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Special Article

Cardiac Manifestations of Parasitic Infections Part 2: Parasitic Myocardial Disease

Carlos Franco-Paredes, M.D., M.P.H.,*,§ Nadine Rouphael, M.D.,* José Méndez, M.D.,† Erik Folch, M.D., M.SC.,*,** Alfonso J. Rodríguez-Morales, M.D.,‡ José Ignacio Santos, M.D.,§ J. W. Hurst, M.D.†

*Department of Medicine, Division of Infectious Diseases; †Department of Medicine, Division of Cardiology, Emory University School of Medicine, Atlanta Georgia, USA; ‡Instituto Experimental José Witremundo Torrealba, Universidad de Los Andes, Trujillo, Venezuela, USA, and the §Hospital Infantil de México, Federico Gómez, México City, Mexico

Summary

This is part two of a three-part series discussing parasites of the heart. In this section, we present an overview on parasitic diseases predominantly involving the myocardium.

Key words: heart, parasites, Chagas disease, pericardium, myocardium

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Parasitic Myocardial Disease

Toxoplasmosis

Humans become infected with *Toxoplasma gondii* (*T. gondii*) either by eating undercooked infected beef or pork, fecal-oral transmission from feline feces, organ transplantation, blood transfusion, or transplacental transmission.[1–8] The clinical expression of toxoplasmosis depends on the level of immunity in the human host.[1–4] In immunocompetent patients, toxoplasmosis can be asymptomatic, or presents in 10–20% of cases as a mononucleosis-like illness.[1,2] Latent infection is due to cyst formation that subsequently reactivates in immunocompromised persons.[1,8–14] Among these populations, toxoplasmosis often presents in the form of encephalitis or chorioretinitis.[1,8,9]

Myocarditis, pericardial effusion, constrictive pericarditis, arrhythmias and congestive heart failure have been described in patients infected with *T. gondii*.[5,6,10] In patients with the acquired immunodeficiency syndrome (AIDS), the heart is the second most commonly affected organ after the brain.[1,10,12] Prevalence varies according to various studies, and diagnosis is usually made postmortem since cardiac involvement is usually clinically silent.[10,12] Approximately 12—22% of AIDS patients had evidence of endomyocardial involvement by *T. gondii* at autopsy.[10–12] Prevalence of cardiac toxoplasmosis confirmed at autopsy in the highly active antiretroviral era has been reported to be less than 10%.[1,10–12] *T. gondii* associated myocarditis can also occur in transplant patients either due to a reactivation or to *de novo* infection from a seropositive donor to a seronegative recipient.[4,7–9] Indeed, toxoplasmosis is the most commonly reported parasitic disease occurring after heart transplantation.[5] Disseminated toxoplasmosis with associated myocarditis can lead to a fatal outcome if no prior prophylaxis is given in transplant patients.[11,14] The diagnosis of toxoplasmosis relies on serology or identification of the bradyzoites in myocardial tissue.[1,8,10,14]

The treatment of choice is based on a combination of pyrimethamine and sulfadiazine or pyrimethamine and clindamycin.[1,11]

Address for reprints:

Carlos Franco-Paredes, M.D., M.P.H.
Division of Infectious Diseases
69 Jesse Hill Jr. Drive
Atlanta GA 30303, USA
e-mail: cfranco@sph.emory.edu

**Current affiliation for Dr. Fulch is the Division of Pulmonary and Critical Care, Cleveland Clinic Foundation, Cleveland, OH, USA.

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Trichinellosis

Trichinellosis is caused by *Trichinella spiralis* (*T. spiralis*) and has a worldwide distribution. Humans become infected when eating undercooked contaminated meat.[15–17]

The clinical picture of trichinellosis is directly related to the number of larva ingested and manifesting with two clinical stages: the intestinal stage and the muscular stage.[15–17] Larval migration into the muscles can cause periorbital and facial edema, subungal, conjunctival and retinal hemorrhages, myalgias, weakness, and fever.[18–20] The tropism of *T. spiralis* for striated muscle may lead to involving the myocardium in 21–75% of infected patients.[18,19] Complications such as cardiac arrhythmias are considered the most common cause of death associated with trichinellosis.[19,20] *T. spiralis* associated myocarditis is not caused by the direct larval invasion of the myocardium with encystation but is likely induced by an eosinophilic-enriched inflammatory response resulting in eosinophilic myocarditis similar to the pathogenic process associated with tropical endomyocardial fibrosis.[18–20] In addition, pericardial effusions have also been reported during *T. spiralis infection.*[18] The clinical suspicion of trichinellosis is based on the epidemiology associated with the typical clinical presentation and the presence of eosinophilia; confirmation is based on serology and muscle biopsy.[15,16] Electrocardiographic findings are considered nonspecific. According to a large study which included 560 patients, 59 had myocardial damage with two-thirds manifesting repolarization disturbances and one-third presented depolarization disturbances.[19,20]

Treatment consists of the administration of albendazole or mebendazole in conjunction with steroids for severe cases.[15–19]

Chagas' Disease

Trypanosoma cruzi (*T. cruzi*) is an obligate intracellular parasite that causes American trypanosomiasis or Chagas' disease, a chronic and debilitating parasitic infection that affects millions of people in Latin America and is increasingly reported in nonendemic settings due to reactivation among immigrant populations.[21,22] Approximately 25% of the population living in Latin America lives at risk of acquiring the infection.[21] The hematophagous reduviidae bugs responsible for transmitting *T. cruzi* to humans usually live in cracks and crevices of poor quality houses in rural areas (Fig. 1).[21,22] These insects emerge at night to bite and suck blood. The feces of these insects contain vast amounts of *T. cruzi*, which can enter the wound left after the blood meal, usually when it is scratched or rubbed.[21,22] In addition, Chagas' disease can also be transmitted through blood transfusions, transplants, or perinatally.[23–26] Recently, an outbreak of foodborne Chagas' disease in Brazil showed another form of transmission.[27]

The pathogenesis of myocarditis and subsequent myocardial dysfunction during *T. cruzi* infection is still a matter of intense debate. It has been postulated that a repetitive inflammatory response resulting in progressive neuronal damage, microcirculatory alterations and heart matrix deformation are the main pathogenic features in Chagas cardiomyopathy.[28–30] However, recent evidence has suggested that the chronic chagasic cardiomyopathy appears to be a continuous process associated with the persistence of the parasites in the myocardium.[21,28,29] Despite the demonstration of a low number of parasites during the chronic phases of Chagas cardiomyopathy, both polymerase chain (PCR)-based assays, and histological analysis have confirmed the presence of amastigotes

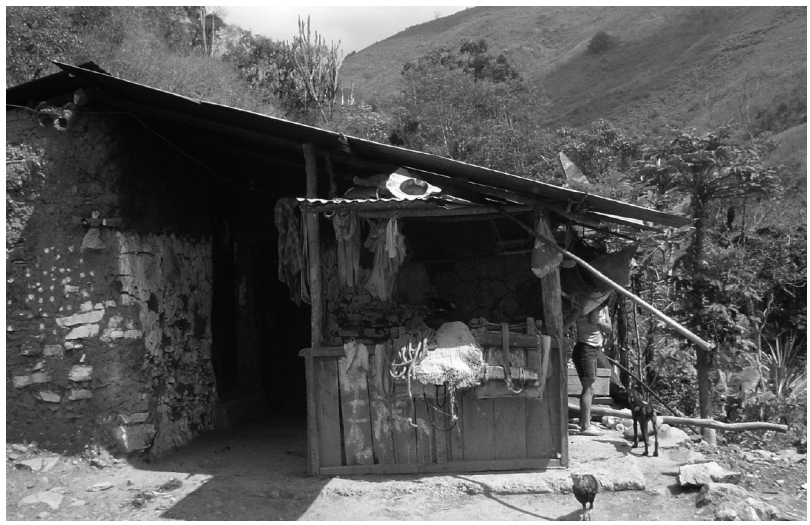

FIG. 1 Human dwellings conducive for transmission of Chagas' disease in endemic areas (rural area in Venezuela).

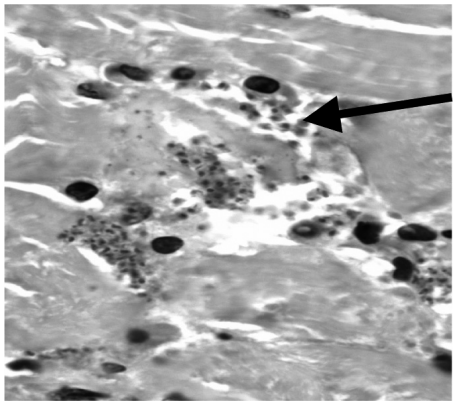

FIG. 2 *Trypanosoma cruzi* amastigotes (arrow) in the myocardium in the mouse animal model of Chagas disease cardiomyopathy.

in these patients possibly leading to irreversible long-term consequences of the megasyndromes or chagasic cardiomyopathy[28–31] (Fig. 2). These findings are further supported by the frequent reactivation of Chagas' disease among HIV-infected individuals.[1] Therefore, there is a growing consensus that elimination of *T. cruzi* in myocardial tissue is a prerequisite to halt the progression of the disease.[21,28,29] Furthermore, a role for parasite genetic variability in the spectrum of clinical disease associated with Chagas' disease is emerging. *T. cruzi* has been divided into two highly divergent genetic subgroups, lineages 1 and 2, isolated from humans, insect vectors, and sylvatic mammals.[30] The evolutionary origin of these two lineages and the clinical importance of their identification have been the subject of intense debate.[21,29,30]

The initial descriptions of the cardiac involvement in Chagas disease were completed by Carlos Chagas in the early 20th century.[22] In his early descriptions, he eloquently described the occurrence of significant cardiac conduction abnormalities, arrhythmias, and sudden cardiac death in his patients.[22] We now recognize that Chagas' disease has three different clinical stages. The acute stage follows the entry and invasion of the bloodstream by the protozoan parasite.[1,21–23] After the acute phase, the infected individual enters the chronic stage, which has a variable duration usually more than 10 or 20 years. At its end, the disease may follow three different paths: (i) development of megasyndromes; (ii) myocarditis with associated fibrosis which is considered the terminal form with highest mortality; (iii) or individuals may remain asymptomatic for the rest of their lives.[1,32] The cardiomyopathy associated with Chagas disease manifests as a biventricular failure with both systolic and diastolic dysfunction and associated cardiac arrhythmias or sudden cardiac death.[1,32] Sudden cardiac death accounts for 55–65% of deaths in Chagas' disease.[1,33,34] Pulmonary or systemic embolism arising from mural thrombi in dilated cardiac chambers may be identified at autopsies of patients who died of Chagas' disease.[34] Chagas' disease has become an important opportunistic infection among patients with HIV-infection or other types of immunosuppression such as organ transplantation causing reactivation of chronic latent *T. cruzi* infection and manifested as myocarditis or meningoencephalitis.[1]

The diagnosis of *T. cruzi* infection is made by epidemiological, clinical and serological criteria.[35–38] ECG findings are numerous but consist mainly of bundle-branch blocks and various degrees of atrioventricular blocks (Fig. 3).[35,36] Echocardiograms may reveal apical aneurysms, segmental wall motion abnormalities or diffuse hypokinesis.[35,36] Brain natriuretic peptide measurements could be a useful method to screen patients with Chagas' disease.[38]

Treatment of Chagas' disease is directed at both eradicating the parasite and targeting the cardiac manifestations of the disease.[1,21,32,39,40] Benznidazole and nifurtimox are used in the acute phase and in reactivation under immunosuppressive conditions.[1,21,32] Chemotherapy can shorten the acute phase and achieve a parasitological cure in 50% of the cases but causes significant toxicity.[1,21,32] However, there is no evidence that drug treatment of persons in the chronic phase can alter the natural history of the disorder.[32,39,40] There are many new compounds being considered that have discernible activity against *T. cruzi,* which appear to have better safety profiles and efficacy.[21]

Heart failure and arrhythmias in Chagas'disease are treated similar to other etiologies of heart failure.[1,32] Cardiac transplantation has been successfully performed in selected patients and survival was better compared to patients transplanted for other types of cardiac disease.[41] Results from dynamic cardioplasty and partial ventriculectomy are controversial.[42] Patients at high risk of sudden death can benefit from implantable cardioverter-defibrillator.[43]

African Trypanosomiasis

There are two forms of African trypanosomiasis: the West African form caused by *T. brucei gambiense* (*T. b. gambiense*) and the East African form caused by *T. brucei rhodesiense* (*T. b. rhodesiense*).[44–46] Both subspecies are indistinguishable but cause diseases that differ in their epidemiology, clinical presentation, and prognosis.[45,46] Humans are infected after they are bitten by a tsetse fly. Travelers can become exposed to African trypanosomiasis during safari trips.[44]

African trypanosomiasis manifests in three clinical stages.[46,47] The first stage is characterized by a painful chancre at the site of the inoculation followed by a Hemolymphatic stage, and subsequently to a third stage of meningoencephalitis. Infection with *T. b. gambiense* is a slowly progressive infection where no symptoms can be noted for months to years.[44–46] In contrast,

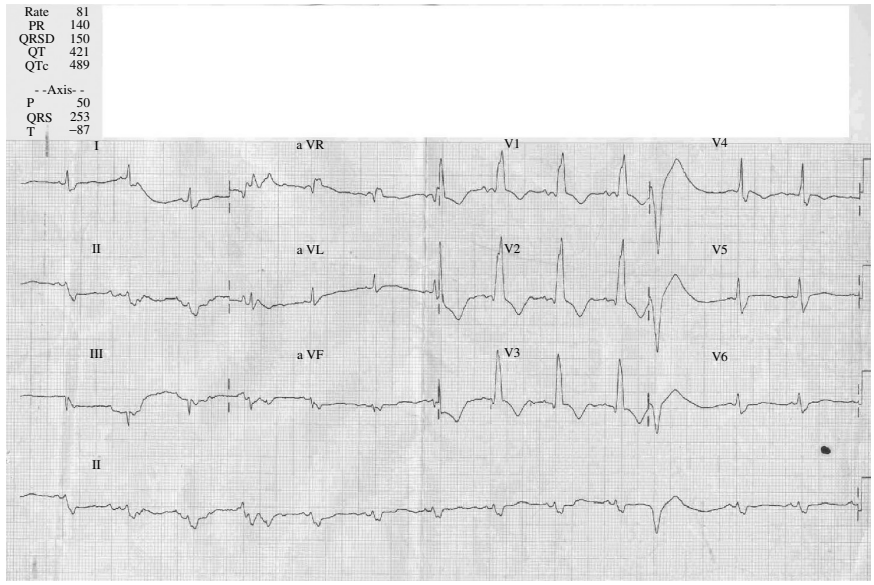

FIG. 3 Electrocardiogram from a patient with Dilated Cardiomyopathy due to Chagas' disease in Venezuela showing a complicated right bundle branch block ** and premature ventricular complexes. ** The conduction abnormality is considered to be complicated because the duration of the QRS interval is greater than 0.12 s, the mean QRS vector is directed at least—170° in the frontal plane and more than 50° anteriorly; and there is a primary T wave abnormality. This type of EKG tracing is commonly seen in various types of cardiomyopathy not exclusive of Chagas' disease.

T. b. rhodesiense infection tends to progress rapidly to the third stage of involvement.[45–48]

Myocarditis, with occasional pancarditis may occasionally develop during the hemolymphatic stage, leading to arrhythmias and heart failure with *T. b. rhodesiense* infection.[45–48] The pathophysiology of cardiac involvement in African trypanosomiasis is secondary to endarteritis and fibrosis caused by perivascular infiltration by trypanosomes and lymphocytes.[46,47] ECG abnormalities are present in half the cases sometimes manifested as cardiac conduction delays. A chest radiograph may show cardiomegaly and echography can identify ventricular dilatation and/or pericardial thickening.[45–48] Diagnosis is made by visualization of the trypanosomes from chancre fluid, lymph node aspirates, blood or cerebrospinal fluid.[44,46,47] Choices for treatment of African trypanosomiasis depend on the type of trypanosomiasis and on the clinical stage.[45,46]

References

1. Centers for Disease Control and Prevention. Treating opportunistic infections among HIV-1 Adults and Adolescents. *MMWR* 2004;53(RR15):1–112
2. Matturri L, Quattrone P, Varesi C, Rossi L: Cardiac toxoplasmosis in pathology of acquired immunodeficiency syndrome. *Panminerva Med* 1990;32(4):194–196
3. Hofman P, Drici MD, Gibelin P, Michiels JF, Thyss A: Prevalence of toxoplasma myocarditis in patients with the acquired immunodeficiency syndrome. *Br Heart J* 1993;70(4):376–381
4. Ryning FW, McLeod R, Maddox JC, Hunt S, Remington JS: Probable transmission of *Toxoplasma gondii* by organ transplantation. *Ann Intern Med* 1979;90(1):47–49
5. Gallino A, Maggiorini M, Kiowski W, Martin X, Wunderli W, et al.: Toxoplasmosis in heart transplant recipients. *Eur J Clin Microbiol Infect Dis* 1996;15(5):389–393
6. Mayes JT, O'Connor BJ, Avery R, Castellani W, Carey W: Transmission of *Toxoplasma gondii* infection by liver transplantation. *Clin Infect Dis* 1995;21(3):511–515
7. Reynolds ES, Walls KW, Pfeiffer RI: Generalized toxoplasmosis following renal transplantation. Report of a case. *Arch Intern Med* 1966;118(4):401–405
8. Slavin MA, Meyers JD, Remington JS, Hackman RC: *Toxoplasma gondii* infection in marrow transplant recipients: a 20 year experience. *Bone Marrow Transplant* 1994;13(5):549–557
9. Mary AS, Hamilton M: Ventricular tachycardia in a patient with toxoplasmosis. *Br Heart J* 1973;35(3):349–352
10. Politi Okoshi M, Rubens Montenegro M: Pathology of the heart in AIDS. Study of 73 consecutive necropsies. *Arq Bras Cardiol* 1996;66(3):129–133
11. Wreghitt TG, Gray JJ, Pavel P, Balfour A, Fabbri A, et al.: Efficacy of pyrimethamine for the prevention of donor-acquired *Toxoplasma gondii* infection in heart and heart-lung transplant patients. *Transpl Int* 1992;5(4):197–200
12. Hoffman P, Bernard E, Michiels JF, Thyss A, Le Fichoux Y, et al.: Extracerebral toxoplasmosis in the acquired immunodeficiency syndrome (AIDS). *Pathol Res Pract* 1993;189(8):894–901
13. Sahasrabudhe NS, Jadhav MV, Deshmukh SD, Holla VV: Pathology of Toxoplasma myocarditis in acquired immunodeficiency syndrome. *Indian J Pathol Microbiol* 2003;46(4):649–651
14. Wagner FM, Reichenspurner H, Uberfuhr P, Weiss M, Fingerle V, et al.: Toxoplasmosis after heart transplantation: diagnosis by endomyocardial biopsy. *J Heart Lung Transplant* 1994;13(5):916–918
15. Moorhead A, Grunenwald PE, Dietz VJ, Schantz PM: Trichinellosis in the United States, 1991–1996: declining but not gone. *Am J Trop Med Hyg* 1999;60(1):66–69
16. Lazarevic AM, Neskovic AN, Goronja M, Golubovic S, Komic J, et al.: Low incidence of cardiac abnormalities in treated trichinosis: a prospective study of 62 patients from a single-source outbreak. *Am J Med* 1999;107(1):18–23
17. Andy JJ, O'Connell JP, Daddario RC, Roberts WC: Trichinosis causing extensive ventricular mural endocarditis with superimposed thrombosis. Evidence that severe eosinophilia damages endocardium. *Am J Med* 1977;63(5):824–829

18. Kirschberg GJ: Trichinosis presenting as acute myocardial infarction. *Can Med Assoc J* 1972;106(8):898–899
19. Compton SJ, Celum CL, Lee C, Thompson D, Sumi SM, et al.: Trichinosis with ventilatory failure and persistent myocarditis. *Clin Infect Dis* 1993;16(4):500–504
20. Siwak E, Dron D, Pancewicz S, Zajkowska J, Snarska I, et al.: Changes in ECG examination of patients with trichinosis. *Wiad Lek* 1994;47(13–14):499–502
21. Urbina JA, Docampo R: Specific chemotherapy of Chagas disease: controversies and advances. *Trends Parasitol* 2003;19(11):495–501
22. Punukollu G, Gowda RM, Khan IA: Early twentieth century descriptions of the Chagas heart disease. *Int J Cardiol* 2004;95:347–349
23. de Faria JB, Alves G: Transmission of Chagas' disease through cadaveric renal transplantation. *Transplantation* 1993;56(6): 1583–1584
24. Gurtler RE, Segura EL, Cohen JE: Congenital transmission of *Trypanosoma cruzi* infection in Argentina. *Emerg Infect Dis* 2003;9(1):29–32
25. Ferreira MS, Nishioka Sde A, Silvestre MT, Borges AS, Nunes-Araujo FR, et al.: Reactivation of Chagas' disease in patients with AIDS: report of three new cases and review of the literature. *Clin Infect Dis* 1997;25:1397–1400
26. Barcan L, Lunao O, Clara L, Sinagra A, Valledor A, et al.: Transmission of *T. Cruzi* infection via liver transplantation to a non reactive recipient for Chagas' disease. *Liver Transpl* 2005;11(9):1112–1116
27. ProMED-mail. Trypanosomiasis, foodborne - Brazil (Santa Catarina) ProMED-mail 2005; 24 Mar: 20050324.0847. <http://www.promedmail.org>. Accessed December 31, 2006
28. Machado FS, Koyama NS, Carregaro V, Ferreira BR, Milanezi CM, et al.: CCR5 plays a critical role in the development of myocarditis and host protection in mice infected with *Trypanosoma cruzi*. *J Infect Dis* 2005;191(4):627–636
29. Añez N, Carrasco H, Parada H, Crisante G, Rojas A, et al.: Myocardial parasite persistence in chronic chagasic patients. *Am J Trop Med Hyg* 1999;60(5):726–732
30. Elias MC, Vargas N, Tomazi L, Pedroso A, Zingales B, et al.: Comparative analysis of genomic sequences suggests that *Trypanosoma cruzi* CL Brenner contains two sets of non-intercalated repeats of satellite DNA that correspond to *T. cruzi* I and *T. cruzi* II types. *Mol Biochem Parasitol* 2005;140:221–227
31. Lages-Sila E, Crema E, Ramirez LE, Macedo AM, Pena SD, et al.: Relationship between *Trypanosoma cruzi* and human chagasic megaesophagus: blood and tissue parasitism. *Am J Trop Med Hyg* 2001;65(5):435–441
32. Pinto Dias JC: The treatment of Chagas disease (South American trypanosomiasis). *Ann Intern Med* 2006;144(10):772–774
33. Rassi A Jr, Rassi SG, Rassi A: Sudden death in Chagas' disease. *Arq Bras Cardiol* 2001;76(1):75–96
34. Samuel J, Oliveira M, Correa De Araujo RR, Navarro MA, Mucillo G: Cardiac thrombosis and thromboembolism in chronic Chagas' heart disease. *Am J Cardiol* 1983;52(1):147–151
35. Garzon SA, Lorga AM, Nicolau JC: Electrocardiography in Chagas' heart disease. *Sao Paulo Med J* 1995;113(2):802–813
36. Scanavacca M, Sosa E: Electrophysiologic study in chronic Chagas' heart disease. *Sao Paulo Med J* 1995;113(2):841–850
37. Ferreira AW, de Avila SD: Laboratory diagnosis of Chagas' heart disease. *Sao Paulo Med J* 1995;113(2):767–771
38. Ribeiro AL, dos Reis AM, Barros MV, de Sousa MR, Rocha AL, et al.: Brain natriuretic peptide and left ventricular dysfunction in Chagas' disease. *Lancet* 2002;360(9331):461–462
39. de Andrade AL, Zicker F, de Oliveira RM, Almeida Silva S, Luquetti A, et al.: Randomised trial of efficacy of bensnidazole in treatment of early *Trypanosoma cruzi* infection. *Lancet* 1996;348:1407–1413
40. Villar JC, Marin-Neto JA, Ebrahim S, Yusuf S. Trypanocidal drugs for chronic asymptomatic *Trypanosoma cruzi* infection. *Cochrane Database Syst Rev* 2002;1;CD003463
41. Bocchi EA, Fiorelli A: The paradox of survival results after heart transplantation for cardiomyopathy caused by *Trypanosoma cruzi*. First Guidelines Group for Heart Transplantation of the Brazilian Society of Cardiology. *Ann Thorac Surg* 2001;71:1833
42. Moreira LF, Seferian P, Bocchi EA, Pego-Fernandes PM, Stolf NA, et al.: Survival improvement with dynamic cardiomyoplasty in patients with dilated cardiomyopathy. *Circulation* 1991;84(5 Suppl 1):III296–III302
43. Rodriguez H, Munoz M, Llamas G, Iturralde P, Medeiros A, et al.: Automatic, implantable cardioverter-defibrillator in a patient with chronic Chagas cardiopathy and sustained ventricular tachycardia. *Arch Inst Cardiol Mex* 1998;68(5):391–399
44. Sinha A, Grace C, Alston WK, Westenfeld F, Maguire JH: African trypanosomiasis in two travelers from the United States. *Clin Infect Dis* 1999;29:840
45. Moore A: Prospects for improving African trypanosomiasis chemotherapy. *J Infect Dis* 2005;191:1793–1796
46. Schmid C, Richer M, Bilenge CMM, Josenando T, Chappuis F, et al.: Effectiveness of a 10-day melarsoprol schedule for the treatment of late-stage human African trypanosomiasis: confirmation from a multinational study (IMPAMEL II). *J Infect Dis* 2005;191:1922–1931
47. Bertrand E: Cardiac involvement in human African trypanosomiasis. *Med Trop (Mars)* 1987;47(1):91–93
48. Jones IG, Lowenthal MN, Buyst H: Electrocardiographic changes in African trypanosomiasis caused by *Trypanosoma brucei* rhodesiense. *Trans R Soc Trop Med Hyg* 1975;69(4):388–395