatment trials using immunosuppressants (Table 59.5). The average proportion of patients showing improvement with a variety of immunosuppressants was 54%.[361] A large number of the trials predated the development of the Dallas criteria; thus, the histologic definition of myocarditis was not uniform. Immunosuppressive regimens were arbitrary, and the lack of control groups made interpretation of these trials arduous. It was unclear whether immunosuppression was beneficial in those patients with myocarditis, as they can improve spontaneously. Further, the infectious complications of immunosuppression were frequently seen and occasionally reported.[310,362]

The conflicting results from these nonrandomized observations led to the MTT.[274] In a multicenter, prospective, randomized design, the MTT enrolled patients with heart failure of recent onset (<2 years), left ventricular dysfunction (LVEF

TABLE 59.5. Selected nonrandomized trials of immunosuppressive treatment in myocarditis

Investigators	*Year*	*Patient treated (n)*	*Treatment*	*Improved n (%)*
Mason et al.[310]	1980	8	P + (A, P)	4 (50)
Fenoglio et al.[312]	1983	18	P, (A, P)	7 (39)
Daly et al.[314]	1984	1	P	0
Dec et al.[319]	1985	9	A + P	4 (44)
Mortenson et al.[320]	1985	12	A + P, CyA	8 (67)
Hobbs et al.[324]	1989	34	A + P, P, CyA	25 (74)

A, azathioprine; P, prednisone; CyA, cyclosporine.

<45%), and biopsy-proven myocarditis (per the Dallas criteria). The study screened 2333 patients; 214 (9%) had endomyocardial biopsy evidence of myocarditis, and 111 patients had a qualifying LVEF of less than 45% and agreed to enrollment. Patients were randomized to three treatment arms: prednisone and cyclosporine, prednisone and azathioprine, and no immunosuppressant treatment. All patients received conventional therapy for heart failure. The prednisone and azathioprine group was subsequently eliminated owing to low patient recruitment in the trial. Patients were treated for 24 weeks, and the primary end point was comparison of the mean increase in LVEF at 28 weeks. Secondary analysis of other markers of left ventricular function, survival, and several immune parameters was performed.

At both 28 and 52 weeks, no difference in LVEF was observed in immunosuppressive-treated patients compared with untreated patients. At 1 and 5 years, there was no difference in survival or need for cardiac transplantation between groups (Fig. 59.5). On multivariate analysis, better baseline LVEF, less intensive conventional therapy, and shorter illness duration were independent predictors of improvement in LVEF during follow-up. Analysis of immunologic variables (cardiac IgG, circulating IgG, natural killer and macrophage activity, helper T-cell level) suggested an association between better outcome and a more robust immune response. A higher level of cardiac IgG was associated with a higher LVEF and a smaller left ventricular size. The mortality rate for the entire trial was 20% at 1 year and 56% at 4.3 years. The results of the MTT were important for diagnostic management because the authors recommended that in patients with unexplained CHF, the performance of endomyocardial biopsy for the sole purpose of instituting immunosuppressive therapy was not warranted.

Nonetheless, certain subgroups may benefit from immunosuppressant therapy, including those with GCM, hypersensitivity myocarditis, or cardiac sarcoidosis. Using a multicenter database, Cooper and colleagues[108] reviewed 63 patients with GCM. The rate of death or cardiac transplantation was 89%. Median survival was 5.5 months from symptom onset to death or transplantation. The median survival in patients treated with corticosteroids was 3.8 months versus 3.0 months in untreated patients. However, patients treated with corticosteroids and azathioprine had an average survival of 11.5 months. Cyclosporine in combination with corticosteroids, corticosteroids and azathioprine, and corticosteroids, azathioprine, and orthoclone OKT3 survived an average of 12.6 months. The uncontrolled nature of this report decreases the reliability of its conclusions.

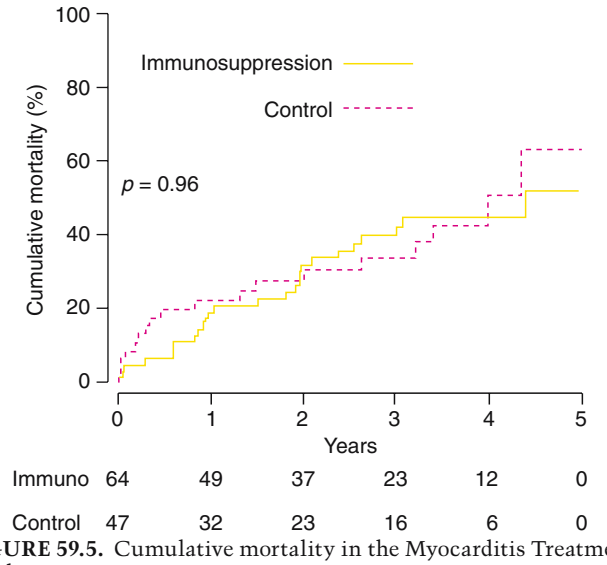

FIGURE 59.5. Cumulative mortality in the Myocarditis Treatment Trial.

Patients with myocarditis associated with a known immune-mediated disease, such as systemic lupus erythematosus, may benefit from immunosuppressive therapy. Other potential indications for a trial of immunosuppressant therapy include failure of myocarditis to resolve, progressive left ventricular dysfunction despite conventional therapy, continued active myocarditis on biopsy, or fulminant myocarditis that does not improve within 24 to 72 hours of full hemodynamic support, including mechanical assistance, and persistent ventricular tachycardia or fibrillation.

Smaller studies have used differing immunosuppressant regimens. Kühl and Schultheiss[363] treated 31 patients with biopsies classified as immunohistologically positive (more then two cells per high-power field and expression of adhesion molecules), negative Dallas criteria, and left ventricular dysfunction. Patients were treated with conventional therapy for 3 months, followed by gradual tapering of methylprednisolone doses over 24 weeks (following biopsy and LVEF response). Therapy was associated with an improvement in ejection fraction in 64% and improved New York Heart Association (NYHA) functional class in 77%. Four patients (12%) had no change in ejection fraction despite improvement in inflammatory infiltrates. However, study conclusions are limited by the absence of a control group.

Drucker and coworkers[364] retrospectively reviewed 46 children with congestive cardiomyopathy and Dallas criteria of borderline or definite myocarditis. Twenty-one patients were treated with intravenous IgG (2 g/kg over 24 hours) and were compared to 25 historical controls. Overall survival was not improved, although there was a trend toward improvement in 1-year survival rates in the treated group. In the intravenous IgG group, the left ventricular function was improved and persisted after adjustment for age, biopsy status, and use of ACEIs and inotropes.

In a comparative study of IFN-α, thymomodulin, and conventional therapy in patients with biopsy-proven myocarditis or idiopathic DCM, an improvement in the active treatment groups was reported for ejection fraction (at rest and during exercise), maximal exercise time, functional class, and ECG abnormalities.[365] In 10 patients with CHF, NYHA class III or IV, with symptoms of less than 6 months' duration, intravenous IgG resulted in an improvement in LVEF and a functional improvement to NYHA class I or II at 1 year of follow-up, in all nine patients who survived, regardless of biopsy results.[366]

Perhaps strategies with alternative immunosuppressive regimens and different diagnostic criteria will be more successful in demonstrating the utility of immunosuppressants. The ESETCID[7,367] is a prospective multicenter, placebo-controlled, double-blind study intended to address the natural course of myocarditis, myopericarditis, pericarditis, and

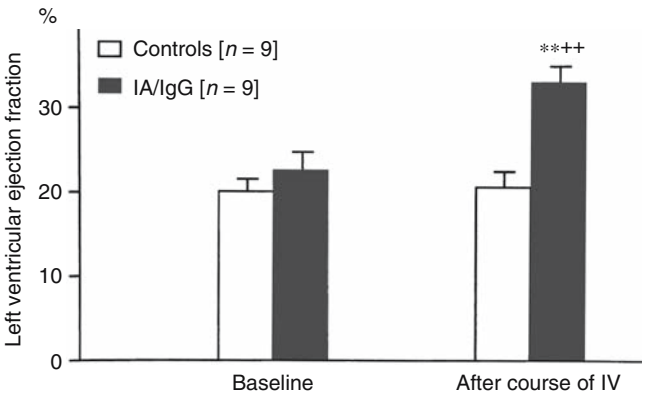

FIGURE 59.6. Efficacy of immunomodulation: significantly improved left ventricle (LV) function after immunoglobulin G (IgG) adsorption (**++ $p < 0.01$ vs. both baseline and control).

postmyocarditic muscle disease; the underlying processes that influence the progression to chronic disease states or DCM; and the benefit of immunosuppressant therapy based on etiology (autoimmune-, enterovirus-, or CMV-induced). The treatment regimens include conventional therapy with diuretics, ACEIs, digoxin, and antiarrhythmics or defibrillators; specific therapy for CMV and enteroviral myocarditis; and prednisolone and azathioprine for myocarditis without detectable virus. The duration of blinded therapy is 6 months, with follow-up for 24 months.

The possible utility of more flexible diagnostic criteria for identification of responders to immunosuppressive therapy was recently suggested in a retrospective analysis by Frustaci and colleagues.[10] They found that the patients who had improved with immunosuppression had detectible circulating cardiac-specific autoantibodies but no detectible viral genomic material in their myocardium, while nonresponders had the opposite findings. These observations could be explained by successful suppression of an autoimmune response without the liability of suppressing ongoing antiviral immune activity.

Immunomodulatory therapies should be considered in cases of myocarditis that display ongoing adverse immune and autoimmune activity. Immunosuppressive drug therapy, intravenous IgG, TNF-α, and immunoadsorption are the forms of immunomodulation discussed above that have been used in humans (Fig. 59.6). Immunoadsorption has been applied primarily in dilated cardiomyopathy, but may hold promise in myocarditis,[349] perhaps especially in phase 2 (Fig. 59.2A) of lymphocytic myocarditis. Manipulation of cytokines, chemokines, and other factors that regulate proinflammatory and antiinflammatory processes[191,196,201,368–371] should receive attention in the development and assessment of new immunomodulatory therapies.

Device Therapy

Myocarditis has emerged as a special indication for device therapy in recent years. Circulatory-assist devices are especially attractive in myocarditis because the disease is usually self-limited. As a result, a relatively short period of circulatory assistance may allow time for the myocardium to recover and the injurious infectious, immune, and autoimmune processes to dissipate. This concept has been successfully tested in patients with severe heart failure due to myocarditis.[372–374]

Implanted cardioverter-defibrillator devices have been used to treat ventricular tachyarrhythmias commonly associated with myocarditis.[265] While such therapy may be lifesaving, consideration should always be given to antiarrhythmic drug therapy with protracted monitoring so as to avoid device implantation if possible.[244] Those patients with myocarditis who have survived cardiac arrest are candidates for implantable defibrillator devices.

Cardiac Transplantation

In a small series ($n = 12$) composed predominantly of female patients (75%), the outcome of patients with active lymphocytic myocarditis confirmed by histologic examination of the explained heart was significantly worse than in controls undergoing transplantation for other diagnoses.[375] This concern has not been validated in the analysis of outcome of 14,055 cardiac transplant recipients in the registry of the International Society for Heart and Lung Transplantation. One-year actuarial survival in all groups transplanted (idiopathic DCM, myocarditis, peripartum cardiomyopathy, versus other diagnoses) was 80%.[376] Nonetheless, myocarditis may recur in the transplanted heart.[377]

Prevention

Prevention of myocarditis is an important developing strategy given the likelihood that a substantial proportion of cases of DCM worldwide are the result of preceding or ongoing myocarditis. Several strategies have been considered, including immunization against the most common cardiotropic viruses,[112,202,378–381] functional disablement of the Coxsackie-adenovirus sarcolemmal receptor,[382,383] and early induction of immune tolerance.[384] While immunization seems to have the greatest potential, scientific, medical, geographic, and political impediments are formidable.

Other Variants of Infectious Myocarditis

Human Immunodeficiency Virus and Myocarditis

The advances in treatment strategies for HIV-infected patients have successfully resulted in prolonged survival times, and noninfectious complications of AIDS, such as dementia and heart disease, have become increasingly prevalent. Early in the history of the AIDS epidemic, reports emerged of a rapidly fatal DCM affecting HIV-infected patients.[385,386] Since the early reports, several clinical and echocardiographic series[56,387–391] have suggested that a subgroup of HIV-infected patients are predisposed to the development of progressive heart disease. In a prospective echocardiographic survey of 296 HIV-infected adults over a period of 4 years, 44 patients were found to have significant cardiac dysfunction. Dilated cardiomyopathy occurred in 13 of 44 and was strongly associated with a CD4 count of less than 100/mm^3 and poorer survival.[391] It has been estimated

that clinically significant cardiac disease occurs in 6% to 7% of HIV-seropositive individuals.[392]

An interesting hypothesis to explain the high frequency of dilated heart muscle disease is the presence of myocarditis in HIV-infected patients with left ventricular dysfunction. Reilly and colleagues[393] reported in an autopsy series of 58 consecutive AIDS patients a significantly higher incidence of myocarditis in those with clinically apparent cardiac disease or DCM. There have been other reports of higher prevalence of myocarditis in an endomyocardial biopsy series of HIV-seropositive patients compared with those without risk factors for HIV who were biopsied for suspected myocarditis.[394]

Human immunodeficiency virus–related myocarditis has unique and atypical immunopathogenic features. It is characterized by increased CD8 T lymphocytes and sole induction of MHC class I, perhaps as a part of the systemic depletion of CD4 T cells. The myocarditis may not be readily apparent on histology owing to the accompanying lymphopenia, and special immunohistology and histochemistry techniques may need to be employed.[395] Although in situ hybridization techniques have demonstrated HIV-1 transcripts in cardiac myocytes, interstitial dendritic cells, and endothelial cells, the pathologic significance of this finding is still unclear because patients with evident transcripts may or may not have clinical disease. Also, it is not evident that myocyte injury is a result of direct cytotoxicity of the virus, transcripts, cytokines, or other cardiotropic viruses.[396] A large number of HIV-seropositive patients with left ventricular dysfunction also manifest evidence of nonpermissive or latent infection of myocytes with CMV immediate-early (CMV IE-2) genes. Although evidence for classic intranuclear inclusions of active lytic CMV infection is rarely found, there is increasing speculation that the latent viral infection may be responsible for enhanced MHC expression and provide a stimulus for ongoing immune injury, as seen with most models of myocarditis.[397]

A role for direct cytokine-mediated cardiac injury has also been proposed in HIV-infected populations with myocardial dysfunction. Both TNF-α and IL-6, known to be elevated in HIV infection, directly inhibit cardiac contractility in vitro,[368] and the former has been implicated in causing myocardial dysfunction. Increased catecholamines may be responsible for microvascular spasm and chronic ischemic dysfunction.

The clinical management of patients with HIV-related myocarditis and cardiomyopathy is targeted toward improving congestive symptoms, afterload reduction, and digitalis for improved neurohormonal axis. A specific role for antiviral therapies is controversial, since medications like zidovudine and IFN-α are themselves recognized as cardiotoxins. Zidovudine has been known to result in premature termination of myocyte mitochondrial DNA chain replication.[398]

Smallpox Vaccination

Despite worldwide eradication of smallpox, the bioterrorism threat arising from the existence of stored variola virus has prompted military and civilian smallpox vaccination programs in the United States.[399] Myocarditis emerged as a known, rare complication of smallpox vaccination during the eradication effort in the 1950s and 1960s. Its incidence varied with the vaccinia strain used to produce the vaccine, and with the method used to detect myocarditis. The true incidence is not known. Current vaccination programs use the original New York City Board of Health strain of vaccinia (Dryvax) and new vaccines. While the occurrence of myocarditis in the United States's current military Dryvax vaccination program appears to be higher (0.01%, or about one in 10,000)[400] than historical estimates, its incidence after new vaccines has not been determined. Previously vaccinated individuals have a much lower risk of developing myocarditis. Full functional and symptomatic recovery occurs in most patients. While involvement of eosinophils has been noted,[401] the mechanisms responsible for postvaccination myocarditis are not known.

Nonviral Infectious Myocarditis

Bacterial Myocarditis

Bacterial infection of the myocardium occurs frequently in association with infective endocarditis, usually in the form of myocardial abscesses adjacent to the valve ring (see Chapter 4). Myocardial involvement has also been reported in association with a wide range of bacterial pathogens in the absence of endocarditis.[42,402–408] With most of these agents, myocardial involvement is uncommon and occurs principally in the setting of overwhelming systemic infection.

Streptococcus

Cardiac involvement after streptococcal infection is usually manifested as acute rheumatic fever, which develops 2 to 3 weeks after onset of pharyngitis and has a distinctive histologic appearance (see Chapter 4). Streptococcal pharyngitis may also be associated with a nonrheumatic form of myocarditis that occurs concurrently with the febrile illness.[409–412] The most common clinical manifestations are chest pain and marked ST-segment and T-wave abnormalities on the electrocardiogram, which correlate with segmental wall motion abnormalities observed with echocardiography.[409] Cardiomegaly and CHF are uncommon. Histologic examination reveals lymphocytic infiltrates and myocyte necrosis in the absence of Aschoff bodies, similar to the findings in viral or idiopathic myocarditis.[412] Bacteria are not present in the myocardium, and it is hypothesized that inflammation is caused by streptococcal exotoxins in a manner similar to that in diphtheritic myocarditis.

Diphtheria

Although vaccination has virtually eliminated diphtheria in most Western nations, it remains an important public health problem in many underdeveloped countries,[413] and may be the most common etiology of myocarditis worldwide. Infection with *C. diphtheriae* is usually confined to the respiratory mucosa. Systemic manifestations are due to secretion of a potent exotoxin. The ECG abnormalities suggesting myocardial involvement are present in a high proportion of patients,[414] but clinical evidence of cardiac dysfunction occurs in only 10% to 25% of cases. Nevertheless, cardiac involvement is the most common cause of death in fatal infections.[415] Disturbances of AV conduction, including

bundle branch blocks and complete AV block, are observed frequently in affected patients and are associated with a mortality rate of 60% to 90%. Patients may also present with progressive cardiac dilatation and CHF. Histologic study reveals diffuse mononuclear cell infiltrates associated with myocyte necrosis.[416] Corticosteroid therapy does not appear to be effective in the prevention or treatment of diphtheritic myocarditis, although only one prospective trial has been performed.[417] One report suggested that administration of carnitine may decrease the incidence and severity of cardiac involvement.[418]

Spirochetal Myocardial Disease

Lyme Disease

Lyme disease is caused by the spirochetal organism *B. burgdorferi*, which is transmitted to humans by certain species of deer ticks in endemic areas of North America, Europe, and Asia. The acute phase of the illness is characterized by fever, myalgia, lymphadenopathy, and a characteristic rash known as *erythema chronicum migrans*.[419] The organism persists in many tissues, and chronic manifestations include arthritis and a variety of neurologic syndromes. Manifestations of cardiac involvement develop in 4% to 10% of patients at an average of 4.8 weeks (range, 4 days to 7 months) after the acute illness.[41,420,421] Disturbances of AV conduction are the most common manifestations, occurring in 87% of cases, with complete or high-grade block in more than 50%. The AV block is usually supra-Hisian, with a narrow complex escape rhythm.[422] Temporary transvenous pacing is required frequently, but AV block almost always resolves within 7 to 10 days. Endomyocardial biopsy may reveal lymphocytic infiltrates with associated myocyte necrosis,[422] and spirochetes may be identified in biopsy specimens. Lyme carditis occasionally develops in patients without a preceding rash or other symptoms of acute Lyme disease.[423]

Therapy with a 2 to 3 week course of antibiotics (doxycycline, amoxicillin or cefuroxime) is recommended for patients with Lyme carditis.[420,421] Antibiotic therapy has proved effective in the prevention and treatment of chronic arthritic and neurologic syndromes, but its use in cardiac disease has not been tested prospectively. Evidence of diffuse myocardial involvement is common, including evolving ST-segment and T-wave abnormalities on the electrocardiogram, reversible abnormalities of left ventricular wall motion,[420] and diffuse myocardial uptake on gallium scan.[422] One fatal case of pancarditis has been reported, but frank heart failure is uncommon.

A high incidence of positive serologies for *B. burgdorferi* was reported in European patients with chronic DCM, and in two patients the organism was cultured from myocardial biopsies.[424,425] It has been suggested that unrecognized Lyme carditis may be responsible for a small but significant proportion of cases of idiopathic DCM.

Leptospirosis and Relapsing Fever

Evidence of severe myocarditis is present at autopsy in a high proportion of fatal cases of leptospirosis and relapsing fever.[425,426] Nonspecific ECG abnormalities are common in these diseases, but clinical evidence of left ventricular dysfunction is rare.

Fungal Myocarditis

Although previously uncommon, the incidence of fungal infections of the heart has increased markedly since the early 1970s. This increased incidence is due to several factors, including the increasing use of antibiotics, immunosuppressive agents for transplantation, and chemotherapy, as well as the increasing application of cardiac surgery and the increasing prevalence of intravenous drug abuse.[427]

Candida *Infection*

The most common fungal organisms causing cardiac infection are *Candida* species. *Candida* endocarditis occurs most frequently after thoracic surgery and in intravenous drug abusers. Immunocompromised patients, on the other hand, are more likely to develop *Candida* myocarditis without involvement of the valves or endocardium, usually in the setting of disseminated systemic infection.[428–430] Autopsy studies reveal extensive myocardial involvement in 10% to 63% of patients who die of systemic candidiasis.

Histologically, *Candida* myocarditis consists of focal abscesses (usually microscopic, although gross nodules may be present) interspersed with areas of normal myocardium. Clinical manifestations typically include nonspecific ECG abnormalities, disturbances of AV conduction, including complete heart block, and tachyarrhythmias.[428] Cardiomegaly and CHF are rare. Myocardial involvement is usually not recognized antemortem.

Aspergillus *Infection*

Myocardial involvement is present in 22% of patients with disseminated aspergillosis,[431] and myocardial invasion is almost always present in patients with *Aspergillus* endocarditis. As in other tissues, histology is characterized by microscopic and macroscopic abscess formation.[431,432] Extensive vascular invasion by fungal hyphae results in thrombosis and coagulation necrosis. Although *Aspergillus* endocarditis has been treated successfully, myocarditis is uniformly fatal.

Actinomyces *Infection*

Cardiac involvement in actinomycosis occurs in only 2% of cases and usually develops by direct extension from a contiguous focus of pulmonary or mediastinal infection.[433–435] Hematogenous seeding of the myocardium occurs occasionally. Myocardial involvement is characterized by necrotizing abscess formation with masses of mycelial bodies and characteristic sulfur granules. In many cases, cardiac symptoms are absent, but patients may present with chest pain characteristic of pericarditis,[433] pericardial tamponade,[434] or CHF.[435]

Other Mycoses

Myocardial involvement has rarely been reported in immunocompromised patients with disseminated coccidioidomycosis and cryptococcosis.[431–439] Cardiac involvement is usually not clinically apparent antemortem, although death due to progressive CHF has been reported.[439] Cardiac involvement with blastomycosis and histoplasmosis is extremely uncommon and usually results from direct extension from a contiguous intrathoracic focus.

Rickettsial Myocarditis

Rocky Mountain spotted fever caused by infection with *Rickettsia rickettsii* is characterized by a diffuse vasculitis, and in fatal cases, death is usually due to vascular collapse. Vasculitis of the coronary vessels may also be present, and lymphocytic infiltrates with myocyte necrosis are present in approximately 50% of fatal cases.[440,441] Although cardiac dilatation and cardiogenic pulmonary edema occur infrequently,[442] echocardiography demonstrates systolic left ventricular dysfunction in the majority of patients.[443,444] Clinical evidence of myocarditis has been reported in association with scrub typhus due to *Rickettsia tsutsugamushi*, whereas Q fever (*Coxiella burnetii*) usually causes endocarditis in its chronic form.

Protozoal Myocarditis

American Trypanosomiasis (Chagas' Disease)

It is estimated that 10 to 18 million people in South and Central America are infected with *T. cruzi*, and Chagas' cardiomyopathy resulting from this infection is the most common cause of CHF and cardiac death in these endemic areas.[445,446] The parasite is transferred to humans by triatomine insects known as *reduviid bugs*. The clinical course of infection is characterized by an acute phase, an indeterminate or latent phase of variable duration, and a chronic phase.[446,447]

After inoculation, parasites are disseminated throughout the body, with the highest concentrations appearing in striated and cardiac muscle and autonomic ganglia. A lesion may appear at the point of entry, and an acute illness develops, characterized by fever, myalgia, edema of the face and lower extremities, hepatomegaly, and generalized lymphadenopathy. Because of the nonspecific nature of the symptoms, the acute phase of the disease is usually unrecognized.

Rarely, acute inflammatory myocarditis develops during the acute phase, with ECG abnormalities, cardiomegaly, and CHF. Histologic examination in these cases demonstrates inflammatory infiltrates adjacent to myocytes containing large numbers of intracellular parasites. These findings suggest that cardiac manifestations during the acute phase of the illness may be due to direct lysis of myocytes by parasites.[448,449]

The acute illness resolves over a period of weeks to months, and patients enter the indeterminate phase. These patients are asymptomatic, with low-level parasitemia, and antibodies to *T. cruzi* are present. Although the electrocardiogram is normal, echocardiography and left ventricular cineangiography demonstrate focal wall motion abnormalities in a high proportion of cases, most commonly involving the left ventricular apex and posterior wall. Endomyocardial biopsy is frequently normal but may reveal hypertrophy, fibrosis, and inflammatory infiltrates in up to 37% of patients without clinical manifestations.[450]

Manifestations of chronic Chagas' disease develop in 30% to 70% of infected patients after a highly variable period, which may be as long as 50 years.[445,449] Involvement of autonomic ganglia may cause megacolon or megaesophagus, but the heart is the organ most commonly affected. Histology is characterized by focal areas of inflammation or fibrosis interspersed with areas of normal myocardium. Endomyocardial biopsy reveals myocarditis in approximately 60% of patients.[451,452] This process frequently involves the specialized conducting tissue, and therefore disturbances of AV conduction, especially RBBB with or without associated left anterior fascicular block, are present in up to 60% of patients. Complete heart block may require permanent transvenous pacing. Ventricular arrhythmias are also frequent, and the initial manifestation of the disease may be sudden death due to ventricular tachyarrhythmia or complete heart block. Decreased ventricular function is present in almost all patients with chronic Chagas' disease, and in its most advanced form, Chagas' disease presents as a congestive cardiomyopathy with four-chamber dilatation. A characteristic apical aneurysm is usually present.[453–455] Left ventricular thrombus is frequently observed, and systemic embolization is common.[456,457] This advanced form of the disease is usually fatal within a few years.

Diagnosis of chronic Chagas' cardiomyopathy is dependent on detection of circulating antibodies to *T. cruzi* by one of several serologic methods. Parasites are usually not detected in the myocardium, but low-level parasitemia can be demonstrated by hemoculture or xenodiagnosis, using uninfected reduviid bugs allowed to ingest the patient's blood.[446]

The pathogenic mechanisms leading to myocardial injury, in some patients occurring many years after the initial infection, are poorly understood. The presence of inflammatory infiltrates in the absence of detectable parasites suggests the possibility of autoimmune injury, as postulated for viral and idiopathic myocarditis. Support for this hypothesis includes the demonstration of antibodies to *T. cruzi* as well as antiidiotypic antibodies that cross-react with myocyte antigens.[458,459] Histologic studies demonstrate loss of autonomic ganglia, and physiologic studies are suggestive of marked autonomic dysfunction.[460–462]

Withdrawal of parasympathetic tone may lead to excess sympathetic stimulation, which can cause cardiomyopathy. Histologic studies also demonstrate abnormalities of the microvascular bed,[447,463] and in vitro experiments demonstrate altered endothelial cell function and increased platelet-endothelial cell adhesion.[447,464] All three reports suggest that progressive focal myocardial disease is the result of ischemia due to obstruction of the microvascular bed.

Treatment of chronic Chagas' cardiomyopathy is supportive, with the use of standard therapy for CHF. Dynamic cardiomyoplasty has resulted in symptomatic improvement in some patients. The role for left ventricular reduction or the commonly known Batista procedure is controversial. Antiarrhythmic therapy may be indicated for sustained ventricular tachyarrhythmias, and a permanent pacemaker should be implanted in patients with high-degree AV block.

Two antiparasitic drugs are available for the treatment of American trypanosomiasis. Both nifurtimox and benznidazole decrease the level and duration of parasitemia and decrease mortality in patients with acute Chagas' disease.[446] Low-level parasitemia persists in most treated patients, however, and it is unclear whether therapy in the acute phase decreases the incidence of subsequent progression to chronic Chagas' disease. Whereas earlier studies with these drugs have not been shown to decrease progression from latent phase to chronic disease or to decrease symptoms or improve

cardiac function in patients with chronic disease,[446,447] the recent studies with itraconazole and allopurinol have shown partial success with parasitologic cure and normalization of ECG changes in nearly half the patients.[465] In a randomized, placebo-controlled trial of benznidazole, there was successful negative seroconversion of 55% of patients with early chronic disease as manifested by seropositivity for *T. cruzi*–specific antibodies after treatment for 60 days.[466] Immunosuppressive therapy in patients with malignancies or after organ transplantation has been associated with reactivation causing acute Chagas' disease.[467,468] Reactivation of Chagas' disease in this setting has usually responded promptly to therapy.[469–471]

African Trypanosomiasis

African trypanosomiasis is caused by *Trypanosoma gambiense* or *T. rhodanese* and characteristically presents with progressive somnolence owing to central nervous system involvement. Autopsy studies demonstrate a pancarditis involving the mural and valvular endocardium as well as the myocardium in up to 50% of fatal cases.[472–475] The conduction system and autonomic ganglia may also be involved. Nonspecific abnormalities are often present on the electrocardiogram, but other clinical manifestations of the frequent cardiac involvement are apparently uncommon.

Toxoplasmosis

Patients with acute infection by *T. gondii* are usually asymptomatic, but they may have a transient syndrome of fever and lymphadenopathy. The infection usually persists in a latent phase, with cysts deposited predominantly in the brain and myocardium. Immunosuppression after chemotherapy, in transplant recipients, and in patients with AIDS may be associated with disseminated infection characterized by severe encephalitis and myocarditis.[476–479] Myocarditis after transplantation occurs frequently in seronegative recipients of hearts from seropositive donors.[477–479] Endomyocardial biopsy demonstrates intracellular *Toxoplasma* pseudocysts and a mixed interstitial infiltrate, frequently including eosinophils (Fig. 59.7D). *Toxoplasma* myocarditis can be successfully prevented by a 6-week course of pyrimethamine imitated after early transplantation or treated with pyrimethamine and sulfadiazine.

Metazoal Myocardial Infection

Cardiac involvement in metazoal infections is uncommon. Up to 2% of patients with echinococcosis have cardiac cysts.[480–482] These patients may present with pericardial or atypical chest pain, CHF owing to inflow or outflow obstruction, ventricular arrhythmias, or pulmonary hypertension owing to diffuse pulmonary embolization of scolices. The diagnosis is usually documented by two-dimensional echocardiography, and surgical excision is indicated, when possible, even in asymptomatic patients.

Trichinosis, caused by the parasite *T. spiralis*, is usually a benign syndrome characterized by fever, myositis, and eosinophilia. Mild, asymptomatic myocardial involvement is probably common, as suggested by frequent ECG abnormalities and pericardial effusion noted by echocardiography.[483] Rarely, a severe myocarditis develops, which is the apparent cause of death in most fatal cases.[484–486] Eosinophils are prominent in the interstitial infiltrate. *T. spiralis* does not become encysted in the heart, and larvae are seldom identified in the myocardium. Myocardial injury is thought to be immune mediated, and therapy with corticosteroids is generally recommended, although prospective trials have not been performed owing to the infrequent occurrence of this syndrome.

Kawasaki Disease

The mucocutaneous lymph node syndrome or Kawasaki disease occurs predominantly in children under the age of 10 years and is most prevalent in Japan.[487,488] It has been recognized worldwide, and in the United States and the developed world, it has replaced rheumatic fever as the most common cause of acquired heart disease in children. It is widely believed to have an infectious etiology, but no agent has yet been identified. Its diagnosis is based on recognition of clinical features of the illness, which include remittent high-spiking fever with distinctive conjunctival injection, anterior uveitis, strawberry tongue with erythema, dryness, fissuring and peeling of the lips and mouth, erythematous truncal rash, redness of palms and soles with periungual desquamation, and cervical lymphadenopathy.[489] The principal cardiovascular manifestation of the disease is a multisystem arteritis with frequent involvement of the coronary arteries.[490] Coronary arteritis leads to aneurysm formation and thrombosis. The most common cause of death is myocardial infarction due to aneurysm rupture or coronary occlusion. Myocardium obtained by endomyocardial biopsy or at autopsy reveals histologic evidence of myocarditis in a high proportion of patients.[490–493] Segmental wall motion abnormalities and nonspecific ECG changes are frequently present in the absence of coronary aneurysms.[494,495] These findings have been attributed to myocarditis, but they might also reflect ischemia due to small vessel arteritis. Congestive heart failure in the absence of infarction is uncommon. Intravenous gamma-globulin and high-dose aspirin are effective in the prevention of coronary aneurysms and thrombosis,[496] but their effect on myocarditis is not known.

Noninfectious Myocarditis

Giant Cell Myocarditis

Giant cell myocarditis is a rare but frequently fatal disorder. It is defined histologically by extensive but patchy myocyte necrosis with areas of intense multicellular inflammatory infiltration that includes histiocytes, lymphocytes, and the characteristic multinucleated giant cells (Fig. 59.7B).[105,497–499] There has been a great deal of controversy as to whether GCM and cardiac sarcoidosis are distinct pathologic entities because multinucleated giant cells in GCM seldom organize to form granulomas.[107,500,501] Litovsky and associates[501] showed that GCM is characterized by myocytic destruction mediated by cytotoxic T cells, macrophagic giant cells, and eosinophils. In contrast, cardiac sarcoid is an interstitial granulomatous disease without myocytic necrosis.[270]

Although the etiology of GCM is unknown, it has been associated with a medley of autoimmune disorders and

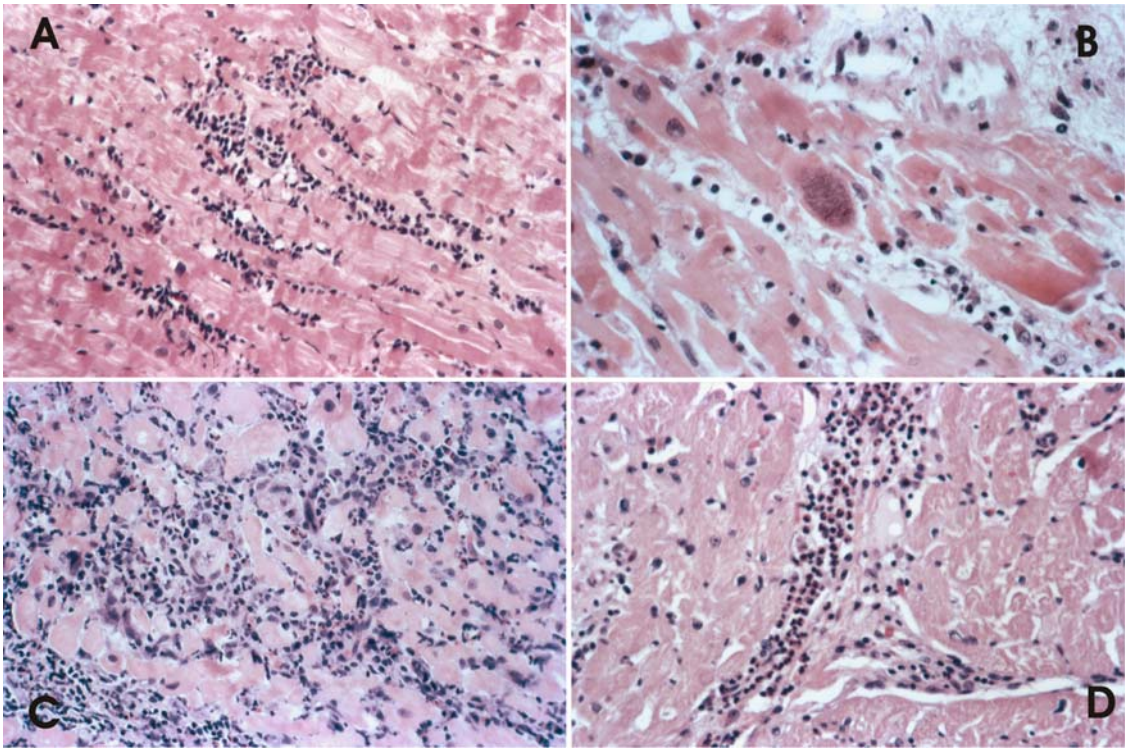

FIGURE 59.7. (A) Lymphocytic myocarditis. (B) Giant cell myocarditis. (C) Eosinophilic myocarditis. (D) Toxoplasma myocarditis. Hematoxylin and eosin.

perhaps is immunologically mediated. Thymomas, systemic lupus, rheumatoid arthritis, Wegener's granulomatosis, ulcerative colitis, chronic hepatitis, myasthenia gravis, myositis, pernicious anemia, Takayasu's arteritis, and lymphomas have been associated with GCM.[502–509] The clinical presentation of GCM may mimic lymphocytic myocarditis, although arrhythmias and heart failure are usually more severe and rapidly progressive.[510,511] Frequently, patients with GCM present with conduction system abnormalities, ventricular tachycardia, or even sudden cardiac death.[107–110,251,270,502,512,513] Giant cell myocarditis has also been reported to present as asymmetric septal hypertrophy.[512]

The natural history of GCM is obscure owing to its rare occurrence, but the isolated reports in the literature suggest that it carries a poor prognosis. Davidoff and coworkers[110] reported that 70% of patients with GCM required cardiac transplantation or died during a 4-year follow-up period compared with the 29% of patients with lymphocytic myocarditis. Cooper and colleagues[108] reported on 63 patients with GCM collected in a worldwide registry. The registry patients had an 89% rate of death or need for transplantation, which was significantly worse than that for the 111 patients with lymphocytic myocarditis seen in the MTT. The median survival with GCM was 5.5 months. The patients treated with immunosuppressive regimens including cyclosporine, azathioprine, and prednisone had an average cardiac survival of 12.3 months compared with 3.0 months for the untreated patients. The rate of recurrent GCM in the transplanted patients was 25% (nine of 36).

The role of immunosuppressive therapy for GCM is unknown, but at least anecdotal and registry reports suggest possible benefit of cyclosporine and prednisone with or without azathioprine. Cardiac transplantation remains the last therapeutic resort for these patients, although there is risk of recurrent disease,[108,514,515] which seems to be associated with abatement of immunosuppressive therapy after transplantation[516] and may represent atypical rejection in the allograft.[517] It usually resolves with intensification of the immunosuppressive regimen.

Eosinophilic Myocarditis

Loffler[518] first described the association of eosinophils with cardiac disease, and reported "endocarditis parietalis fibroplastica" in association with eosinophilia. The endocardial disease with eosinophilia is well recognized and extensively reviewed elsewhere.[519,520] Myocardial involvement is rare and frequently fatal; hence, diagnosis is often made postmortem. Endomyocardial biopsy is essential to the antemortem diagnosis of eosinophilic myocarditis (Fig. 59.7C).[521] Myocarditis is believed to represent a more fulminant and necrotic form of the endocardial disease.[522]

Eosinophils have the ability to secrete highly toxic cationic proteins into areas of inflammation and to produce harmful oxygen radicals and potent lipid mediators, leading to myocyte necrosis as seen in proximity to degranulating cosinophils.[523] Animal experiments have confirmed that exposure of myocytes to eosinophil granule proteins is lethal,

and ventricular function in the intact heart is reduced in hypereosinophilic states.[524] Eosinophilic myocardial infiltrates have been reported in association with profound eosinophilia caused by an allergic diathesis, parasitic infection, drug hypersensitivity, vasculitis, or Churg-Strauss syndrome,[66,525,526] but eosinophilic myocarditis can occur in the absence of profound eosinophilia.[527] Further, eosinophilic myocarditis may present as acute myocardial infarction, sudden death, cardiogenic shock, or nonspecific chest pain and dyspnea.

The natural history of eosinophilic myocarditis is usually swift and ominous with rapid evolution to refractory heart failure or intractable arrhythmias, leading to death. Early biopsy-aided histologic confirmation is fundamental to antemortem diagnosis. Clinical improvement may occur with corticosteroid therapy.[527]

Cardiac Sarcoidosis

Sarcoidosis is a multiorgan, noncaseating granulomatous disorder of unknown etiology. Histologically, it may involve the lung, lymph nodes, skin, liver, spleen, parotid glands, and heart.[528] Right heart failure owing to pulmonary manifestations of pulmonary hypertension and pulmonary fibrosis is the predominant cardiac finding.[529] Asymptomatic cardiac involvement is common, with a quarter of the patients having sarcoid granulomas in the heart at autopsy.[530] Characteristically, the noncaseating granulomas infiltrate the ventricular walls and become fibrotic. They may involve the conduction system, although there is no definite predilection for specialized tissues. There may be transmural involvement with fibrous replacement of portions of the myocardium and aneurysm formation.[531] The fibrous transition of granulomas may result in early diastolic dysfunction, but as the disease progresses and with extensive involvement, systolic impairment occurs. Whereas cardiac involvement in sarcoidosis commonly occurs as part of the systemic affliction, isolated cardiac sarcoidosis in the absence of systemic disease has been described.[532]

The clinical presentation of cardiac sarcoidosis is variable and may depend on the amount of myocardium replaced with granulomas and the amount and location of scar tissue. Rhythm abnormalities and conduction disorders predominate,[533] although asymptomatic patients with mildly restrictive filling patterns may elude medical attention. Patients with CHF may show clinical features of restrictive cardiomyopathy or DCM.[534] Papillary dysfunction with mitral regurgitation and pericardial involvement with effusive-constrictive disease have also been described.[533] Radionuclide myocardial imaging with thallium 201 and gallium 67 is helpful in identifying patients with myocardial involvement.[535] Magnetic resonance imaging has also been proposed as a diagnostic modality.[536,537] Histologic diagnosis with endomyocardial biopsy is corroborative, but a negative biopsy does not rule out the possibility, owing to sampling error.

The combination of bilateral hilar adenopathy and myocardial disease suggests cardiac sarcoidosis in a young person. Corticosteroids are indicated when myocardial involvement, conduction abnormalities, and ventricular arrhythmias are present.[538] Patients with scintigraphic uptake of gallium 67 may be more responsive to corticosteroid therapy.[539] Permanent pacemakers may be needed to treat the conduction abnormalities. Implantable defibrillators may be utilized in the prevention of sudden death.[540] Heart failure is treated in the conventional manner, whereas heart transplantation is reserved for intractable heart failure.[541] Heart-lung transplants are performed infrequently for patients with pulmonary involvement, but there is a significant risk of recurrent disease.[541]

Peripartum Myocarditis/Cardiomyopathy

Virchow and Porak first reported the association of pregnancy with DCM in 1870 in an autopsy series.[542] Peripartum myocarditis/cardiomyopathy occurs in one of every 3,000 to 15,000 pregnancies. The incidence is higher in Africa, and it increases with older age, multiparity, multiple gestations, and prior history of peripartum myocarditis/cardiomyopathy. Peripartum cardiomyopathy is currently believed to be a myocarditis of unknown etiology, perhaps an infectious, autoimmune, or idiopathic process. The viral myocarditis hypothesis stems from the observations that pregnant mice are more susceptible to cardiotropic viruses, with increased viral replication,[543] and with the increased hemodynamic burden of pregnancy, the myocardial lesions worsen.[544] Recently, it has been postulated that after delivery, the rapid degeneration of the uterus results in fragmentation of tropocollagen by enzymatic degradation. This releases actin, myosin, and their metabolites, and antibodies are formed that then cross-react with the myocardium.[542] An association between tocolytic therapy and cardiomyopathy has also been reported.[545]

While the diagnosis of peripartum myocarditis/cardiomyopathy is traditionally made during the last trimester or during the first 5 months postpartum, earlier occurrence has been reported.[546] The presentation is usually of decompensated ventricular systolic failure in the absence of any identifiable cardiac pathology. The LVEF normalizes in approximately 50% of women and is more likely to normalize if the initial LVEF is >30%. Therapy is tailored to the decompensated state with diuretics, digoxin, and vasodilators (ACEIs are contraindicated in pregnancy). Inotropic therapy may be needed for supporting those in cardiogenic shock, along with the use of mechanical circulatory-assist devices. Although there are anecdotal reports of benefit of immunosuppressive therapy,[547] the routine use of these agents cannot be recommended; in fact, the only indication would be biopsy-proven fulminant myocarditis. Cardiac transplantation is an alternative therapeutic option and may be offered to those with intractable heart failure, but it is preferred that transplantation be delayed. The early outcome after transplantation in these patients is often unfavorable, with increased allograft rejection, and the natural history of peripartum myocarditis/cardiomyopathy suggests that more than half of the patients have spontaneous resolution.[548] There are perhaps two different subgroups. One presents with a rapidly progressive, fulminant course with often near-complete resolution of myocardial dysfunction within days and excellent long-term prognosis.[547] The other group has late, insidious onset and presents with progressively worsening heart failure with poor prognosis. It is often difficult to differentiate this from the common variety of DCM.

Summary

Myocarditis is a focal or diffuse inflammation of the myocardium, which has multiple infectious and noninfectious etiologies. Autoimmunity, triggered most often by viral infections, is a prominent pathophysiologic mechanism of myocarditis. Overt and clinically inapparent myocarditis is an important cause of dilated cardiomyopathy. Virus-induced lymphocytic myocarditis progresses through three stages: active viral infection, autoimmunity, and dilated cardiomyopathy. Myocarditis is no longer a diagnosis of exclusion; histology, histochemistry, DNA and RNA detection, tissue and circulating antibody detection, and a variety of imaging techniques can be used together or, in some cases, independently to make the diagnosis and to establish the disease stage. Treatment of myocarditis must be tailored to the phase of disease. Many new therapies based on knowledge of the molecular pathophysiology of myocarditis are under development.

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