CHAPTER

20 Chagas Heart Disease

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INTRODUCTION

American trypanosomiasis and its etiologic agent *Trypanosoma cruzi* were first described by Carlos Chagas in 1909.[1,2] Chagas single-handedly characterized this new disease in all of its aspects by first discovering the causative agent and its vector and then seeking out and describing human cases of infection.[3]

Chagas was assigned as a malaria officer in the state of Minas Gerais in Brazil in 1908 (Fig. 20-1), where he observed bloodsucking reduviids infesting the dwellings of the local people. In the gut of the reduviids he discovered a new species of trypanosome, which he named after his colleague and mentor Oswaldo Cruz. Using only the crude methods available to him, he fully elucidated its life cycle and its pathogenicity in wild and domestic animals. Postulating that a human disease might be caused by this trypanosome, he cultured the trypanosome from a specimen from a 9-month-old child with an acute febrile illness and facial swelling and later from adults with cardiac disorders, which he then transmitted back into experimental animals. He described in detail the epidemiologic, microbiologic, and pathologic features of the disease,[4,5] including cardiac involvement. He later reported the clinical features of late cardiac and gastrointestinal tract involvement and correctly estimated their high prevalence, years before the development of electrocardiography and serologic testing for the disease.[6]

Fig. 20-1. Photograph of Carlos Chagas. (Photo from Chagas Filho, 1959.) (From Lewinsohn R.[3] By permission of the Royal Society of Tropical Medicine and Hygiene.)

Cardiac involvement is the most frequent manifestation of Chagas disease and is a form of chronic myocarditis. This chapter presents an overview of Chagas heart disease, reviewing its epidemiology, pathology and pathogenesis, clinical features, and treatment. In particular, we focus on advances in the understanding of the disease, our own experience with Chagas disease outside an endemic area, and advances in prevention and treatment.

EPIDEMIOLOGY

T cruzi, the etiologic agent of Chagas disease, is a hemoflagellate protozoan transmitted by the bite of a bloodsucking insect of the family Reduviidae, subfamily Triatominae (Fig. 20-2). Free-living reduviids transmit *T cruzi* infection in an enzootic cycle to a wide variety of wild animal hosts, such as rodents, opossums, and raccoons, and to domestic animals,[7] which serve as reservoirs of infection. Although most of the known species of reduviids harbor *T cruzi* in their gut, not all are capable of adapting to human habitation, and only a dozen species are epidemiologically important vectors of *T cruzi* infection in humans. Differences

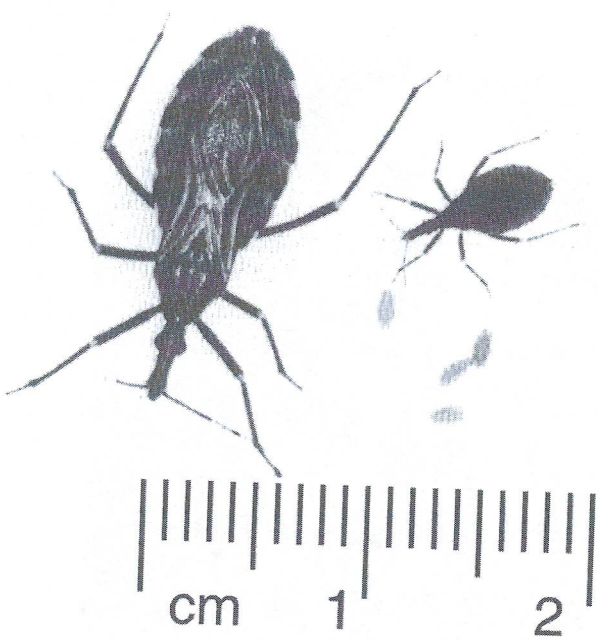

Fig. 20-2. Rodnius prolixus, one of the major vectors of *Trypanosoma cruzi* in Central America. Eggs, immature nymph, and adult forms are shown. (From Kirchhoff LV, Neva FA. *Trypanosoma* species [Chagas' disease]. In: Mandell GL, Douglas RG Jr, Bennett JE, eds. Principles and practice of infectious diseases. 2nd ed. New York: Wiley, 1985:1531-1537. By permission of the publisher.)

among species influence their ability to transmit *T cruzi* to humans and the types of measures likely to be most effective in their control.[8]

The types of housing found in impoverished rural areas of Central and South America facilitate transmission of *T cruzi* from reduviids to humans. Earthen floors, thatched roofs, and cracks in walls provide shelter for reduviids to live and breed in abundance.[9] More modern types of dwellings (eg, brick or stucco with concrete floors and metal roofs) are less likely to support breeding of reduviids. *T cruzi* is transmitted most often to humans when a reduviid takes its blood meal from a human victim, often during sleep. Bites are often on the face or other exposed skin. The reduviid defecates as it feeds, depositing *T cruzi*-laden feces near the bite. The victim then scratches the bite, inoculating *T cruzi* into the bite. Transmission through blood transfusion is the second most frequent method of transmission and is discussed below. Maternal-fetal transmission occurs in up to 10% of cases of chronic maternal infection and frequently results in spontaneous abortion or premature birth.[10,11]

T CRUZI LIFE CYCLE AND BIOLOGY

T cruzi completes its life cycle in a complex series of transformations within its insect vector and mammalian host. Reduviids acquire *T cruzi* by feeding on the blood of infected animals, in the form of free-living trypomastigotes, which have a membrane and flagellum. These develop in the insect's hindgut into metacyclic trypomastigotes, a form in which they are capable of infecting an animal host. Once the trypomastigotes invade the host via the feces of the reduviid, they enter macrophages in cutaneous tissues and multiply as intracellular amastigote (leishmanial) forms, which lack a membrane or flagellum. With the death of the macrophage, released amastigotes infect additional macrophages while others become trypomastigotes and circulate in peripheral blood. Ultimately, these invade remote tissues for which they exhibit varying degrees of tropism, particularly skeletal and cardiac muscle, and continue to multiply as amastigotes (Fig. 20-3).

PARASITE GENETICS AND HOST FACTORS

There is a great deal of variability in the morphology, antigenicity, and infectivity of different strains of *T cruzi* from patient to patient and between regions. Distinct strains of *T cruzi* can be identified according to their zymodemes, the electrophoretic classification of enzyme subtypes,[12] which may correlate with clinical differences in disease manifestations and resistance to antiparasitic drugs. Surface glycoproteins may also play a role in determining *T cruzi* invasiveness or virulence. Genetic polymorphisms can be identified within the *T cruzi* genome by using polymerase chain reaction (PCR)-based methods. PCR can be used to classify strains according to their zymodeme[13] and thus their virulence.[14] One small study found that different clinical forms of the disease are the result of genetic variability

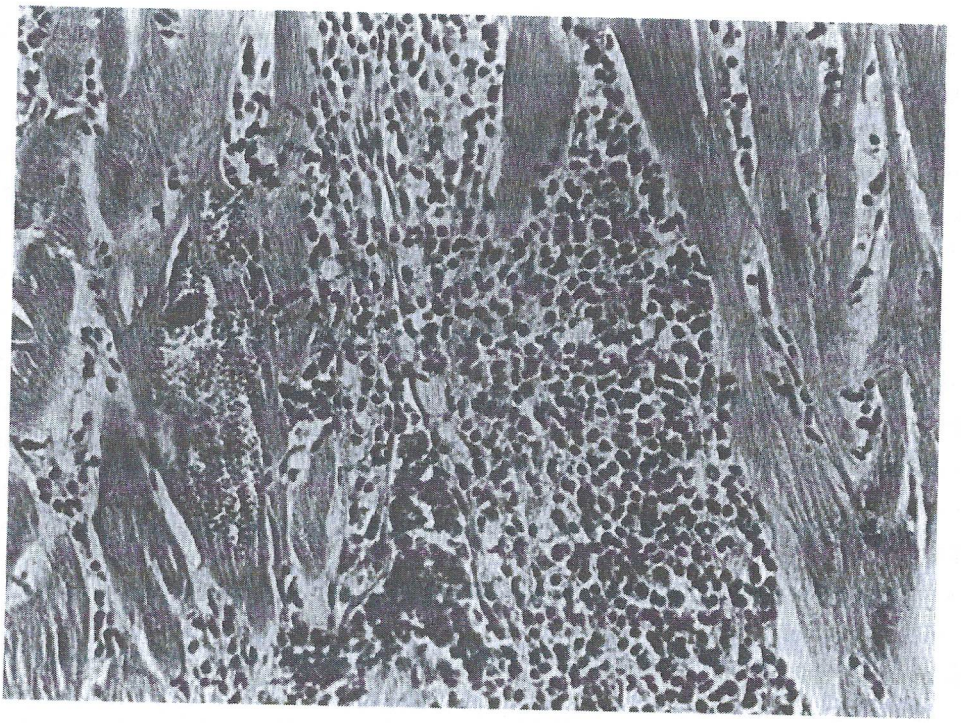

Fig. 20-3. Cardiac muscle in acute Chagas disease. An infected myocyte has become distended with *Trypanosoma cruzi* amastigotes, formed a pseudocyst, and ruptured. There is intense inflammatory reaction at this site. (Courtesy of Dr. Maria de Lourdes Higuchi.) (From Hagar and Rahimtoola.[38] By permission of Mosby-Year Book.)

in *T cruzi* strains.[15] Currently, genetic typing of *T cruzi* is useful mainly to study evolutionary development and geographic distribution of strains,[16] but one day it could be used to determine prognosis, end-organ disease, or drug sensitivity. The *T cruzi* Genome Project[17] is a multinational collaborative effort to sequence and provide a database for the genome of a *T cruzi* strain, *T cruzi* polymorphisms, and expressed sequence tags. This project undoubtedly will contribute greatly to knowledge in many areas, such as identifying new targets for pharmacotherapy.[18]

Host immunologic factors and environmental conditions are also important in determining the pattern and severity of disease that develops in an infected individual. Although human data are scant, in experimental animals, factors such as elevated environmental temperature[19] and protein malnutrition[20] alter the host immune response and tissue injury. Repeated reinfection and variation in the initial inoculum affect the severity of the infection and modify host immunity.[21] Intercurrent infection, especially viral infection, markedly enhances host susceptibility and the disease process. Overall, it is the balance among parasite tropism and invasiveness and host defenses that determines the pattern, severity, and course of the resulting cardiac disease.[22]

EPIDEMIOLOGY OF HUMAN CHAGAS DISEASE

Natural reservoirs of *T cruzi* can be found throughout most of the western hemisphere, as far north as Maryland and northern California, and as far south as the southern portions of Chile and Argentina. It has not been found outside of the Americas or in the Caribbean. Human infection with *T cruzi* is frequent throughout nearly all of South America, Central America,[23] and southern Mexico.[24] Human infection becomes less frequent at more northern latitudes; it is much less common in northern Mexico and is extremely rare in the southwestern United States. Although reduviid species are widely distributed in North America and frequently carry *T cruzi*,[25] infection acquired in the United States (other than laboratory- and transfusion-acquired infection) is extremely rare, with only 5 such cases reported.[26-29] This is mostly the result of better housing, but it may also result from differences in reduviid behavior and infectivity of *T cruzi* strains in temperate climates.

Estimates from the World Health Organization, based on seroepidemiologic studies, conservatively place the number of infected persons at 18 to 20 million,[30] with 90 million living in zones where transmission of *T cruzi* is endemic. An estimated 550,000 new cases and 50,000 deaths related to Chagas disease occur annually. In endemic countries, the overall prevalence of human infection averages about 10%, and in highly endemic rural areas rates ranging from 20% to 75% have been found. The prevalence of infection varies widely even among cities and provinces within one country, due to variations in climate, housing conditions, public health measures, and urbanization.

The number of cases of clinical Chagas disease and the number of case fatalities are not well known, because there is no case reporting in most areas. Individuals are exposed to *T cruzi* early and repeatedly throughout life, and the prevalence of infection in cross-sectional studies increases rapidly beginning in infancy and childhood. For example, in a highly endemic region of rural Venezuela, 16% of children aged 5 to 9 years had positive serologic results, increasing to 56% by ages 20 to 24 years, and 74% by age 65 years.[31] The prevalence of infection actually declines in the middle and older age groups, probably due to premature cardiovascular death in those infected.[32] The prevalence of right bundle branch block, an indicator of cardiac involvement, increased rapidly in the third decade of life among seropositive individuals, reaching 85% by age 50 years. Overall, 17% of the population had signs or symptoms of overt heart disease, nearly all attributable to Chagas disease. Chagas heart disease is the most common cause of dilated cardiomyopathy in endemic countries. In highly endemic areas it is the leading cause of cardiovascular death[33] and the leading cause of all deaths among persons ages 25 to 44 years.[34]

T cruzi infection and Chagas heart disease are sometimes encountered outside of endemic countries. In the United States, *T cruzi* infection has been found in as many as 4.9% of immigrants from highly endemic areas,[35] although the prevalence was lower in other surveys and depends on the demographic mix of subjects. A study at our institution

found 1.1% of 988 blood donors positive for *T cruzi* by complement fixation, with 0.2% of those from endemic areas positive by radioimmunoprecipitation assay.[36] Reports of Chagas heart disease in the United States include our series of 42 cases,[37,38] and 8 additional cases.[39-45] Estimates of the number of infected persons residing in the United States have ranged from 400,000 to 500,000.[35,46]

The country of origin of persons with Chagas disease found in a nonendemic country is determined by the relative proportion of immigrants from each country, their socioeconomic status, and the prevalence of infection in those countries. Thus, our patients were most frequently from Central America, followed by Mexico, and the smallest number were from South America[35] (Table 20-1). Cases of Chagas disease and asymptomatic *T cruzi* infection have been reported from numerous other nonendemic countries around the world as a result of worldwide immigration.[47]

TRANSFUSION-ACQUIRED CHAGAS DISEASE

Transfusion-acquired Chagas disease has long been a serious problem in endemic areas; transfusion is the second most frequent route of human infection. Transfusion-related transmission occurs outside of rural areas or even internationally because of population migration. The prevalence of *T cruzi* infection among blood donors in endemic countries

Table 20-1
Country of Origin of North American Patients With Chagas Heart Disease and Proportions of United States Immigrants From Endemic Areas

	Immigrant population from endemic countries, no. (%)	
Origin	LAC + USC series	2000 census*
Mexico	12 (29)	7,841 (67)
Central America	26 (62)	1,948 (17)
El Salvador	17 (40)	765 (7)
Guatemala	4 (10)	327 (3)
Nicaragua	3 (7)	245 (2)
Honduras	2 (5)	250 (2)
South America	4 (10)	1,876 (16)
Argentina	2 (5)	89 (1)
Colombia	1 (2)	435 (4)
Bolivia	1 (2)	44 (0.4)

*U.S. Census Bureau. The Foreign-Born Population (Table 3-4). Country or Area of Birth of the Foreign-Born Population From Latin America and Northern America: 2000. Published February 2000. <http://www.census.gov/population/socdemo/foreign/pp1-145/tab03-4.xls>. Numbers of persons in thousands. LAC + USC is Los Angeles County + University of Southern California Medical Center.

has been studied widely and indicates the prevalence of *T cruzi* infection in the population. Reported rates vary from less than 1% to more than 60%, depending on the region and whether the population studied is primarily an urban or a rural one.[48]

A recipient of infected blood develops persistent seropositivity, indicating transmission of chronic infection, in 14% to 49% of cases.[49,50] A few persons infected in this way develop fulminant acute Chagas disease, usually infants and the immunocompromised.[51] Most have no sign of disease or develop a mild nonspecific febrile illness that is easily overlooked.[52] They are not discovered until cardiac or gastrointestinal tract disease develops decades later.

In areas where there is a significant prevalence of infection, there is general agreement that screening of all donated units is necessary to eliminate transfusion-related transmission of *T cruzi*. Such screening is now required by law in nearly all endemic countries, and it is being implemented well in most.[53] Transfusion-acquired Chagas disease also occurs in the United States and other nonendemic countries, usually after transfusion of infected blood to immunocompromised individuals.[54,55] The optimum strategy for screening of donated units in these areas continues to be debated. In some areas, screening of all donated units may be necessary. In our institution, a screening geographic questionnaire is used, which identifies approximately 40% of donors as being at higher risk of *T cruzi* infection; only blood from these donors undergoes serologic screening.[56] Among such individuals, 0.5%, representing 0.2% of the entire population, were positive for *T cruzi* (confirmed by radioimmunoprecipitation assay).[57] This appears to be a reasonable strategy, although there are rare cases without a geographic history, which represent disease acquired within the United States.[58] In other areas of the United States the prevalence of *T cruzi* in the blood supply is negligible.[59] Thus, the best strategy to prevent transfusion-related disease may be different in each institution.

PREVENTION AND ERADICATION OF CHAGAS DISEASE

Public health preventive measures are the most important means of controlling the devastating impact of Chagas disease. The goal of these programs is to prevent new cases in children and young adults through interruption of insect-borne transmission and elimination of transfusion-related transmission. Spraying of housing twice yearly with residual pesticides coupled with entomologic surveillance can successfully eradicate domiciliary transmission and is the cornerstone of current control efforts in most countries. Permanent improvement in the quality of housing available in rural areas is a more long-term solution. When pursued intensively, as in the case of the cooperative multinational Southern Cone Initiative and similar projects,[60] disease transmission to humans has been markedly reduced or interrupted altogether.[61] Complete elimination of human *T cruzi* transmission in many of these countries is predicted within the next 5 years.[62]

PATHOLOGY AND PATHOPHYSIOLOGY OF CHAGAS HEART DISEASE

PATHOLOGIC FINDINGS

The acute and chronic phases of Chagas heart disease differ markedly in their pathologic appearance and pathogenesis. Cases of acute human Chagas disease with myocarditis bear many similarities to the commonly studied murine model of acute Chagas myocarditis. Such cases are characterized by intense inflammatory pancarditis and have abundant mononuclear and polymorphonuclear cells (Fig. 20-3). Amastigote forms and parasitic pseudocysts are easily found in cardiac muscle cells, skeletal muscle, central nervous system, and autonomic ganglia. Myocytolysis and edema are evident and may be direct effects of the parasite or mediated by eosinophils and neutrophils.[63]

Chronic Chagas heart disease presents a picture of chronic myocarditis, which is located focally but affects multiple areas. Scattered mononuclear inflammatory infiltrates are always found although they may be infrequent. There is focal and diffuse loss of myocytes (Fig. 20-4), ultimately leading to replacement with fibrosis (Fig. 20-5). These confluent areas of dense fibrosis replace muscle tissue and lead to the segmental wall motion abnormalities characteristic of the disease.[64,65] Irregular myocyte hypertrophy is found in other areas. This process of inflammation and fibrosis is widespread throughout ventricles and atria but has a particular predilection for the cardiac conduction system and the apex of the left ventricle. Degradation of extracellular collagen struts and dilatation of coronary microvessels are prominent. Such pathologic features are unique to Chagas myocarditis and are quite different from the findings in idiopathic dilated cardiomyopathy.[66]

The resulting loss of myocytes in confluent areas and extracellular collagen degradation routinely lead to segmental thinning and akinesis. This often results in the classic narrow-necked left ventricular aneurysm at the apex, which may be large or small and often contains mural thrombus. Aneurysms can be found at other sites, such as adjacent to the mitral annulus. Localized areas of thinning and akinesis are frequently present throughout the left or right ventricle. When myocardial involvement is diffuse, a picture of dilated cardiomyopathy develops.

Another unique characteristic is the early and preferential involvement of the cardiac conduction system at all stages of the disease.[67,68] The anterior fascicle of the left bundle and of the right bundle typically are involved, showing chronic fibrosis and progressive obliteration, as in the right bundle branch shown in Figure 20-6. This leads to the characteristic electrocardiogram (ECG) abnormalities of right bundle branch block or left anterior fascicular block (or both), found in up to 80% of patients with cardiac disease. These abnormalities frequently progress to complete atrioventricular block, sometimes with little other overt evidence of myocardial damage. The sinus node may be involved.[69]

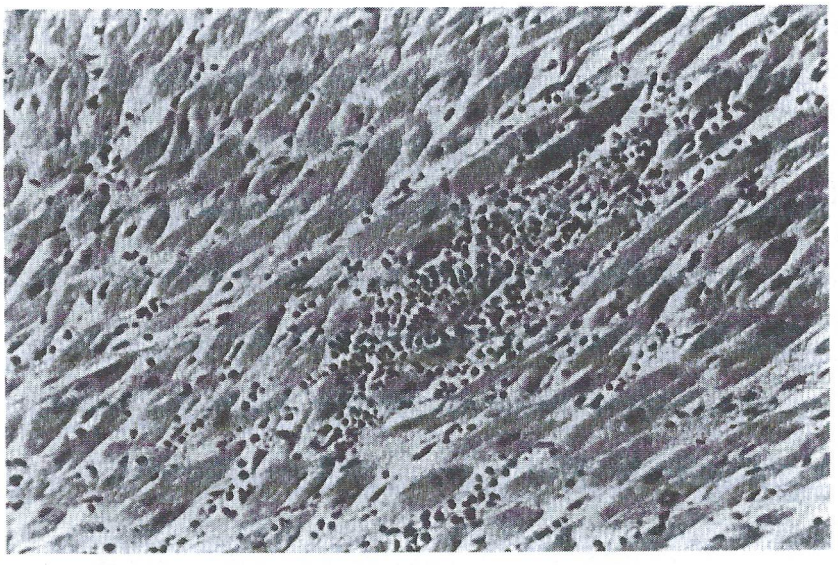

Fig. 20-4. Ventricular myocardium in chronic Chagas disease. There are scattered foci of mononuclear cell infiltrate and focal cytolysis without fibrosis. (From Suarez JA, Puigbo JJ, Nava Rhode JR, Valero JA, Yepez CG. Study of 210 cases of cardiomyopathies in Venezuela. In: Acquatella H, Pulido PA, eds. Miocardiopatias. Barcelona: Salvat Editores, 1982:5.)

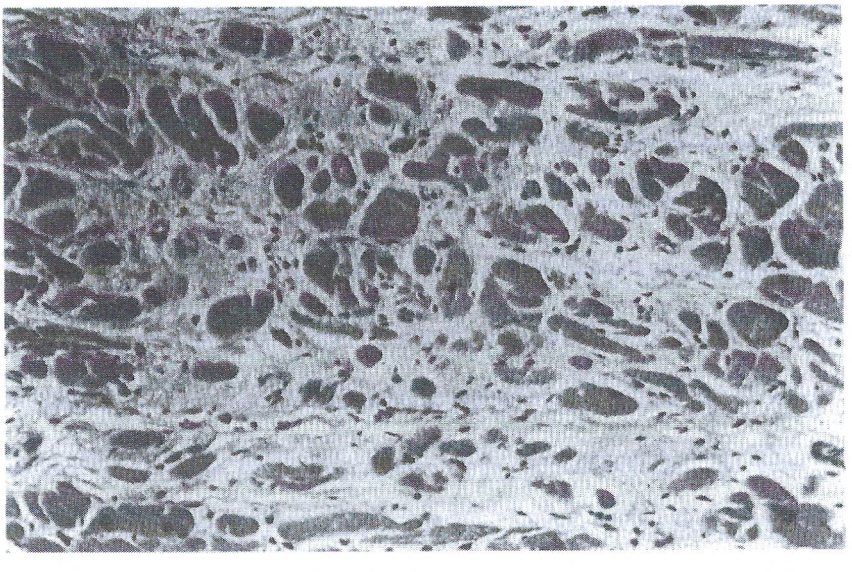

Fig. 20-5. The late stage of chronic Chagas heart disease. There is interstitial fibrosis and replacement of myocardium. Inflammatory cells are infrequent. (From Suarez JA, Puigbo JJ, Nava Rhode JR, Valero JA, Yepez CG. Study of 210 cases of cardiomyopathies in Venezuela. In: Acquatella H, Pulido PA, eds. Miocardiopatias. Barcelona: Salvat Editores, 1982:5.)

AUTONOMIC DYSFUNCTION

Loss of cardiac innervation is a frequent and unique pathologic feature of Chagas heart disease. This abnormality develops early in the course of the disease, preceding other evidence of cardiac involvement, and is a unique feature of Chagas heart disease that distinguishes it from other cardiomyopathic disorders.[70] Pathologically, abnormalities may be found in acute and chronic Chagas disease,[71] including periganglionitis, perineuritis, damage to neuron sheaths, direct parasitism of neurons, and a reduced number of vagal ganglion cells.[72] Clinically, autonomic dysfunction manifests as abnormal cardiovascular and baroreceptor

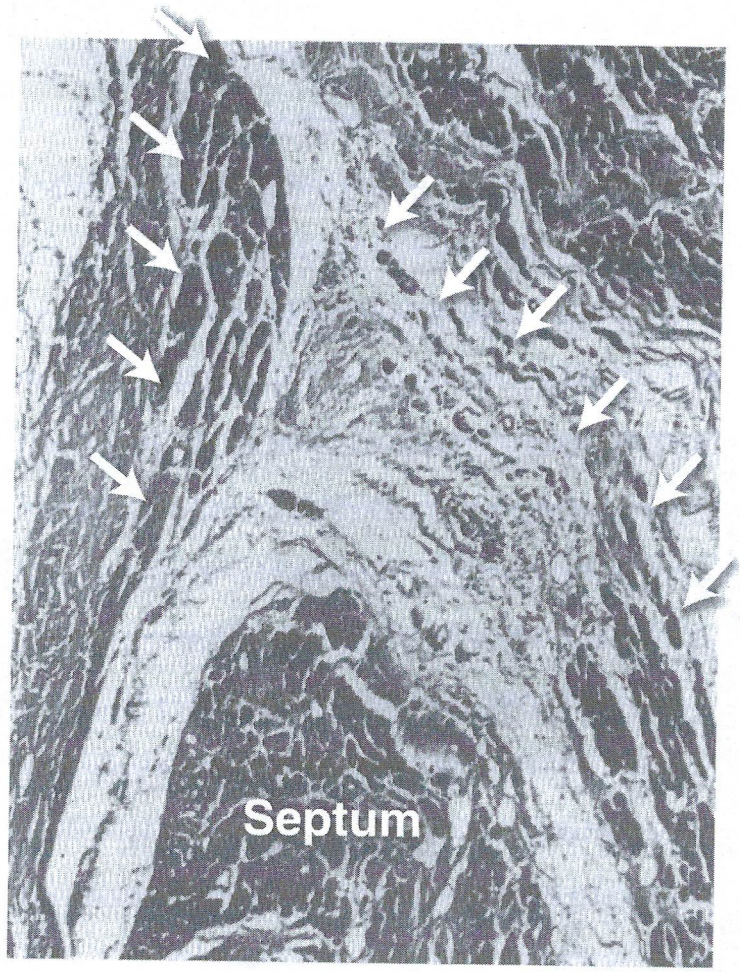

Fig. 20-6. Involvement of the conducting system in Chagas heart disease. There is fibrosis and destruction of the initial portion of the right bundle branch (*on right*) that extends into the septum. The left bundle (*on left*) is relatively spared. This process explains the typical findings of right bundle branch block. (Courtesy of Dr. Maria de Lourdes Higuchi.) (From Hagar and Rahimtoola.[38] By permission of Mosby-Year Book.)

reflexes. When this process occurs in the gastrointestinal tract, megaesophagus or megacolon results,[73] characterized by severe dysfunction and dilatation of the respective organs but without the extensive tissue destruction seen in the myocardium. Whether cardiac autonomic dysfunction is clinically important or how it might contribute to the development of the cardiomyopathy is still uncertain.

PERSISTENCE OF INFECTION IN THE CHRONIC PHASE

Amastigote forms are extremely rare in conventionally stained histologic sections of cardiac tissues from patients in the chronic phase of the disease. When they are present, they appear to bear little relation to the pathologic features encountered. However, immunohistochemical staining, confocal microscopy, and DNA labeling consistently show *T cruzi* antigens and DNA in cardiac tissues in chronic Chagas heart disease, and those areas are clearly associated with foci of inflammatory infiltrate.[74,75] Endomyocardial biopsies confirm the continuing presence of *T cruzi* amastigotes and antigens in 85% to 92% of patients in the chronic phase.[76,77] In animal models, clearance of *T cruzi* DNA is associated with disappearance of inflammatory changes.[78] *T cruzi* DNA is found in the peripheral blood in 80% to 85% of chronically infected individuals, when sensitive PCR-based methods are used for its detection.[79] Thus, parasites and parasitic antigens are present much more frequently than was recognized in the past, strongly supporting the concept that persistent parasitism is the major stimulus driving ongoing tissue injury and progression of the disease.

IMMUNE RESPONSES

Cell-mediated and humoral immunity play major roles in all phases of cardiac *T cruzi* infection. In the acute phase of the disease, foci of intense polymorphonuclear and eosinophilic inflammation predominate, with a major role for $CD8^+$ cytotoxic T lymphocytes[80] and macrophages.[81] In chronic disease, the intensity of inflammatory exudate is less and is predominantly mononuclear, although eosinophils may be associated with foci of cytolysis. Antibodies directed toward trypomastigotes are a major mechanism of host resistance.[82] In acute and chronic disease, $CD4^+$ Th1 lymphocytes are the main effector cell, providing helper cell functions and producing interferon-γ, a stimulus for induction of nitric oxide synthase.[83] Cytotoxic $CD8^+$ T lymphocytes in the myocardial interstitium, once sensitized to trypanosomal antigens, may produce myocyte injury and perpetuate the immune response by elaborating cytokines that stimulate macrophage migration into the tissues.

Mechanisms used by the parasites to produce tissue injury directly have been studied. Entry of *T cruzi* into host cells requires specific recognition sites, its trans-sialidase activity,[84] which is a major virulence factor, and the complement system.[85] *T cruzi* also induces apoptosis in host cells.[86]

The host immune response to *T cruzi* undoubtedly contributes to tissue injury, but *T cruzi* epitopes might also trigger host autoimmune responses by virtue of molecular mimicry. Antibodies have been described that react with antigens common to *T cruzi* and striated muscle,[87] peripheral nerve,[88] and cholinergic[89] and beta-adrenergic[90] receptors, which alter their function, although such studies have often lacked reproducibility.[91] T lymphocytes from infected humans and mice exert a negative inotropic effect[92] or produce myocarditis[93] in normal animals. Shared epitopes between *T cruzi* trypomastigotes and cardiomyocytes have been described.[94,95] Antibodies to a lymphocyte-activating antigen that depress lymphocyte proliferation[96] may explain the decreased cellular immune response to *T cruzi* antigens found in patients with advanced Chagas disease.[97] *T cruzi* kinetoplast DNA can be incorporated stably into human macrophage cell lines, altering their membrane antigens and allowing specific recognition by antibodies from *T cruzi*-infected patients.[98] These are fascinating hypotheses, but it has not been proven that such mechanisms are responsible for any of the pathologic changes found in cardiac tissues in human Chagas disease.[99]

EXTRACELLULAR MATRIX

The progressive loss of myocytes in chronic Chagas heart disease is associated with a concomitant increase in cardiac fibrosis, replacing necrotic myocytes and surrounding viable myocytes and blood vessels. There is progressive deposition of fibronectin, laminin, and type III and IV collagen in areas of inflammatory cell infiltration, which expand and distort the extracellular matrix[100] and could interfere with myocardial function. *T cruzi*-infected mesenchymal and endothelial cells secrete soluble factors that directly stimulate fibroblast proliferation and collagen formation[101] and an abnormal extracellular matrix.[102]

The normal extracellular matrix may be a site of injury in Chagas disease. Proteases from parasites and activated macrophages degrade native collagen and other matrix proteins.[103] There is progressive focal destruction of the collagen matrix throughout the course of the disease (Fig. 20-7), which is particularly prominent in the left ventricular apex.[104] Such extracellular matrix damage would lead to fiber slippage, apical thinning, segmental wall motion abnormalities, and adverse ventricular remodeling.

MICROVASCULAR ABNORMALITIES

Abnormalities of the coronary microvasculature have been hypothesized to contribute to the pathogenesis of Chagas heart disease. Basement membrane thickening was described in the myocardial microvessels of some patients with advanced cardiac disease.[105] Vascular proliferation and focal reversible vasoconstriction are found in the mouse model of acute *T cruzi* infection.[106] Clinically, endothelial function of large and small coronary vessels is abnormal in patients with Chagas heart disease.[107] Such structural and functional

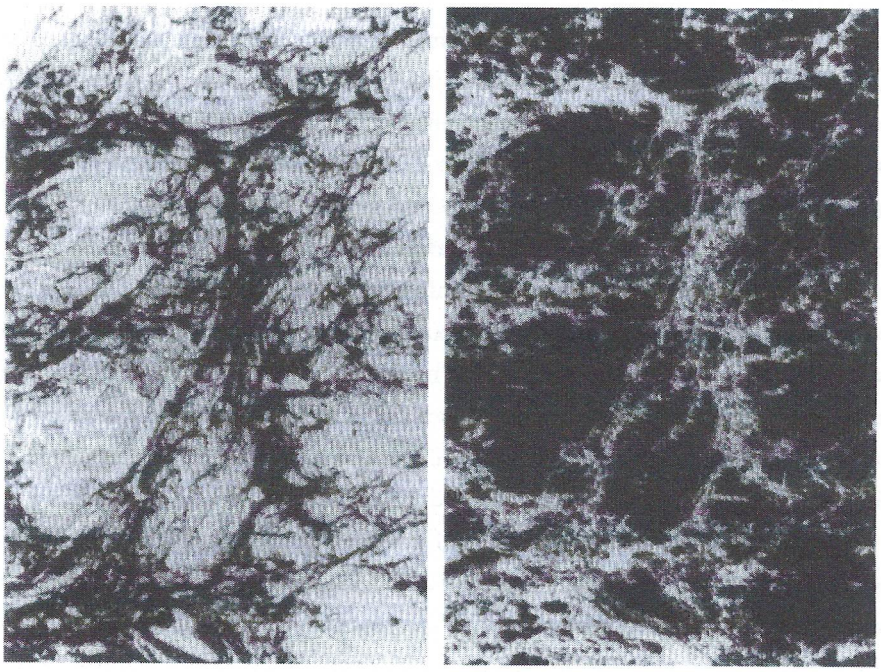

Fig. 20-7. Pattern of interstitial fibrosis encasing myocyte bundles and coronary blood vessels. Picrosirius red stain (*Left*) and polarized light (*Right*). (From Rossi MA. The pattern of myocardial fibrosis in chronic Chagas' heart disease. Int J Cardiol 1991;30:335-340. By permission of Elsevier Science Publishers.)

changes could be the result of infection of endothelial cells with *T cruzi*,[108] the action of *T cruzi* neuraminidase, or the autocrine or paracrine (or both) action of cytokines[109] and endothelin-1[110] elaborated by infected cells. Such microvascular alterations could lead to hyperresponsiveness to vasoconstrictor stimuli, microvascular ischemia, and focal myocytolysis.[111]

CLINICAL FEATURES OF CHAGAS HEART DISEASE

Cardiac involvement is typically present at all stages of Chagas disease. *Acute Chagas disease* is uncommon and is characterized by a febrile illness sometimes associated with facial or unilateral palpebral edema (Romaña sign) or localized indurated swelling at the site of inoculation (chagoma). Acute myocarditis is usually present at this stage but is rarely detected. Clinically evident acute myocarditis develops in approximately 1% of cases, and it is fatal in about 10%.[112] The remainder, who have no signs or symptoms of disease, enter the *indeterminate phase* of chronic infection.[113]

Such persons remain infected for life, with persistence of the parasite in tissues and measurable parasitemia in most. Active myocarditis and fibrosis are frequently present in this phase[114,115] and correlate with increasing severity of subsequent clinical disease.[116] Myocardial damage is thus a steadily progressive, cumulative, but variable process in the indeterminate phase of Chagas disease. This progression of myocardial damage leads to overt end-organ damage, most often cardiac, after a latent period of at least 15 to 20 years.

The percentage of infected individuals ultimately developing heart disease depends on how carefully the disease is sought. Approximately 30% to 40% of infected individuals develop detectable cardiac abnormalities during their lifetime,[117,118] such as an abnormal ECG or echocardiogram, whereas overt symptomatic cardiac involvement develops in 10% to 20%.[119] Of the remainder, usually classified as indeterminate, many actually have subclinical cardiac involvement when studied carefully.[120] Therefore, clinically evident Chagas heart disease represents only the tip of the iceberg of the cardiomyopathy.

It is sometimes useful to classify patients with Chagas disease according to the extent and severity of end-organ involvement (and thus prognosis). One such system[121] takes into account the early manifestations of disease, such as minor segmental wall motion abnormalities, autonomic dysfunction, and diastolic dysfunction (Table 20-2). However, a

Table 20-2
Clinical Classification of Chagas Heart Disease

Stage	Symptoms	ECG	Heart size	LVEF	LV wall motion	Autonomic function
I						
A	None	Normal	Normal	Normal	Normal	Normal
B	None	Normal	Normal	Normal	Mild abnormalities or diastolic dysfunction	May be abnormal
II	Minimal	Conduction abnormalities or PVCs	Normal	Normal	Segmental akinesis or aneurysm	May be abnormal
III	CHF, arrhythmias	Conduction abnormalities, pathologic Q waves, complex arrhythmias	Enlarged	Reduced	Global dysfunction with segmental WMA	Usually abnormal

CHF, congestive heart failure; ECG, electrocardiogram; LV, left ventricle; LVEF, left ventricular ejection fraction; PVCs, premature ventricular complexes; WMA, wall motion abnormalities.
Modified from Puigbó et al.[121] By permission of the publisher.

clinically based classification does not take into account the extent and severity of cardiac inflammation and parasitism, which may influence treatment and outcomes. With advances in laboratory testing, such information may provide additional clinical utility.

When *T cruzi* infection of the heart is demonstrated by pathologic examination of cardiac tissues, the diagnosis is certain. All other cases must meet a strict case definition that requires a combination of epidemiologic, serologic, and clinical criteria.[122] This is particularly important in populations where Chagas disease is uncommon relative to other forms of heart disease. The case definition we have used[37,38] requires 4 criteria be met: 1) a history of residence in an area endemic for Chagas disease, 2) an unequivocally positive serologic test for *T cruzi* by 2 methods, 3) a clinical syndrome compatible with Chagas heart disease, and 4) no evidence of another cardiac disorder to which the findings can be attributed.

LABORATORY DIAGNOSIS OF CHAGAS DISEASE

T cruzi infection can be diagnosed by finding the parasite, its antigens, or its DNA in blood or tissues or by a positive serologic test. Historically, the reference method of detection has been xenodiagnosis, in which laboratory-raised reduviids feed on blood of individuals with suspected *T cruzi* infection and are then examined after 4 to 6 weeks for the presence of trypomastigotes. Although specific, xenodiagnosis is cumbersome and has poor sensitivity in the chronic phase of the disease.[123] Instead, PCR-based methods to detect *T cruzi* nuclear or kinetoplast minicircle DNA sequences in blood or tissue have replaced xenodiagnosis for the direct diagnosis of *T cruzi* infection in most research centers. The sensitivity of PCR is greater than that of xenodiagnosis, with the most sensitive assays able to detect < 1 parasite/mL;[124] its sensitivity is 80% or higher in chronic infection but is still lower than that of serologic tests. PCR testing promises to be most useful for diagnosis of the disease when there is an equivocal or even negative serologic result[125] and for monitoring the effectiveness of antiparasitic drug therapy.

Serologic testing for Chagas disease is the mainstay of clinical diagnosis. Numerous methods are available to detect IgG antibodies to *T cruzi* trypomastigote antigens, which begin to appear within 3 to 6 weeks of infection and remain for life. Although useful in diagnosis, their titer and the change in titer over time do not correlate with disease activity. Testing is usually performed by 2 different methods to enhance the accuracy. The complement fixation, or Guerreiro-Machado, test was the first test developed and is still in use. It has a sensitivity of more than 90% and a specificity of more than 99% in cases of late disease.[126] In acute disease, however, the sensitivity is as low as 60%. The indirect immunofluorescence test is a simple slide test that is performed easily and is more sensitive than the complement fixation test,[127] although low titer false-positive results sometimes occur in patients infected with leishmaniasis or with nonpathogenic trypanosome strains. Enzyme-linked immunosorbent assay is simple and can be automated, and widely used

commercially available kits have a 98% to 100% sensitivity and a 93% to 100% specificity.[128] However, the newer enzyme immunoassay has a nearly 100% sensitivity and specificity.[129] More specialized antibody tests have been used for specific research purposes.[130,131] The radioimmunoprecipitation[132] and enzyme immunoassays with their high specificity are most useful as a confirmatory test in populations with a low incidence of positivity, such as blood donors in nonendemic areas.

CLINICAL MANIFESTATIONS OF CHAGAS HEART DISEASE

Because the panmyocarditis of Chagas heart disease progressively involves the various cardiac tissues, patients may present with a wide variety of clinical manifestations. The most important of these are ventricular arrhythmias, congestive heart failure, thromboembolism, and complete atrioventricular block.

In early cardiac disease, when the cumulative extent of myocardial damage is small (stage IA and IB), ventricular abnormalities are minimal or absent and the ECG is normal. These patients are typically asymptomatic and have a good prognosis. When myocardial damage is more advanced (stage II), areas of abnormal wall motion may be evident and conduction abnormalities usually are present due to lesions within the His-Purkinje system. In such patients, global ventricular function is preserved, but sudden cardiac death or complete atrioventricular block may develop. Nonspecific symptoms such as chronic fatigue, weakness, palpitations, and chest pain[133] may be present. Such chest pain is vague and atypical of myocardial ischemia, but it sometimes prompts diagnostic evaluation. When the extent of myocardial damage is severe (stage III), the disease manifests as myocardial dysfunction that may be segmental, typically a ventricular aneurysm, or global, resembling a dilated cardiomyopathy. The clinical manifestations at this stage are those of severe congestive heart failure, ventricular arrhythmias, systemic thromboembolism, and complete heart block. However, the severity of symptoms frequently does not correlate with the degree of structural abnormality present; asymptomatic patients with profoundly abnormal ventricles are encountered frequently, whereas some with milder disease may have prominent constitutional symptoms.

The initial clinical manifestations of the 34 women and 8 men in our series are shown in Table 20-3. Most had received treatment for other presumed cardiac diagnoses, usually coronary artery disease or idiopathic dilated cardiomyopathy, before Chagas disease was considered.

ECG ABNORMALITIES

Involvement of the conduction system is ubiquitous and progressive when there is cardiac involvement. It was the study of Chagas heart disease that led to our modern understanding of the pathologic features of right bundle branch block and the discovery of the fascicular blocks.[134] The characteristic ECG abnormalities of right bundle branch block or

Table 20-3
Clinical Presentation of North American Patients With Chagas Heart Disease*

Clinical presentation	Patients, no. (%)
Atrioventricular block	9 (21)
Congestive heart failure	8 (19)
Chest pain	6 (14)
Conduction abnormality on ECG	8 (19)
Aborted sudden death	3 (7)
Sustained ventricular tachycardia	3 (7)
Embolic event	3 (7)
Other	2 (5)

ECG, electrocardiogram.
*Age at diagnosis (mean ± SEM) = 52 ± 2 years; duration of prior symptoms = 20 ± 6 months (range, 0 to 108); and no symptoms before initial presentation = 10 (24%).
Modified from Hagar and Rahimtoola.[37] By permission of the Massachusetts Medical Society.

left anterior fascicular block (or both) are found in up to 80% of patients with overt cardiac disease in our patients and in 2 other large series (Table 20-4). Conduction abnormalities were present in all of those in our series who had ventricular aneurysm or severe ventricular dysfunction. The prevalence of right bundle branch block in some endemic areas is so high that it has been used as a marker for Chagas heart disease in some studies. The presence of right bundle branch block (complete, incomplete, or induced by the antiarrhythmic agent ajmaline[135]) or left anterior fascicular block virtually always indicates the presence of significant myocarditis,[136] although the extent of myocardial damage may vary. Left bundle branch block is infrequent. This apparent preference for the right bundle branch and anterior fascicle is explained by the anatomic vulnerability of these highly localized conducting tissues (Fig. 20-6).

Ventricular premature beats occur in virtually all patients with Chagas heart disease, and generally they become more frequent and complex with more advanced disease.[137] Sinus bradycardia is not infrequent, indicating sinus node involvement or autonomic neuropathy, but does not indicate an adverse prognosis. Atrial fibrillation, on the other hand, usually is associated with severe left ventricular dysfunction. Patients who have isolated right bundle branch block as their only ECG abnormality may have a more benign prognosis, whereas those with left anterior fascicular block tend to have more extensive wall motion abnormalities and ventricular arrhythmias.[138]

Pathologic Q waves, primary T-wave changes, and ST-segment elevation were frequent in our patients and always indicate the presence of extensive wall motion abnormalities or ventricular aneurysm.[139,140] Such ECG abnormalities, which resemble myocardial infarction or ischemia (or both), are prominent in advanced cases of Chagas heart disease and may confuse the clinician unfamiliar with Chagas disease.

Table 20-4
Electrocardiographic Findings in 3 Series of Patients With Chagas Heart Disease

	Patients			
	Hagar and Rahimtoola[38]		Laranja et al.[118]	Puigbo et al.[31]
	No.	%	%	%
Conduction abnormality*				
Bundle branch block				
RBBB	20	47	51	45
Without LAD	8	18		19
With LAD	12	29		26
LBBB	4	10	5	7
Left anterior hemiblock only	11	26	–	26
No conduction abnormality	7	17	–	18
Arrhythmias				
Complete heart block	3	7	8	–
Atrial fibrillation with slow response	4	10	7	–
Second degree AV block	2	5	4	6
Ventricular ectopic beats	26	62	47	35
Sinus bradycardia	7	17	–	–
Other abnormalities				
Q wave MI pattern	18	43	14	10
Anteroseptal	6			
Anterolateral	2			
Lateral	5			
Inferolateral	4			
Inferior	1			
With ST elevation (simulating acute MI)	6	14		–
Primary T-wave inversion	19	45	23	66
ST depression	2	5		

AV, atrioventricular; LAD, left axis deviation; LBBB, left bundle branch block; MI, myocardial infarction; RBBB, right bundle branch block.
*Complete and incomplete bundle branch blocks classified together.
From Hagar and Rahimtoola.[38] By permission of Mosby-Year Book.

MYOCARDIAL ABNORMALITIES

Chagas heart disease is unique among the cardiomyopathies in causing marked segmental wall motion abnormalities and aneurysms of the left ventricle. These abnormalities result in a high incidence of malignant ventricular arrhythmias and systemic thromboembolism in patients with Chagas disease. The classic lesion of Chagas disease is a localized aneurysm of the left ventricular apex, with relatively normal surrounding wall motion (Fig. 20-8 through 20-10). This results in a narrow neck when visualized by echocardiography or

ventriculography;[141] when present, this can usually distinguish an aneurysm of Chagas heart disease from one due to coronary artery disease.[142] The aneurysms and segmental abnormalities are thought to result from localized destruction of extracellular matrix collagen along with myocyte loss, which leads to focal weakening of the ventricular wall. The apical location is particularly vulnerable because of the nature of the collagen structure at this location, normal apical thinning, and a relatively increased wall stress, which would promote the gradual development of aneurysmal dilatation of the weakened segment. Regional dyssynergia caused by segmental conduction abnormalities could also contribute to aneurysm formation.

Echocardiography has proved useful to identify the presence and extent of end-organ damage. Areas of segmental hypokinesis or akinesis are commonly found early in the chronic phase,[143] even in those with normal ECGs who would otherwise be given a diagnosis of indeterminate phase disease. Right ventricular abnormalities may be present,[144] and diastolic dysfunction frequently is found. In time, the disease results in progressively larger areas of akinesis or aneurysm, declining systolic dysfunction, mitral insufficiency, and overt congestive heart failure.

Table 20-5
Left Ventricular Function and Coronary Arteriographic Findings in North American Patients With Chagas Heart Disease

Finding	Patients, no. (%)	
Left ventricular function		
Global systolic function abnormal*		20 (48)
Wall motion abnormalities		30 (71)
Left ventricular aneurysm (coronary arteriogram in 14, normal in all)	15 (36)	
Segmental wall motion abnormality without aneurysm	7 (16)	
Apical akinesis 6, apical hypokinesis 1		
Diffuse hypokinesis	8 (19)	
Multiple abnormalities	7 (17)	
Both left ventricular wall motion and global function normal		12 (29)
Coronary arteriography (n = 25)		
Normal	23	
Minimal atherosclerotic disease	2†	

*Ejection fraction < 50% by contrast ventriculography (n = 21) or radionuclide angiography (n = 6); echocardiographic fractional shortening < 28% (n = 15).
†Less than 60% obstruction small diagonal in 1; < 50% obstruction distal right coronary artery.
From Hagar and Rahimtoola.[38] By permission of Mosby-Year Book.

In our series, 71% of patients had left ventricular abnormalities—most often an aneurysm (Table 20-5). Wall motion abnormalities were often multiple. Nearly half of patients with ventricular aneurysms had normal overall left ventricular function. Aneurysms usually involved the apex and sometimes the posterolateral wall. Aneurysms varied in size and morphology from fingertip-sized outpouchings to massive structures (Fig. 20-8 through 20-10).

The segmental nature of the myocardial abnormalities extended to myocardial perfusion scintigraphy. All 10 patients studied with exercise and redistribution thallium perfusion scans had abnormal studies.[145] Fixed defects were found in 2 patients, a reversible defect in 1, and both fixed and reversible defects in 4. These defects corresponded to areas of abnormal left ventricular wall motion or aneurysm, although none had coronary artery disease in any artery supplying these regions. Such a study is shown in Figure 20-11. There was also reverse redistribution in 1 or more segments in 3 cases, which is a frequent finding when there is cardiac involvement,[146] but which does not correspond to areas of abnormal wall motion. Fixed defects might be expected where there is focal myocyte loss and fibrosis; the finding of reversible defects could be interpreted as supporting a microvascular ischemia hypothesis. Practically, it means that myocardial perfusion imaging cannot be used to exclude coronary artery disease in patients with Chagas heart disease.

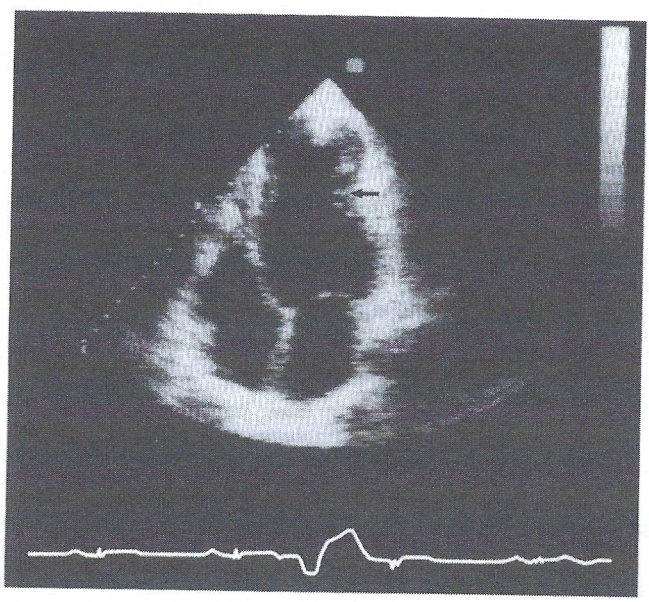

Fig. 20-8. Two-dimensional echocardiogram, apical 4-chamber view. There is a large but relatively narrow-necked apical aneurysm with mural thrombus (*arrow*). (From Hagar and Rahimtoola.[38] By permission of Mosby-Year Book.)

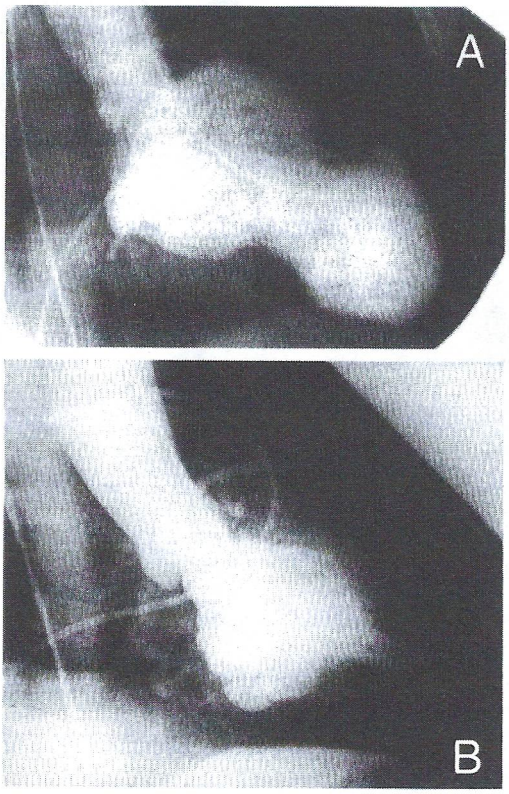

Fig. 20-9. Diastolic (*A*) and systolic (*B*) frames of cineventriculogram demonstrate a classic narrow-necked apical aneurysm. Basal akinesis is also present. From an asymptomatic patient with right bundle branch block. (From Hagar and Rahimtoola.[38] By permission of Mosby-Year Book.)

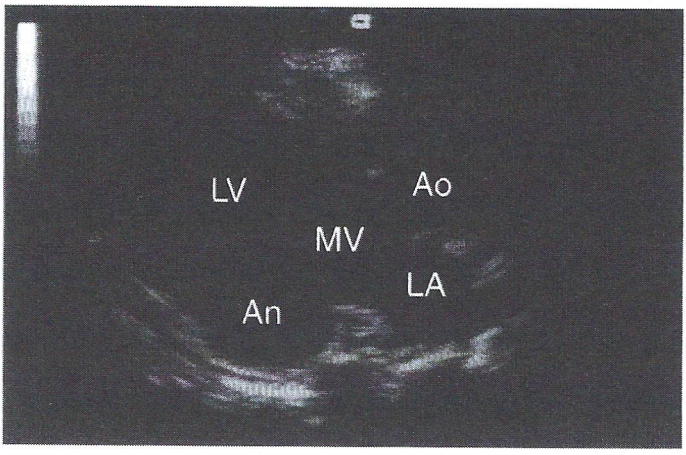

Fig. 20-10. Two-dimensional echocardiogram in parasternal long-axis view shows a large basal posterior aneurysm (*An*) and a small pericardial effusion discovered incidentally in a patient presenting with tuberculous pericarditis. *Ao*, aorta; *LA*, left atrium; *LV*, left ventricle; *MV*, mitral valve. (From Hagar and Rahimtoola.[38] By permission of Mosby-Year Book.)

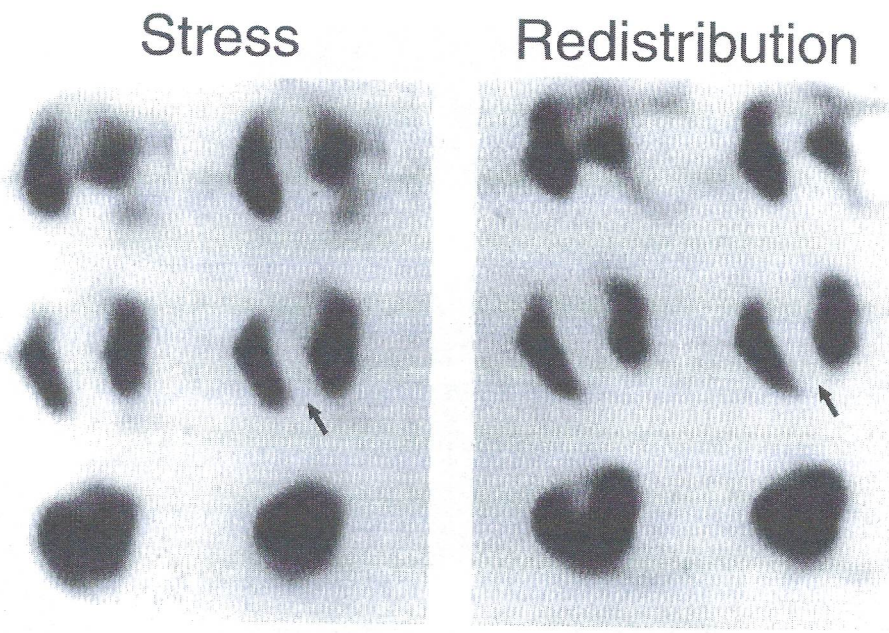

Fig. 20-11. Exercise and redistribution thallium perfusion images in Chagas disease from a patient with a large apical aneurysm who presented with cerebral embolus. There is a large fixed apical defect (*arrows*) without redistribution. (From Hagar and Rahimtoola.[38] By permission of Mosby-Year Book.)

VENTRICULAR ARRHYTHMIAS

The pathology of Chagas heart disease is highly conducive to the development of ventricular arrhythmias. Malignant ventricular arrhythmias and sudden cardiac death are the most frequent causes of death in Chagas disease, occurring more often than in dilated cardiomyopathy.[147] Life-threatening arrhythmias may be the first manifestation of the disease, as in several of our patients. Ventricular ectopy is remarkably frequent in all stages of the disease, even when there is no other evidence of cardiac involvement.[148] Ectopy is dense and temporally unvarying, with patients often having tens of thousands of ectopic beats per day.[149] In our series, 14% of patients presented with aborted sudden death, and sustained ventricular tachycardia or sudden death occurred subsequently in 39% of patients with left ventricular aneurysm or dysfunction.

The severity and complexity of ventricular ectopy are related to the extent of myocardial disease. Nonsustained ventricular tachycardia has been found by ambulatory monitoring in 10% of patients with mild wall motion abnormalities, in 56% of those with severe wall motion abnormalities or aneurysms without heart failure, and in 87% of those with advanced congestive heart failure.[137] The 25 patients in our series who had ambulatory ECG monitoring all had frequent ventricular premature beats. Nonsustained ventricular tachycardia was found in 9, of whom 5 had inducible sustained ventricular tachycardia on

subsequent programmed ventricular stimulation. However, 6 other patients with inducible ventricular tachycardia and 4 with subsequent spontaneous ventricular tachycardia or sudden death had no ventricular tachycardia on a single 24-hour ECG.

Electrophysiologic testing in asymptomatic patients with cardiac involvement has shown that sinus node dysfunction is present in 18%, pacing-induced atrioventricular block in 41%, and multiple sites of conducting system dysfunction often coexist.[150] Sustained ventricular tachycardia is inducible with programmed ventricular stimulation in most patients who present with sustained ventricular arrhythmias and in half of those who have symptomatic nonsustained ventricular tachycardia.[151] The sites of origin of ventricular tachycardia are typically left ventricular or septal, are frequently at the edge of an area of abnormal wall motion, and may be multiple. When the sites of earliest activation of ventricular tachycardia within aneurysms have been examined histologically, these sites contain subendocardial islets of viable but often damaged myocytes interdigitated with areas of dense fibrous connective tissue.[152] Treatment of arrhythmias and the role of invasively guided antiarrhythmic therapy are discussed in a later section.

CONGESTIVE HEART FAILURE

Congestive heart failure is a late manifestation of Chagas heart disease that indicates an extensive amount of irreversible myocardial damage and structural abnormality. Congestive heart failure usually develops after age 40 years and tends to occur later in the course of the disease than symptomatic atrioventricular block or ventricular aneurysm. When congestive heart failure does develop in a patient younger than age 30 years, it indicates a particularly fulminant form of the disease, with aggressive myocarditis and a poor prognosis.[153]

Diastolic dysfunction is frequently found by echocardiography in patients with Chagas disease and develops early in the course of the disease. It manifests as impaired isovolumic relaxation and diminished ventricular filling and is usually not associated with segmental wall motion abnormalities or systolic dysfunction.[154] Nearly one-half of patients who would otherwise be classified as indeterminate phase have this abnormality, as do nearly all with symptomatic cardiac disease. The clinical and prognostic significance of diastolic dysfunction in Chagas disease is uncertain, but it should be taken as evidence of cardiac involvement in seropositive patients if other causes of diastolic dysfunction are excluded.

THROMBOEMBOLISM

Thromboembolism, arterial and venous, appears to be quite frequent in advanced Chagas disease, and its occurrence is probably underdiagnosed.[155,156] At autopsy, 73% of patients have left or right ventricular mural thrombi, with evidence of pulmonary or systemic embolization in 60%.[157] The apical aneurysm typical of Chagas disease is particularly prone to the formation of thrombi[158] and is associated with a high incidence of thromboembolic events.

Three of the patients in our series presented with systemic thromboembolic events as the initial manifestation of their disease (Table 20-3). During follow-up, 1 patient had an acute myocardial infarction and another had unstable angina with marked transient T-wave changes; both patients had left ventricular mural thrombi and normal coronary arteries, suggesting coronary artery embolism.[159]

ATRIOVENTRICULAR BLOCK

In cross-sectional studies it has been appreciated that the conduction block in Chagas heart disease progresses steadily over time: from incomplete to complete right bundle branch block, left anterior fascicular block, and finally to complete atrioventricular block. In these studies, complete atrioventricular block is found in approximately 1% of all seropositive individuals, 5% to 8% of those who meet criteria for heart disease (Table 20-4), and 20% to 30% of patients with advanced cardiac disease. Many of these patients have nearly normal ventricular function and a good prognosis with permanent pacing. On the other hand, complete heart block commonly develops in patients with advanced heart failure and may be manifest when antiarrhythmic drug treatment is required. Syncope or near-syncope is the usual symptom on presentation. Some cases of unexplained cardiac death in rural areas may also be due to atrioventricular block. In our series, 9 patients (21%) had symptomatic second degree or third degree block at diagnosis. Ultimately, 15 patients (36%) required permanent pacemaker insertion, usually VVI or VVIR, for these indications. Left ventricular aneurysm or dysfunction was not more frequent in patients who received pacemakers, and congestive heart failure, arrhythmic events, and death did not develop more frequently during follow-up.

CARDIOVASCULAR AUTONOMIC DYSFUNCTION

Cardiovascular autonomic dysfunction is found frequently in patients with Chagas disease, consistent with the autonomic nervous system abnormalities described earlier. Although such abnormalities are sometimes found in dilated cardiomyopathy of any cause, they are more frequent and more severe and develop earlier in Chagas disease. Reported abnormalities include blunted hemodynamic response to exercise,[160] postural hypotension,[161] and diminished heart rate variability,[162] predominantly due to parasympathetic denervation. Abnormal responses to baroreflex testing,[163] handgrip,[164] atropine,[165] and the Valsalva maneuver[166] are frequently found at all stages of the disease. Plasma norepinephrine concentrations correlated with increasing degrees of autonomic dysfunction.[167] Such abnormalities are sometimes found in the absence of other signs of heart disease, but they are more frequent when some degree of cardiac or gastrointestinal tract disease is present.[168] The clinical significance of such autonomic abnormalities is uncertain, but some have suggested a relationship to the development of sudden cardiac death.[169]

PROGNOSIS AND NATURAL HISTORY

Infection with *T cruzi* significantly shortens the life expectancy of affected persons. Mortality rates vary greatly between geographic regions, suggesting that environmental factors, comorbid infections, or trypanosome strain may influence the severity or progression of disease.[170] In a rural Venezuelan population with a prevalence of infection of 47% studied for 4 years, heart disease developed in initially seropositive patients at a rate of 1.1%/year.[171] Mortality due to Chagas heart disease in this period was 7% in those younger than age 50 years and 3% in the entire group, accounting for 69% of all deaths. Death typically results a minimum of 15 years after infection, with most persons dying of Chagas heart disease between age 25 and 45 years. Chagas disease is by far the leading cause of death in this young age group in endemic areas, making it a major public health problem.

The cause of death in Chagas heart disease is sudden cardiac death in approximately 50% of patients, congestive heart failure in 40%, and cerebral embolism in 10%. Among the patients in our series, 9 of the 11 deaths were sudden. Sudden death is more frequent than death from congestive heart failure in younger patients, in stage II patients (segmental wall motion abnormalities without heart failure),[172] and in those with complex and sustained ectopy on ambulatory ECG.[173] Sudden death in Chagas heart disease, usually due to ventricular tachycardia or fibrillation, is frequent in endemic countries; autopsy studies of fatal traffic accidents and sudden death often reveal that Chagas heart disease is the sole finding.[172] Half of those dying suddenly are asymptomatic before death, and death is the first sign of Chagas disease. Nearly all such individuals have significant, often extensive, ventricular abnormalities and conduction system disease.[174,175]

The presence of congestive heart failure is the strongest predictor of subsequent mortality in all studies. Mortality in such patients is high, probably higher than in patients with congestive heart failure from other etiologies.[176] Ten-year survival in a typical study was 9% after development of congestive heart failure (stage III) compared with 65% in those with ECG abnormalities without heart failure (stage II), and it was normal in seropositive patients with a normal ECG (stage I).[177] Among those who have congestive heart failure, maximum oxygen consumption, functional class, and ejection fraction predict survival.[178]

In our series (average follow-up, 56 ± 9 months), 5-year survival was 64%[38] (Fig. 20-12). Five-year survival was 30% in those with left ventricular dysfunction versus 88% in those with normal function. No deaths occurred in patients without either ventricular aneurysm or systolic dysfunction versus 42% survival in patients having either one. Factors associated with decreased survival are shown in Table 20-6. Congestive heart failure at initial presentation and its occurrence during follow-up were the 2 historical features most strongly associated with a fatal outcome. In a multivariate model, initial congestive heart failure and the presence of either left ventricular aneurysm or systolic dysfunction ($P = 0.03$) were the only independent predictors of subsequent death.

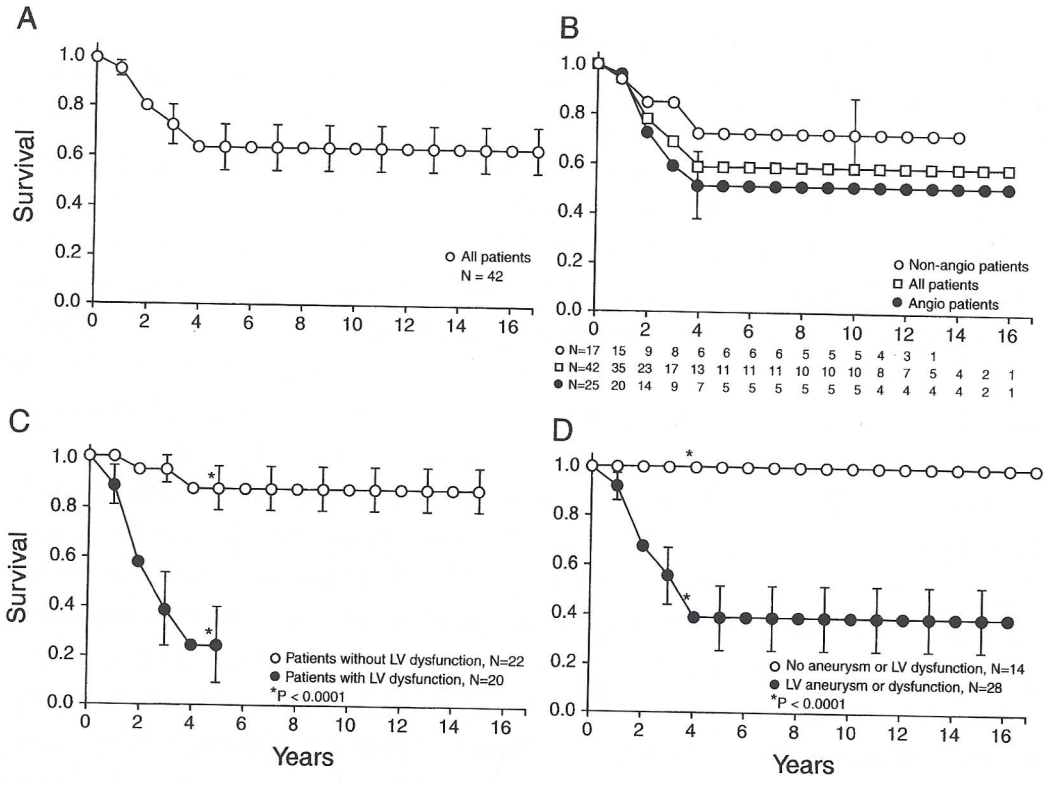

Fig. 20-12. Actuarial survival of Chagas heart disease patients seen in the United States. *A*, Survival of the entire group. *B*, Survival of patients having or not having coronary angiography (see text). *C*, Survival of patients with and without left ventricular (*LV*) dysfunction. *D*, Survival of patients with either LV aneurysm or dysfunction or without either. (*A* and *C* from Hagar and Rahimtoola.[38] By permission of Mosby-Year Book. *B* and *D* from Hagar and Rahimtoola.[37] By permission of the Massachusetts Medical Society.)

DIAGNOSIS OF CHAGAS HEART DISEASE OUTSIDE OF ENDEMIC AREAS

To correctly diagnose and treat Chagas heart disease, clinicians outside of endemic areas must become familiar with its protean manifestations and aware of its true prevalence. North American physicians may believe that Chagas heart disease does not exist there or that it is found only in persons from South America. With increased awareness on the part of North American clinicians, it is likely that Chagas heart disease will be recognized more often and earlier.

One reason for problems in diagnosis is that Chagas disease may mimic other forms of heart disease, particularly coronary artery disease, and commonly used noninvasive tests cannot reliably distinguish them. Chest pain is a frequent complaint of patients with Chagas disease. Although it is usually atypical of angina, it may prompt diagnostic evaluation. ECG changes suggestive of myocardial infarction or ischemia are quite typical of this disease. Further complicating matters, radionuclide perfusion scans are consistently abnormal in Chagas heart disease, with abnormalities consistent with myocardial infarction or

Table 20-6
Univariate Predictors of Survival in North American Patients With Chagas Heart Disease

Feature	Patients with feature, %	RR	*P**
Congestive heart failure on initial presentation	24	4.8	0.002†
Aneurysm or LV dysfunction present	67	2.4	0.002†
LV dysfunction present	48	5.8	0.001
ST-segment elevation present on ECG	14	2.8	0.002
Pathologic Q waves present on ECG	43	4.5	0.01
Congestive heart failure during follow-up	26	3.4	0.04
Left atrial enlargement	31	3.4	0.02
Moderate or severe mitral regurgitation present‡	19	2.5	0.007

	Mean of patients dying	Mean of patients surviving	*P*
LV end-diastolic volume index‡	200 ± 25 mL§	102 ± 8 mL	0.006
Left atrial dimension‡	47 ± 3 mm§	40 ± 2 mm	0.05

ECG, electrocardiogram; LV, left ventricular; RR, relative risk.
*From linear regression of survival time with log-rank test (n = 42).
†Variables independently predicting survival in multivariate model.
‡Mitral regurgitation greater than 1+ (1-4+ scale) by 2-D color Doppler echocardiography or cineventriculography (n = 42). Left atrial dimension by M-mode echocardiogram (n = 31). Mean ± SEM.
§Mean differences significant $P < 0.05$ by Student t test.
From Hagar and Rahimtoola.[38] By permission of Mosby-Year Book.

ischemia (or both). In fact, 55% of our patients had been treated previously by physicians for other presumed diagnoses, usually coronary artery disease, for periods up to 9 years. Although the clinical syndromes, ECG, and ventricular abnormalities in our North American patients do not differ from those in endemic countries, the clinical findings of Chagas heart disease usually are attributed to coronary artery disease or dilated cardiomyopathy in a country where these diseases are much more prevalent. Coronary angiography may be necessary to exclude atherosclerotic heart disease in nonendemic countries, especially in older patients and in those with segmental wall motion abnormalities.

Finally, the criteria for the diagnosis of Chagas disease in populations with a low prevalence of infection are problematic. Some patients with cardiac disorders have low-level positive or equivocal serologic tests for *T cruzi*, and others who have never resided in an endemic area have false-positive results. Such patients should not be considered to have definite Chagas heart disease. Additional serologic or parasitologic testing is useful in such cases. This emphasizes the importance of the case definition described above, which requires

epidemiologic, serologic, and clinical criteria to be met. Although not appropriate in all populations, the use of such a definition is essential in populations where the number of false-positive serologic results exceeds the number of cases of Chagas disease or where other forms of cardiomyopathy are far more frequent than Chagas heart disease.

TREATMENT

Management of patients with Chagas heart disease is mostly oriented toward treating and preventing its complications: congestive heart failure, atrioventricular block, thromboembolism, and malignant ventricular arrhythmias. The role of antiparasitic drugs in all phases of *T cruzi* infection has begun to expand as our understanding of the disease has increased, but many important questions about their use will remain unanswered until randomized trials can be done.

TREATMENT OF CONGESTIVE HEART FAILURE

Congestive heart failure in Chagas heart disease responds to digitalis, diuretics, and vasodilators as in heart failure due to other cardiomyopathic disorders. There is little evidence to suggest that outcome is improved with pharmacologic therapy, and the ominous prognosis associated with development of congestive heart failure has already been discussed. Angiotensin-converting enzyme inhibitors are useful to improve symptoms in patients with advanced Chagas cardiomyopathy and to reduce neurohormonal activation,[179,180] but there is no evidence that their use improves survival. Long-term anticoagulation therapy is almost certainly appropriate in patients with severe left ventricular dysfunction or left ventricular aneurysm, in view of the high incidence of thromboembolism and the morbidity that results from it. However, routine anticoagulation therapy is not often used in endemic areas because of socioeconomic factors, and controlled trials of its benefits are therefore not available. Second-generation β-blockers (bisoprolol, metoprolol CR/XL, or carvedilol) may be tried in those with chronic heart failure.

MANAGEMENT OF HEART BLOCK WITH PACING

Experience with permanent ventricular pacing in Chagas disease is extensive in South American tertiary care centers. In general, the symptomatic status and probably the longevity of patients with Chagas disease are improved by permanent ventricular pacing.[181] Single-chamber ventricular pacing is generally used, and dual-chamber or rate-responsive pacing offers little additional benefit for most patients.[182] Mortality in patients with permanent pacemakers depends mainly on the severity of the underlying myocardial disease and averages 5% per year.

MANAGEMENT OF VENTRICULAR ARRHYTHMIAS

Ventricular tachyarrhythmias are clearly the most serious and difficult to treat of the complications of Chagas disease, dubbed a "tachycardiomyopathy" by some authors.[183] At present, there is no consensus on the indications, efficacy, or choice of the available antiarrhythmic agents and treatments. What is generally agreed is that ventricular arrhythmias often are highly malignant, drug therapy is frequently disappointing, and none of the available agents is very effective at preventing arrhythmic events in patients with advanced Chagas heart disease.

Invasively guided antiarrhythmic drug therapy seems to offer a good method for risk stratification and drug selection in patients with symptomatic or high-grade ventricular arrhythmias (or both). Sustained ventricular tachycardia is inducible in more than 80% of patients with clinical sustained ventricular tachycardia and in 50% of those with nonsustained ventricular tachycardia or presenting with syncope; a prolonged HV interval is also found in a third.[184] Arrhythmias that are inducible frequently can be rendered noninducible by drug therapy,[185] which has been found to prolong survival.[186] However, only 29% of all patients studied were in this category. In the remainder, sustained ventricular tachycardia was noninducible or an effective drug could not be identified. Nonpharmacologic therapy or empiric therapy with amiodarone typically is used in such patients.

In our series, 9 of 15 patients studied with programmed ventricular stimulation (indications of nonsustained ventricular tachycardia in 6, syncope or near-syncope in 4, aborted sudden death in 3, and sustained ventricular tachycardia in 2) had inducible sustained ventricular tachycardia or ventricular fibrillation. They were treated with invasively guided antiarrhythmic therapy or, failing this, an implantable cardioverter defibrillator or left ventricular aneurysmectomy. There has been only 1 sudden death in this group. Two patients had inducible monomorphic ventricular tachycardia that terminated spontaneously; 1 of these had sudden death. Four patients had no inducible arrhythmia and were treated with empiric antiarrhythmic therapy; 3 of the 4 subsequently died suddenly. Three of 5 patients treated empirically with amiodarone subsequently died suddenly. This experience, in patients with advanced disease, emphasizes the highly malignant nature of the arrhythmias, the limitations of pharmacotherapy, the value of an invasively guided approach in some cases, and the need to treat high-risk individuals even if tachycardia is noninducible on electrophysiologic testing.

Essentially all known antiarrhythmic drugs have been used in patients with Chagas heart disease.[187] Unfortunately, these trials usually have been uncontrolled, noninvasively guided or empiric, and short-term. No drug has been shown to prolong survival in a randomized trial. In comparative studies using ambulatory electrocardiography, Haedo et al.[188] and Rosenbaum et al.[189] showed that amiodarone is the most effective of the antiarrhythmic agents and is well tolerated. Patients with malignant arrhythmias treated with amiodarone

and followed for 26 months with ambulatory ECG had few arrhythmic events.[190] In another study,[191] there was a low risk of recurrence or death when the ejection fraction was above 30%, but there was a 100% recurrence rate and an 80% mortality in functional class III-IV patients with an ejection fraction less than 30%. An implantable defibrillator would be more appropriate in such patients. Proarrhythmia appears to be common in patients with Chagas disease[192] and occurred in 4 of our patients. Proarrhythmia has been reported with all agents, including amiodarone.[193] This is emphasized by a report of 10 patients with Chagas heart disease who died during ambulatory ECG monitoring. In 6 of 10 patients, the terminal event was torsades de pointes due to type IA antiarrhythmic drugs.[194] These data support the concept that drug therapy cannot prevent arrhythmic death in patients with Chagas heart disease and highlight the need for a greater use of nonpharmacologic therapies.

The implantable cardioverter-defibrillator has been used successfully in small numbers of patients with Chagas heart disease.[195] Implantable defibrillator placement may be the optimum therapy for survivors of sudden cardiac death syndrome whose arrhythmia cannot be induced during programmed ventricular stimulation or cannot be suppressed with pharmacologic therapy. Nonsustained ventricular tachycardia is frequent in such patients, and additional antiarrhythmic drug therapy frequently is required to reduce inappropriate discharges. Chagas disease patients with implantable defibrillators respond similarly to coronary disease patients,[196] although they tend to experience more shocks.[197] The effect of defibrillator implantation on survival has not been determined. Successful transcoronary[198] and radio frequency catheter ablation[199,200] have been reported in a few cases. These therapies might be considered in patients with refractory arrhythmias who have normal left ventricular function and who are not candidates for aneurysmectomy or an implantable defibrillator.

Aneurysmectomy is an effective treatment for refractory ventricular arrhythmias if there is a localized aneurysm and left ventricular function is preserved.[201,202] Two patients in our series with discrete apical aneurysms and normal overall ventricular function were treated with aneurysmectomy for life-threatening ventricular arrhythmias. These patients subsequently remained free of events for 14 and 18 years until presenting with global ventricular dysfunction, congestive heart failure, and recurrent arrhythmias. This indicates the effectiveness of aneurysmectomy in this subset of patients and the relentlessly progressive nature of myocardial damage in Chagas disease.

ANTIPARASITIC THERAPY FOR *T CRUZI* INFECTION

The 2 best studied antitrypanosomal agents for treatment of *T cruzi* infection in humans are nifurtimox and benznidazole. The adult dose of benznidazole is 5 mg/kg per day for 30 to 60 days. Nifurtimox, which is no longer manufactured, is given in an adult dose of 10 mg/kg per day for 60 to 120 days, although gastrointestinal tract toxicity may limit the

duration of therapy. Both drugs may cause leukopenia and polyneuritis. Redox cycling of these agents generates reactive oxygen species toxic to *T cruzi* because it lacks antioxidant enzymes.[203] In the United States, benznidazole is available from the Centers for Disease Control.

The indications for antiparasitic therapy have changed considerably and continue to evolve. Antiparasitic therapy is indicated for 1) all patients with acute phase disease, 2) children and young adults with indeterminate phase disease, 3) adults in the indeterminate phase or with early manifestations of heart disease, 4) infection resulting from laboratory accidents or operations, and 5) reactivation of infection in transplant recipients and other immunosuppressed individuals. Use in those with established heart disease is uncertain.

Treatment with benznidazole or nifurtimox in the acute phase produces long-term negative xenodiagnosis in 90% of patients and negative serologic results in about 80%.[204] However, the rate of parasitologic cure can be as low as 20% in some highly resistant strains.[205] In early indeterminate phase infection, 58% to 62% of schoolchildren treated with benznidazole had negative serologic results after 3 to 4 years.[206,207] Persons who achieve negative serologic results and xenodiagnosis (or PCR) after treatment of acute disease can be considered cured of their *T cruzi* infection, and late end-organ disease does not appear to develop in such patients.

Things are more complicated in the chronic phase. Treatment in the chronic phase results in negative xenodiagnosis in 90% to 98% of cases[208] but rarely results in a negative serologic finding.[209] This represents persistent antibodies cross-reacting with antigenic determinants in intestinal flora or continuing parasitemia below the level of detection of xenodiagnosis. It is important to make this distinction; otherwise parasitologic cure cannot be ascertained. To overcome this limitation, investigators have used highly purified or recombinant *T cruzi* antigens, immunoabsorption of serum samples,[210] the complement-mediated lysis test,[211] or an enzyme-linked immunosorbent assay directed against a panel of anti-Galalpha epitopes[212] to determine parasitologic cure. Detection of *T cruzi* DNA by PCR may be the ideal approach to determine parasitologic cure.[125]

PCR demonstrated the elimination of parasitemia in 67% of patients in the chronic phase and treated with benznidazole, and it was more sensitive than repeated xenodiagnosis.[213] Thus, a third of individuals with persistently negative xenodiagnosis after treatment, who previously would have been considered cured, actually have persistent parasitemia. One study found that in none of the patients treated with benznidazole was the parasite eliminated.[214] In another study, 9 of 10 patients treated with benznidazole for acute disease had persistence of myocarditis on biopsy after 11 months, in spite of negative results of xenodiagnosis, and cardiac disease later developed in several.[215] Thus, the application of PCR and other methods has redefined parasitologic cure and demonstrated the frequent ineffectiveness of drug therapy.

In the chronic phase, evidence suggests that antiparasitic treatment might prevent late end-organ damage in humans, as it does in animals.[216,217] In chronically infected patients treated with benznidazole and followed for 8 years, cardiac disease developed much less frequently than in untreated patients.[218] The role of drug therapy to halt the progression of disease in patients with overt cardiac disease, however, is not well studied. Antiparasitic drugs might be expected to benefit patients with mild or moderate cardiac disease who have a life expectancy of at least several years, given the progressive nature of the cardiac damage, but this is speculative.

New and better antiparasitic drugs are needed. Many other agents have been used empirically to treat Chagas disease but have proven ineffective or excessively toxic. Ketoconazole, although minimally effective alone,[219] may enhance the effectiveness of benznidazole.[220] Allopurinol, which inhibits *T cruzi* purine metabolism, is modestly effective in vivo and in vitro against *T cruzi* and is well tolerated;[221] it may be useful in cases resistant to conventional agents. Thioridazine and other phenothiazines are highly effective antitrypanosomal agents.[222] Their neuropsychiatric side effects preclude their clinical use, but they may serve as a starting point for new drug design. Newer molecular modeling techniques[223] have led to development of a highly effective inhibitor of a *T cruzi* cysteine protease that is undergoing clinical trials.[224]

Attempts to develop an effective human vaccine to *T cruzi* have been unsuccessful. Such a vaccine would be useful in endemic areas where transmission of *T cruzi* still occurs. One vaccine has been partially protective in dogs, but its effectiveness is short-lived and incomplete.[225]

T CRUZI AND IMMUNOSUPPRESSION

Given the importance of host immune mechanisms, especially $CD4^+$ lymphocytes, in protection against *T cruzi*, it is not surprising that immunosuppressive therapy may lead to reactivation or progression of clinical disease, as seen in experimental models.[226] In humans such reactivation may be fulminant or may have unusual manifestations such as brain abscess or panniculitis. Clinically evident reactivation is uncommon in patients undergoing immunosuppressive therapy for hematologic malignancies and collagen vascular diseases; thus, routine administration of prophylactic antiparasitic therapy is not recommended. However, corticosteroid treatment is known to increase levels of parasitemia,[227] and monitoring of parasitemia during treatment may be advisable in some patients.

After renal and bone marrow transplantation in patients with chronic *T cruzi* infection, reactivation occurs in 20% to 25%.[228] Reactivation is diagnosed more reliably by measurement of parasitemia than by serologic testing, which is frequently negative.[229] In such patients, it is recommended that serologic status and parasitemia be monitored routinely and any parasitemia or change in serologic status be treated promptly before clinical disease

develops.[230] Recipients of organs from *T cruzi*-infected donors have a relatively low rate of infection; they should also be monitored and treated as needed.

CARDIAC TRANSPLANTATION

In transplant centers that have significant populations of patients with Chagas disease, Chagas disease is not considered a contraindication to cardiac transplantation, although special concerns must be addressed. Immunosuppression frequently results in acute reactivation of disease, even if antiparasitic therapy is administered prophylactically.[231] Such infection may be particularly fulminant and is often associated with characteristic skin lesions[232] or central nervous system disease.[233] Trypanosomes frequently are present in endomyocardial biopsy specimens in such cases, but standard serologic tests may not parallel the activity of the disease. This acute reactivation generally responds well to treatment with a short course of nifurtimox or benznidazole. In view of the acute toxicity of the available antiparasitic agents, most centers administer such therapy to cardiac transplant patients only when endomyocardial biopsies or clinical findings suggest reactivation of disease.

Several small series found excellent long-term survival in Chagas heart disease patients undergoing cardiac transplantation.[234,235] However, there is a higher incidence of lymphoid and solid tumors in patients who have Chagas disease than in other transplant patients.[236] Careful regulation or reduction of the level of immunosuppression may reduce the incidence of this complication.

CONCLUSION

Chagas disease is a major public health problem in Central and South America that is only recently being controlled through intensive public health measures and improved housing. Cardiac involvement is its most frequent and serious manifestation. As a result of immigration, Chagas heart disease is now encountered outside of endemic countries, especially in the United States.

The manifestations of Chagas heart disease are diverse and are the result of progressive damage to the myocardium, extracellular matrix, cardiac autonomic innervation, and possibly the coronary microvessels. Chagas heart disease often mimics ischemic heart disease and commonly used noninvasive tests cannot reliably distinguish them in populations where the latter is far more common. Prognosis depends largely on the extent of myocardial damage and is poor when left ventricular dysfunction or aneurysm or both are present. Ventricular arrhythmias in these patients are exceptionally malignant. Aggressive public health measures and advances in the understanding of the pathobiology of the disease hold the promise that this fascinating and deadly disease can be eliminated.

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