CHAPTER

18 Cardiac Sarcoidosis

Leslie T. Cooper, Jr., M.D.

INTRODUCTION

Sarcoidosis is an unusual cause of heart disease that occurs as isolated organ involvement and as part of systemic disease. The first case of cardiac sarcoidosis (CS) was reported in 1929 by Bernstein et al.[1] Publications in the subsequent 40 years consisted of isolated case reports and few notable case series.[2] These reports from the mid 20th century reveal the clinical features and syndromes associated with CS. Although the collection of published cases has defined the range of clinical presentations, they also reveal that the incidence and clinical features of the disease vary with the population studied and the diagnostic criteria used.[3-5] Some aspects of the genetics and immunology have been established, but the cause of sarcoidosis remains unknown.

The diagnosis of CS may be ascertained in multiple ways. Magnetic resonance imaging, gallium scintigraphy, endomyocardial biopsy, and serologic markers have been used in various select populations. Each technique has limitations. The incidence and prevalence of the disease vary within and between referral and community-based populations. For example, the range of reported rates of cardiac involvement for patients with systemic sarcoidosis extends from a low of 5% in North Americans with clinical symptoms to 78% in a Japanese autopsy series. Antemortem diagnosis is difficult owing to the low sensitivity of endomyocardial biopsy and lack of specificity of other noninvasive tests.

The present knowledge of CS is limited in many ways. Neither a sensitive and specific test to establish the diagnosis nor a means to predict disease progression exists. A key unanswered question is whether corticosteroids or other immunomodulatory agents can favorably alter the natural history of early CS. This chapter reviews the current state of our understanding of this unusual disease and suggests future directions for research into mechanisms, diagnosis, and treatment.

EPIDEMIOLOGY

The incidence of sarcoidosis in the United States has been estimated at 5.9 per 100,000 person-years for men and 6.3 per 100,000 person-years for women.[6] In the United States, the lifetime risk of sarcoidosis is estimated at 0.85% in whites and 2.4% in blacks.[7] Thus, the lifetime risk of CS with clinical symptoms developing is low.

Certain ethnic groups appear to have a high prevalence of sarcoidosis, and the presentation may vary with ethnicity. For example, Sweden, Denmark, Japan, and US blacks have particularly high prevalence rates, whereas Portugal, Saudi Arabia, Spain, and India have relatively low rates.[8,9] In a case series from Saudi Arabia, 16 of 21 cases of systemic sarcoidosis occurred in women, but there was no cardiac involvement.[10] In a large series from Baltimore, the rate of extrathoracic sarcoid was higher in African-American than in

white patients (2.15 vs. 1.20 manifestations per patient, respectively).[11] From comparative autopsy data, the rate of cardiac involvement in sarcoid patients is higher in Japanese than in US patients.[12]

The frequency of cardiac involvement differs by sex too. Iwai and colleagues[12] compared autopsy records from Japan with those of 2 US medical centers. They found the rate of cardiac involvement was significantly higher in Japanese women older than age 50 years than in Japanese men. In black American women there was also a high incidence of cardiac involvement after age 40 years. In a series of 43 cases from Johns Hopkins Hospital consisting of 33 black Americans and 10 whites, there was also a female predominance (18 males, 25 females).[13] In contrast, the male-to-female ratio of cardiac involvement in whites autopsied with a diagnosis of sarcoidosis was 1:1.[12] Similarly, in a clinical study of 270 cases (249 whites) of CS from the United Kingdom, there were equal numbers of men and women.[14]

CS usually presents in relatively young adults, but rare cases have been reported in children[15] and in the elderly. In Fleming's[14] series from England, patient age ranged from 18 to 88 years, with a peak between ages 25 and 55 years. The majority of patients at Johns Hopkins Hospital presented between ages 30 and 49 years.[13] In Sekiguchi's[16] series, the majority of female patients presented between ages 40 and 59 years, whereas most males presented between ages 20 and 39 years.

In systemic sarcoidosis, the lungs are the most commonly affected organ, but important extrapulmonary manifestations involve the skin (including erythema nodosum), lymph nodes, eye (uveitis), central and peripheral nervous system, and heart.[17] Autopsy data from the 1970s suggested that clinical myocardial involvement occurs infrequently, in about 5% of patients with sarcoidosis.[3] However, the rate of electrocardiographic abnormalities in Japanese patients with systemic sarcoidosis was higher than in control cases at 22.1%, suggesting that a substantial proportion had asymptomatic cardiac involvement.[4] Furthermore, the observed rate of cardiac involvement is also much higher in autopsy series, confirming that many cases of cardiac involvement are clinically silent.[18]

The clinical picture of the disease probably depends on ethnicity, sex, duration of the illness, and the extent of organ involvement. Frequently, extracardiac involvement is subclinical in patients who present with cardiac symptoms.[19] In the author's experience, only about one-third of patients with clinical myocardial involvement have clinical evidence of extracardiac disease.

ETIOLOGY

Because the etiology of sarcoidosis is unknown, the diagnosis remains one of exclusion. As such, there is no one test to confirm the diagnosis. Indeed, sarcoidosis' clinical hetero-

geneity probably reflects multiple disease etiologies. CS may represent a final common clinical and histopathologic presentation for several pathologic sequences. Acknowledging the limitations of our understanding, it is worthwhile summarizing the major studies in epidemiology and immunogenetics in systemic sarcoidosis. Few data exist for isolated cardiac disease, and these are noted when available.

Boeck used the term "sarkoid" in 1899 to describe cutaneous lesions because he thought the lesions resembled sarcoma (reviewed in reference 17). Associations with malignant neoplasms have been described since, suggesting that sarcoidosis might be a form of or a marker for malignancy. Epithelioid granulomas were observed in the regional lymph nodes of a small percentage of patients with carcinomas or in association with non-Hodgkin lymphoma;[20,21] however, a large well-controlled study of 555 sarcoidosis cases in Denmark failed to demonstrate an excess rate of malignancy in sarcoid patients.[22] Currently, the trend of investigation is away from malignancy associations and toward identification of environmental triggers in genetically susceptible individuals.

Infectious and environmental agents have been considered in the search for a cause. Early investigators thought that sarcoidosis could be a variant of tuberculosis.[23] Other putative infectious agents include *Borrelia burgdorferi, Propionibacterium acnes, Mycoplasma,* and several viruses (Table 18-1). Environmental agents that could induce a granulomatous response include aluminum, zirconium, and talc. An epidemiologic report suggested that

Table 18-1
Examples of Agents Suggested to Be Involved in the Etiology of Sarcoidosis*

Type of agent
Infectious agents
Viruses (herpes, Epstein-Barr, retrovirus, coxsackie B virus, cytomegalovirus)
Borrelia burgdorferi
Propionibacterium acnes
Mycobacterium tuberculosis and other mycobacteria
Mycoplasma
Inorganic agents
Aluminum
Zirconium
Talc
Organic agents
Pine tree pollen
Clay

*This table does not include beryllium, which causes berylliosis and not sarcoidosis.
From Hunninghake et al.[17] By permission of PCA Publishing.

exposure to wood stoves and fireplaces, both rurally linked risk factors, was associated with the development of sarcoidosis.[24] The argument for a transmissible agent is supported by the development of sarcoidosis in a transplant recipient who received tissue from a donor with sarcoidosis.[25]

The argument for an environmental cause or person-to-person transmission is further strengthened by the observation that sarcoidosis cases cluster temporally. Clustering has been observed in the Isle of Man,[26,27] and among firefighters[28] and health care workers.[29] Furthermore, some cases occur in families,[30-32] and there is evidence to suggest a seasonal clustering in the winter and early spring.[33] Taken together these data suggest that an environmental or infectious trigger(s) may play a role in some cases of sarcoidosis.

Arguments for a genetic predisposition come from familial clustering, race as a risk factor, and studies of the major histocompatibility complex genes. The most common genotype frequencies in sarcoidosis are class I human leukocyte antigen (HLA)-A1 and B8 and class II HLA-DR.[34-36] The polymorphism for tumor necrosis factor (TNF)-beta (TNFB*1) is associated with good prognosis in pulmonary sarcoidosis.[37] Genetic studies demonstrated an association of certain alleles for angiotensin-converting enzyme (ACE) genotype, interferon (IFN) regulatory factor 4, and interleukin (IL)-1 alpha in certain groups with systemic sarcoidosis.[38,39] The data for cardiac involvement are limited to a report by Takashige et al.[40] that demonstrated a TNF-alpha (A2) gene polymorphism was more common in Japanese patients with CS than in normal controls (RR 11.51, $P = 0.001$). These associations of allelic polymorphisms with phenotype and prognosis may explain some individual differences in susceptibility to disease.

The cellular pathophysiology of sarcoidosis is an area of active research. Studies of pulmonary sarcoidosis suggest that $CD4^+$ T lymphocytes accumulate at sites of inflammation. These cells release cytokines, including IFN-gamma and IL-2,[41] suggesting a T_H1-type T-cell response. Alveolar macrophages are also active, secreting cytokines and growth factors. A T_H1-type response seems to favor the formation of granulomas in the lung.[42] The pathway that leads to granuloma resolution and fibrosis is not well understood. Knowledge of these cellular mechanisms of disease may guide rational, targeted therapeutic trials; however, at the present time, neither the antigenic stimulus nor the mechanism of persistent inflammation and fibrosis is known.

To better define the causes of sarcoidosis, the National Heart, Lung, and Blood Institute sponsored a case-control study of sarcoidosis (ACCESS).[43] This multicenter, observational study includes a comprehensive investigation of genetic, environmental, infectious, and primary immune factors in sarcoidosis. The study has the power to permit testing of multiple hypotheses; 720 cases will be compared with an equal number of matched controls. Enrollment in this study is ongoing.

DIAGNOSIS

Sarcoidosis may be seen first in the heart and has various common clinical presentations. Because it is a rare cause of common clinical syndromes, the diagnosis is frequently overlooked. The 4 clinical syndromes associated with CS are congestive heart failure from systolic or diastolic left ventricular dysfunction, syncope or presyncope from tachyarrhythmias or bradyarrhythmias, pericarditis with or without constrictive physiology, and secondary right ventricular failure from pulmonary disease. Asymptomatic electrocardiographic changes such as right bundle branch block or ventricular ectopy are probably the most common manifestation, but these are nonspecific and usually should not initiate a search for CS.

In patients who initially present with cardiac symptoms and no history of sarcoidosis, a careful family history may reveal affected members. The physical examination may reveal manifestations of extracardiac sarcoidosis including uveitis, erythema nodosum, or lymphadenopathy. Chest radiograph may reveal bilateral hilar adenopathy (stage I) or more advanced stages of pulmonary sarcoidosis. The electrocardiogram is frequently abnormal, with degrees of heart block or tachyarrhythmias (Table 18-2).

The observed complications in a series of 300 cases of cardiac sarcoid are summarized in Table 18-3. Ventricular arrhythmia occurred in 45%, supraventricular arrhythmia in 28%, complete heart block in 26%, and sudden death in 16%. The overall rate of death was 46% (138 of 300). In the series of 43 cases from Johns Hopkins Hospital, cardiomyopathy was seen in 49%, syncope in 33%, tachyarrhythmia in 28%, and pericardial disease in 7% of cases.[13] Mortality was similar in a series of 36 cases from Japan, in which 47% (17 patients) died. The cause of death was congestive heart failure in 11 (65%), sudden death in 3 (18%), fatal arrhythmia in 2 (12%), and cerebral embolism in 1 (6%). A limitation of these data is that time-dependent analysis of the risk of morbidity and death is not available.

Confirmation of CS is extremely challenging because the sensitivity of endomyocardial biopsy is about 25%. The diagnosis is established by noncaseating granulomas on a tissue sample (see Figure 14-5 *B*; see color plate 25, p. 340). In a study by Uemura and colleagues,[44] only 5 of 26 patients (19%) with clinical sarcoidosis and suspected cardiac involvement had diagnostic endomyocardial biopsies. The frequency of a positive biopsy result was higher in those with dilated cardiomyopathy (DCM) than in those with conduction disturbances and normal left ventricular ejection fraction. In select populations, the diagnostic rate may be somewhat higher.[45] The low sensitivity of endomyocardial biopsy is likely because the focal nature of the infiltrates results in sampling error.[3]

Once a granulomatous infiltrate is confirmed in a patient with suspected CS, other causes of granulomatous lesions must be excluded by appropriate serologic studies and special stains. The major causes of myocardial granuloma are listed in Table 18-4. Fungal

Table 18-2
Electrocardiographic Findings and Their Frequency in Cardiac Sarcoidosis

Finding	A (n = 30)	B (n = 15)	C (n = 59)	Total (n = 104)
SA block	1 (3)	1 (7)	1 (2)	3 (3)
AV block				
I	4 (13)	2 (13)	10 (17)	16 (15)
II	1 (3)	0 (0)	6 (10)	7 (7)
III	17 (57)	6 (40)	27 (46)	50 (48)
		*		
RBBB	8 (27)	9 (60)	30 (51)	47 (45)
		*		
IRBBB	2 (7)	2 (13)	1 (2)	5 (5)
LBBB	1 (3)	9 (0)	3 (5)	4 (4)
LAD	5 (17)	7 (47)	13 (22)	25 (24)
Abnormal Q	4 (13)	2 (13)	4 (7)	10 (10)
PSVT	0 (0)	0 (0)	1 (2)	1 (1)
PVC	5 (17)	6 (40)	16 (27)	27 (26)
		*		
VT	12 (40)	4 (27)	10 (17)	26 (25)
ST–T change	1 (3)	4 (27)	7 (12)	12 (12)
LVH	0 (0)	2 (13)	1 (2)	3 (3)
Low voltage	2 (7)	0 (0)	0 (0)	2 (2)

AV, atrioventricular; IRBBB, incomplete right bundle branch block; LAD, left axis deviation; LBBB, left bundle branch block; LVH, left ventricular hypertrophy; PSVT, paroxysmal supraventricular tachycardia; PVC, premature ventricular contraction; RBBB, right bundle branch block; SA, sinoatrial; VT, ventricular tachycardia.

*$P < 0.05$.

Documented case reports and the author's own cases were analyzed in 3 groups: A, autopsy-proven fatal myocardial sarcoidosis; B, biopsy-proven cases with myocardial sarcoidosis; C, clinically diagnosed sarcoidosis cases with apparent cardiac involvement, although the presence of sarcoid granulomas was not confirmed. Percentages in parentheses.

(From Yazaki Y et al. Report for the Intractable Disease Division, Public Health Bureau, Ministry of Health and Welfare of Japan, 1993.)

From Sekiguchi et al.[56] By permission of Kluwer Academic Press.

myocarditis usually occurs in the immunocompromised host in association with endocarditis. Mycobacteria may be identified on acid-fast stain; tuberculosis is suggested by a positive tuberculin test result. Antineutrophil cytoplasmic autoantibodies usually are found in Wegener granulomatosis. Idiopathic giant cell myocarditis usually has prominent myocyte necrosis and eosinophils in a widespread inflammatory infiltrate, but granulomas are not prominent.

Noninvasive tests and serologic markers may support the diagnosis of CS, but the ideal screening and confirmatory tests do not exist. Serum ACE concentrations were first recognized as a biochemical marker of sarcoidosis in 1975.[46] Epithelial cells in the sarcoid

Table 18-3
Complications in 300 Patients With Cardiac Sarcoid

Complication	Patients, %
Ventricular arrhythmia	45
Supraventricular arrhythmia	28
Complete heart block	26
Heart failure	24
Right bundle branch block	23
Partial heart block	23
Mitral systolic murmur	22
Sudden death	16
Left bundle branch block	15
Simulating myocardial infarction	5
Pericarditis	3
Transplantation of heart	1

From Fleming HA. Cardiac sarcoidosis. Lung Biology in Health and Disease 1994;73:323-334. By permission of Marcel Dekker.

Table 18-4
Differential Diagnosis of Cardiac Sarcoidosis

Wegener granulomatosis
Foreign body reaction
Rheumatic carditis (Aschoff nodules)
Atypical drug reaction
Infectious agents
  Mycobacteria, fungal myocarditis, and visceral larval migrans (*T gondi*)
Idiopathic giant cell myocarditis

granulomas produce ACE, the value of which is then increased in serum. The clinical utility of serum ACE as a diagnostic tool in CS is limited because ACE can be increased in other granulomatous disorders and diabetes. Furthermore, although ACE values may decrease with steroid treatment, this decrease does not always correlate with clinical improvement in pulmonary sarcoidosis.[47] Hypercalcemia can also support the diagnosis.

Magnetic resonance imaging has been used to diagnose cardiac abnormalities in patients with systemic sarcoidosis. In 16 patients with biopsy-proven sarcoidosis, gadolinium-enhanced, cardiac magnetic resonance imaging showed enhanced signal intensity in the left ventricle of 8 patients (50%).[48] These abnormalities improved in all 8 patients after 1 month of prednisone therapy. Cardiac abnormalities on magnetic resonance imaging are

also common in nonspecific myocarditis,[49] which would limit the specificity of this technique in a more general population. It is not known whether improvement on magnetic resonance imaging correlates with improved clinical outcome.

Positron emission tomography was used to document myocardial disease in patients with suspected CS.[50] The rate of positive results was 100% compared with 80% by ^{99m}Tc-sestamibi single photon emission computed tomography and 50% by ^{67}Ga scintigraphy. Only 10 of the 16 patients in this study had cardiac involvement suspected on clinical or histologic grounds. The usefulness of this technique needs to be confirmed in larger studies with defined standard criteria for cardiac involvement.

The presentation of biopsy-proven CS is somewhat different than the presentation of lymphocytic myocarditis (LM) and DCM. The clinical and electrocardiographic presentation of 29 patients with sarcoidosis and granulomas on endomyocardial biopsy were compared to LM and DCM diagnosed by biopsy. Subjects with CS had higher rates of ventricular tachycardia, heart block, and syncope (Tables 18-5 and 18-6). Although this study was limited because of possible selection bias, the findings are consistent with results of most published series. Of note, only 33% of the subjects in this series reported extracardiac involvement.

Because of the difficulty in confirming myocardial sarcoidosis, we recommend the following approach to diagnostic evaluation. Patients from high prevalence groups who develop DCM complicated by ventricular tachycardia or heart block are at risk for CS. If enlarged lymph nodes or cutaneous lesions are present, biopsy should be done, because the risk of skin or lymph node biopsy is usually lower than the risk of endomyocardial biopsy. The presence of CS may be presumed if granulomas are present and other causes such as tuberculosis and histoplasmosis are excluded. Gadolinium-enhanced magnetic resonance imaging may be considered in this setting. If more easily accessible lesions are not available, endomyocardial biopsy should be performed and a minimum of 5 samples obtained.

Table 18-5
Patient Characteristics

Characteristic	CS (n = 29)	DCM (n = 58)	LM (n = 27)
Age at onset, y*	47.7 ± 11.9	48.2 ± 12.5	46.8 ± 17.8
Male, %	55.2	72.4	59.3
White, %	24.1	94.8	100
Black, %	41.4	3.4	0
EF, %*	28.8 ± 14.4	26.2 ± 12.1	35.2 ± 18.1

CS, cardiac sarcoidosis; DCM, dilated cardiomyopathy; EF, ejection fraction; LM, lymphocytic myocarditis.
*Mean ± SD.
Modified from Cooper et al.[60] By permission of Monduzzi Editore Spa.

Table 18-6
Symptoms at Hospital Presentation

	Patients, %		
Symptom	CS	DCM	LM
Left-sided heart failure	41.4	84.5	63.0
Right-sided heart failure	6.9	0	0
Both-sided heart failure	13.8	1.7	3.7
Palpitation	24.1	5.2	11.1
Syncope	31.0	0	11.1

CS, cardiac sarcoidosis; DCM, dilated cardiomyopathy; LM, lymphocytic myocarditis.
Modified from Cooper et al.[60] By permission of Monduzzi Editore Spa.

TREATMENT

Supportive treatment of cardiac disease due to CS is similar to treatment of similar syndromes resulting from other causes. For DCM with class II to III congestive heart failure, ACE inhibitors and nonselective β-adrenergic receptor blockers are the mainstay of therapy. Diuretics should be used as needed to maintain optimal preload. We do not routinely use digoxin because of the risk of heart block and proarrhythmia, although limited data exist for or against its use in this population.

Symptomatic heart block is common and is usually treated with a permanent pacemaker, although isolated case reports suggest that prednisone therapy may occasionally improve conduction disturbance. If a patient with compensated DCM develops heart block, β-adrenergic receptor blocker therapy risks progression to complete heart block. In that setting, the decision to withdraw the β-adrenergic receptor blocker or to place a pacemaker and maximize β blockade depends on the individual circumstances.

Ventricular arrhythmias may be difficult to manage with antiarrhythmic therapy, and many patients with symptomatic, sustained ventricular tachycardia receive an automatic implantable cardiac defibrillator.[51,52] Early case reports suggested efficacy of quinidine,[15] but currently amiodarone or therapy guided by electrophysiologic study is common for cardiomyopathy.

Case reports and small case series suggest heart transplantation is effective for refractory arrhythmias or end-stage cardiomyopathy due to CS.[53] A limitation to transplantation is functional impairment of other organs from sarcoidosis. Sarcoidosis can occur after transplantation in the lung,[54] but this is not considered a contraindication to cardiac transplantation.

An area of debate is the role of corticosteroids in the management of CS. There are no prospective data to answer many key questions, including the timing, intensity, and duration of treatment; how different populations respond to treatment; and the risks of

recurrence after tapering or discontinuing steroid therapy. Small, retrospective case series suggest that corticosteroids may prolong survival in sarcoidosis patients who received a pacemaker.[55] However, treatment efficacy early in the disease is difficult to assess because there is sometimes a substantial rate of spontaneous remissions. Furthermore, late in the disease, extensive fibrosis develops that will not reverse with corticosteroids.

Expert opinion forms the basis of treatment recommendations. Sekiguchi et al.[56] recommended 30 mg/day or 60 mg every other day for initial treatment of CS. The dose may be tapered to 5 to 10 mg/day and continued for life. Prednisone usually was started at a somewhat higher dose of 60 mg/day by the group at Johns Hopkins, with a taper of 5 mg every 2 weeks. A maintenance dose of 10 to 15 mg was usually continued "for months or years."[13] We generally treat according to the Hopkins recommendations, if there are no contraindications.

People who are intolerant of steroids may be considered for methotrexate. Chloroquine and tetracycline benefit patients with cutaneous sarcoidosis,[57] but their role in cardiac disease is unknown. Methotrexate has considerable hepatic toxicity and teratogenic effects. This is relevant because many of the CS patients are women of childbearing age.

PROGNOSIS

Few direct comparisons are available of survival in CS and in other disorders. One series[58] from Japan suggested that survival in CS is worse than in DCM; however, patients in that series had frequent extracardiac lesions (53%) and few granulomas on biopsy. These patients may have presented at a late stage when fibrosis had replaced active granuloma. In contrast, a study by Felker et al.[59] suggested that there was no significant difference in survival between CS and DCM. This study was particularly compelling because all patients were diagnosed by endomyocardial biopsy.

In our experience,[60] survival in biopsy-proven CS was similar to survival in DCM and LM (Fig. 18-1). The probability of death estimated from date of biopsy was 72.5% for CS at 1,207 days and 72.5% for LM at 1,199 days and 73.4% at 1,067 days. The *P* values by log-rank test for survival comparisons were 0.667, CS versus LM; 0.428, CS versus DCM; and 0.503, CS versus combined LM and DCM.

Our study was limited because the population of CS patients was gathered from a multicenter registry, whereas the DCM and LM populations were from a single referral center. Comparison of groups gathered from different referral sources raises the possibility of referral and selection bias. Prognosis may also depend on ethnicity, but no comparative data exist and our series was too small to answer this question. Nonetheless, a strength of our study was that all CS patients had diagnostic granulomas, indicating that the disease was active and suggesting we intervened at an early stage.

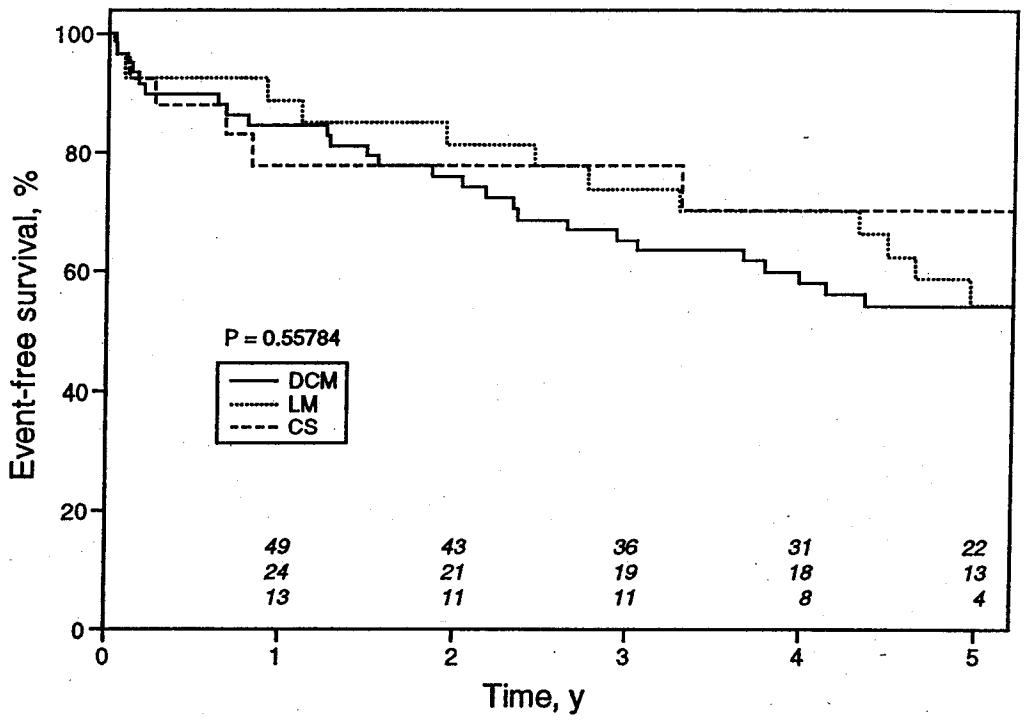

Fig. 18-1. Survival in cardiac sarcoidosis (*CS*), dilated cardiomyopathy (*DCM*), and lymphocytic myocarditis (*LM*) groups by Kaplan-Meier method. *P* value calculated by log-rank test. (From Cooper et al.[60] By permission of Monduzzi Editore Spa.)

FUTURE DIRECTIONS

Progress in our understanding of CS is limited primarily by the rarity of the disease. No single center can accumulate sufficient experience to perform prospective clinical trials. Therefore, expert opinion based on personal experience and the scant published literature forms the basis for present therapeutic guidelines. Fortunately, the multicenter ACCESS study sponsored by the National Institutes of Health should provide essential mechanistic insights and accelerate progress in cardiac and systemic disease.

The triggers of disease activity ought to be better defined. Prevention of disease may someday include avoidance of exposure to key environmental stimuli or vaccine-based prevention in genetically predisposed individuals. Progress in these areas will begin once the influence of ethnicity, sex, and genetic factors on the natural history is better defined by longitudinal surveillance of the ACCESS cohort.

The benefit of immunosuppression in addition to comprehensive supportive care needs to be confirmed in a multicenter, prospective clinical trial. Clearly, for such a trial to be feasible, the method of diagnosis for cardiac disease must be established unequivocally. There are promising but yet unproved noninvasive tests, including magnetic resonance imaging and positron emission tomography, that may emerge as part of composite clinical and test-based diagnostic criteria. To estimate statistical power for a trial, time-dependent analyses of "hard" event rates (death, need for pacemaker or automatic implantable cardiac defibrillator) need to be defined in men and women of several ethnic groups. With the results of the ACCESS project, the feasibility of prospective clinical studies will be known.

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