

Chagas disease: State-of-the-art of diagnosis and management

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Abstract

Chagas' disease or American trypanosomiasis, is a potentially lethal parasitic zoonosis prevalent and endemic only in Latin America, caused by the flagellate protozoa Trypanosoma cruzi. It has 3 different stages, acute, indeterminate and chronic phase, with the chance of an etiological approach in the first stage and pharmacological and non-pharmacological treatment in the chronic phase. There are five main clinical forms of chronic chagasic cardiomyopathy: indeterminate, arrhythmogenic (predominantly dromotropic and extrasystolic), with ventricular dysfunction, thromboembolic and mixed forms. There are several diagnostic tests at the different stages, however, the ECG is the method of choice in longitudinal population studies in endemic areas because it is simple, with a low cost and a good sensitivity. Microscopic examination or parasitological diagnosis in the acute phase or immunodiagnostic tests are used to confirm the disease. The antiarrhythmic drug amiodarone, the most frequently prescribed agent for symptomatic ventricular arrhythmia treatment of Chagas' disease patients, has also recently been shown to have antifungal activity. Cardiac device implantation is very common, and chronic Chagas disease patients require pacemaker implantation at a younger age in contrast with patients with other cardiac pathologies. In summary, Chagas disease is a social disease, endemic in Latin America and shows different prevalence rates in Latin American countries. (Cardiol J 2008; 15: 493–504)

Key words: Chagas' disease, American trypanosomiasis, diagnosis, management

Introduction

Chagas' disease or American trypanosomiasis, is a potentially lethal parasitic zoonosis prevalent and endemic only in Latin America. The entity constitutes an important public health problem in most of the Latin American countries. The illness is caused by the flagellate protozoa *Trypanosoma cruzi* (*T. cruzi*). This parasite belongs to the Kinetoplastida order and the Trypanosomatidae family. It has several vulgar names: vinchuca, barbeiro, kissing bug, cone-nosed bug, chupança, chinchorro and benchuca.

The disease has an incubation or asymptomatic period followed inconstantly by three clinical stages: acute or primary infection, undetermined or latent phase and chronic stage.

Incubation or asymptomatic period

Incubation period lasts approximately seven to ten days in cases of vectorial contamination because metacyclic trypanomastigotes are more active. In these cases, the infection is transmitted via the feces of blood-sucking insect vectors (wild cycle)

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and human disease results from the colonization of the human habitat by some vector species (domestic cycle).

Incubation period duration is one month in cases of transfusion contamination because circulating trypanomastigotes have lesser capacity to invade the cells.

The three clinical stages

Acute phase, primary infection, or first stage

Defined as the phase in which detection of blood parasites is possible, lasting from 1–3 months [1]. This stage occurs unrecognized in most cases and clinically apparent acute chagasic myocarditis may appear in less than 5% of the infected individuals, usually children living in endemic areas. The majority of the cases of acute myocarditis are mild and reversible. Autopsied cases of acute chagasic myocarditis are uncommon and correspond to exceptionally severe or fulminant forms showing diffuse myocardial damage with myocytolysis, degenerative changes of myocardial fibers and marked interstitial cellular infiltration. The mortality during the acute phase of cardiac Chagas' disease is around 5% of the cases and it is mostly related to myocarditis. The acute clinical manifestations of the infected individuals include fever, rash, lesion at the site of entry (Chagoma), muscular pain, sweating, swollen lymph nodes, hepatosplenomegaly, subcutaneous edema localized or generalized (40% of cases), meningitis signs, acute myocarditis and bronchopneumonitis [2]. These non-specific symptoms may often be confused with those of other common childhood illnesses. Specific anti-Chagasic therapy with trypanocide drugs is effective in acute phase [3].

Indeterminate stage or latent phase

A majority of the patients with Chagas' disease remain in the latent phase of disease for 10 to 30 years or even for life. The indeterminate stage begins between eight to ten weeks after the initial infection and may last for many years. In this stage people do not have symptoms and can carry the parasite for years without knowing it. About 20–30% of those infected will go on to develop the chronic form of the disease up to 10 or 30 years after they first contracted it. The ajmaline test and the endomyocardial biopsy are, probably, the most sensitive methods to unmask latent forms of chagasic myocarditis during the indeterminate stage [4].

Chronic phase

Myocardial involvement in this stage might present as cardiac autonomic dysfunction, myocar-

dial apoptosis, and myocardial fibrosis. This phase is mainly attributed to neuronal damage induced by immune and inflammatory processes elicited by the presence of *T. cruzi*.

Symptoms of biventricular heart failure are frequently observed with peripheral edema, hepatomegaly, and thromboembolic events.

Chronic Chagasic cardiomyopathy is an entity with several components: fibrosis, necrosis, vasculopathy, immunopathy, autonomic dysfunction, accumulative, progressive and diffuse myocarditis. It is characterized by [5]:

- **parasite-dependent myocardial damage** with reparative and reactive interstitial fibrosis. The cardiac conduction system is frequently damaged at numerous sites, the lesions including focal inflammatory infiltration with lymphocytes and extensive focal fibrotic degeneration in neighboring regions. These lesions involve myocytes, nerves and blood vessels [6];
- **microvascular disturbances** including necrotizing microvascular arteritis that leads to platelet thrombosis and subsequent hypoperfusion and foci of myocytolytic necrosis, which progressively destroy both myocardial contractile cells (myocytolysis) and the pacemaking/conduction system;
- **immune-mediated myocardial injury** due to cross-over autoimmune reaction, triggered against the MXT antigen of *T. cruzi*, which is homologous to myosin of cardiac structures;
- **autonomic nervous system derangements** of focal character, irregular distribution, variable and unpredictable;
- **extra-cardiac manifestations** include visceromegalies that are the most important digestive system manifestations of Chagas disease and characterized by motor disorders and dilation of organs such as esophagus and colon [7].

Classification of cardiac forms of Chagas disease

There are five main clinical forms of chronic chagasic cardiomyopathy: indeterminate, arrhythmogenic (predominantly dromotropic and predominantly extrasystolic), with ventricular dysfunction, thromboembolic and mixed forms.

- **Chronic indeterminate Chagas' disease:** The indeterminate form of Chagas' disease is defined by the absence of clinical, radiological and electrocardiographic manifestations of cardiac or digestive involvement in persons with

T. cruzi chronic infection. When submitted to advanced cardiovascular tests, these patients may present significant abnormalities [8]. The serum positive subjects have significantly higher serum concentrations of tumor necrosis factor (TNF) and nitric oxide (NO) than the controls and the cases of chronic Chagas disease have significantly higher serum concentrations of TNF and NO than the subjects with the indeterminate form of the disease. It therefore appears that the host's anti-oxidant responses (at least in terms of elevated concentrations of superoxide dismutase (SOD) a prime anti-oxidant enzyme, may inhibit inflammation during the indeterminate phase of Chagas' disease;

— **Arrhythmogenic:**

— dominant conduction defects: characteristic complete right bundle branch block (complete RBBB) associated with left anterior fascicular block (LAFB);

— dominant polymorphic premature ventricular contractions (PVCs) and/or ventricular tachycardia (VT). In implantable cardioverter defibrillator (ICD) recipients with Chagas cardiomyopathy, spontaneous monomorphic VT episodes are typically initiated by late-coupled PVCs, which often show a short-long-short sequence [9];

— both phenomena together;

— **With ventricular dysfunction:** Chronic dilated chagasic cardiomyopathy.

— **Thromboembolic forms:** Cardiac arrhythmias, congestive heart failure, apical aneurysm and mural thrombus are potential embolic factors that partially explain the genesis of chagasic stroke and pulmonary embolism. Chagasic cardiomyopathy is a neglected, frequently unrecognized, source of embolic stroke in South America [10]. It has also been termed "emboligenic cardiomyopathy" since arterial embolism is a very frequent complication. Embolic obstruction of a coronary artery may therefore well be the most probable cause of myocardial infarction in young people with Chagas' disease;

— **Mixed forms:** These cases present features of two or more forms described above.

Transmission modes of human disease

— Vectorial transmission via the feces of *Triatoma* represents 80% of cases. Under natural conditions, *T. cruzi* is transmitted by insects belonging to different species of *Triatoma*. An infected triatomine insect vector feeds on blo-

od and releases trypanomastigotes in its feces near the site of the bite wound;

— Transfusion of infected blood (5% to 20% of cases) [11]. Blood donor education, identification of putatively infected blood donors by questionnaire or serological screening tests, and methods of parasite inactivation may significantly reduce the transmission of *T. cruzi* by allogeneic blood transfusions [12].

— Transplacental or congenital transmission from pregnant woman to her baby: 2% to 10% of cases. Serological screening of pregnant women by rapid diagnostic tests and examination of babies born from serum positive mothers by hematocrit method at birth is a suitable strategy to detect and prevent congenital Chagas disease in non-endemic areas [13, 14].

— Oral transmission: consumption of uncooked food contaminated with feces of infected bugs. *T. cruzi* infection by oral route constitutes the most important mode of transmission in some geographical regions, as illustrated by reports on microepidemics and outbreaks of acute Chagas' disease acquired by ingestion of food contaminated with parasites from triatomine insects [15].

— Organ transplantation [16]. Chagas disease following solid-organ transplantation has occurred in Latin America, an in 2002 in the United States [17]. In areas of U.S. where there is a high number of immigrants from *T. cruzi* endemic countries, screening for anti-*Trypanosoma cruzi* donor antibodies may be beneficial [18].

— Accidental laboratory exposure [19].

Epidemiological aspects

The disease is endemic in Latin America, from the north of Mexico to the South of Argentina and Chile. The number of people with Chagas' disease worldwide is estimated to be about 16–18 million in 18 countries of Latin America [20]. There are 90,000,000 exposed and 120,000 new cases per year diagnosed in Latin America.

Mortality is around 45,000 to 50,000 people/year and the main cause of mortality is cardiac cardiomyopathy:

— ≈ 60% sudden cardiac death. Rarely, it may be the first manifestation of Chagas' disease. The causes are:

— ventricular fibrillation (VF),

— bradyarrhythmia,

— thromboembolism,

— rarely aneurysm rupture;

— ≈ 30% congestive heart failure;

Table 1. Different prevalence rates in Latin American countries.

Country	Infection prevalence rate
Bolivia	20% of population
Argentina	5–10%
Paraguay	5–10%
Honduras	5–10%
El Salvador	5–10%
Chile	1–5%
Colombia	1–5%
Equator	1–5%
Uruguay	1–5%
Brazil	1.3%
Mexico	< 1%
Nicaragua	< 1%

- ≈ 15% cerebral or pulmonary embolism;
- others (≈ 5%) include severe acute myocarditis, meningoencephalitis in the newborn, volvulus of the dilated sigmoid megacolon.

Prevalence in endemic Latin American countries

The Table 1 shows the different prevalence rates in Latin American countries.

It is estimated that ≈ 25% of individuals infected with *T. cruzi* will develop symptomatic heart disease at some point during their lives.

The beetles that transmit Chagas live in cracks in the walls and roofs of mud and straw housing, which are common in rural areas and poor urban slums in Latin America. Population movements from rural to urban areas in the 1970s and 80s brought Chagas' disease into cities, and it became an urban infection transmitted through blood transfusions. Blood banks reported *T. cruzi* infection rates ranging from 1.7% in Sao Paulo, Brazil, to 53% in Santa Cruz, Bolivia, where Chagas infection rates far exceeded those of HIV infection and hepatitis. Chagas disease is most common among the poorest and most vulnerable populations. Treatment of the disease has been systematically sidelined by national and regional health authorities.

Spain

In Barcelona, the immigrant population from Latin America with risk factors for American trypanosomiasis were screened for Chagas disease by immunofluorescence assay and 34% had positive tests [21].

USA

It is estimated that 100,000–675,000 immigrants from México and Central and South America are infected. In 2006, the first human case of insect-transmitted Chagas parasite in Louisiana was discovered [22] and there had only been five reported previously. The blood just began to be screened for the Chagas parasite in the U.S. in 2007. Actually, there are significant numbers of infected blood units identified.

Switzerland

Several cases have been recently diagnosed in Switzerland, where systematic screening of groups at risk should be implemented. As the vast majority of persons at risk belong to marginalized communities with limited access to health care, systematic screening and treatment of infected individuals represent a major challenge in order to interrupt the congenital transmission and improve the long-term prognosis [23].

Diagnostic methods

Laboratory tests

- **microscopic examination or parasitological diagnosis** (utility in the acute phase):
 - fresh anticoagulated blood,
 - thin and thick blood smears stained with Giemsa,
 - inoculation into mice,
 - culture in specialized media (NNN, LIT),
 - xenodiagnosis;
- **immunodiagnostic test:**
 - complement fixation test, Guerreiro-Machado reaction: an indirect method of laboratory diagnosis of American trypanosomiasis. When positive, this test remains so throughout life, thus being a good indicator of previous infection,
 - indirect hemagglutination,
 - indirect fluorescent assay (IFA),
 - radio-immunoassay (RIA),
 - enzyme-linked immunosorbent assay (ELISA).
- **molecular biology techniques: polymerase chain reaction (PCR):** it is a diagnostic tool for congenital Chagas' disease. Comparative analysis between both parasitological methods, on samples taken at birth, showed a higher sensitivity of PCR as compared to the microhematocrit [24].

Specific tests

Non-invasive cardiologic test:

- electrocardiogram,
- vectorcardiogram,

- chest X-ray,
- ambulatory ECG recording,
- cardiopulmonary metabolic exercise test,
- signal-averaged electrocardiogram,
- heart rate variability (HRV) or 24-hour HRV,
- QT-interval dispersion (QTd) [25, 26],
- T-wave alternans (TWA),
- transthoracic echocardiogram (TTE),
- transesophageal echocardiography (TEE) [27],
- real-time three-dimensional (3D) echocardiography (RT3DE),
- cardiac magnetic resonance imaging (MRI), gallium-67 myocardial uptake: it is an accurate and alternative method for the diagnosis of inflammatory process associated with chronic Chagas' cardiomyopathy [28].

Invasive cardiologic tests:

- electrophysiologic study with His Bundle recording. In chronic Chagasic cardiomyopathy among the electrophysiological findings, only the HV interval ≥ 70 ms is associated with cardiovascular events [29],
- electrophysiological programmed stimulation (EPS),
- endomyocardial biopsy (EMB).

Non-invasive non-cardiologic test:

- radiographic contrast study of the esophagus,
- radiographic study of the colon,
- radiographic contrast studies of the colon,
- esophageal endoscopy and manometry.

Importance of ECG in chronic Chagasic disease diagnosis

The ECG is the method of choice in longitudinal population studies in endemic areas because it is simple, with a low cost and a good sensitivity. The patient newly diagnosed with Chagas disease should undergo a medical history, physical examination, and resting 12-lead ECG with a 30 s lead II rhythm strip. If this evaluation is normal, no further testing is indicated; history, physical examination, and ECG should be repeated annually. If findings suggest Chagas heart disease, a comprehensive cardiac evaluation, including 24-hour Holter monitoring, echocardiography, and exercise testing, is recommended [30].

The ECG changes in chronic chagasic cardiomyopathy have prognostic value.

Rhythm. Sinus node dysfunction is manifested by persistent sinus bradycardia, sinoatrial (SA) node block of different degrees, sinus arrest and inappropriate chronotropic response in stress test. The corrected recovery time of the SA node and SA conduction time are frequently altered (18% to 30%). Chronic Chagas disease's patients with sinus node

dysfunction had higher prevalence of muscarinic agonist antibodies, independent of the presence of myocardial dysfunction [31].

Dromotropic alterations in the conduction system. The incidence of second degree type I or II block, trifascicular block and even total atrioventricular (AV) block are high.

The most frequent are cases of the first degree AV block, with broad QRS, which in 50% of cases are located in the AV node and the rest in the His-Purkinje system or in both.

Complete RBBB + LAFB, negative T wave and polymorphic PVCs are typical of Chagasic cardiomyopathy and occur in 25% of patients.

In the developed countries, the most important cause of left anterior fascicular block is coronary insufficiency, particularly the proximal involvement of the left anterior descending coronary artery, and in Latin America, Chagas disease [32].

Sustained VT (S-VT) or non sustained VT (NS-VT). The most frequent location of VT are infero-posterior and lateral regions, followed by septal and apical regions, and their main mechanism is reentry, involving fibrotic and/or aneurysmatic areas [33].

Risk markers of poor prognosis in chronic Chagasic heart disease:

- atrial fibrillation or flutter;
- complete RBBB and decreased ejection fraction;
- complete AV block;
- presence of anterior and inferior electrically inactive area;
- polymorphic PVCs or salvoes;
- NS-VT associated to decreased ejection fraction: mortality rate reached 80% in 13 years of follow up;
- presence of S-VT: mortality is close to 100% in five years.

Typical ECG of chronic Chagasic heart disease (Fig. 1)

Electrocardiographic diagnosis:

- **P wave:** difficult to visualize, which indicates intense fibrosis of atrial tissue;
- **LAFB:** extreme shift of QRS axis in the left superior quadrant, around -75° , qR pattern in I and VL, rS pattern in inferior leads with final broad S wave in V5 and V6;
- **complete RBBB:** triphasic QRS complex, rsr' type, from V1 to V3, broad final r wave in VR and wide final S wave in V5 and V6;
- **coupled PVCs;**
- **classical triad:** complete RBBB + LAFB + + polymorphic PVCs.



Figure 1. Typical ECG of chronic Chagasic heart disease.

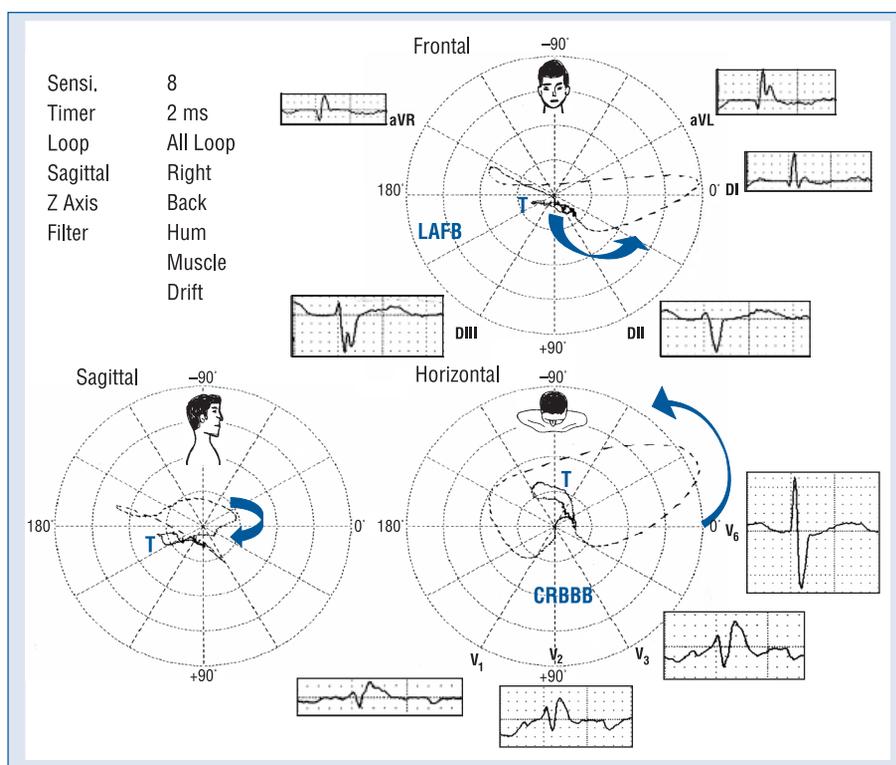


Figure 2. ECG/VCG correlation; CRBBB — complete right bundle branch block; LAFB — left anterior fascicular block.

ECG/VCG correlation (Fig. 2)

- Frontal plane typical QRS loop with LAFB pattern;
- Horizontal plane typical complete RBBB Grishman type (afferent limb of QRS loop located behind the X line);
- Final end conduction delay located in the right anterior quadrant;
- T loop directed to backwards;
- **Clinical diagnosis:** chronic Chagasic heart disease, dromotropic form;
- **Echocardiographic diagnosis:** telesystolic prolapse with mild escape;

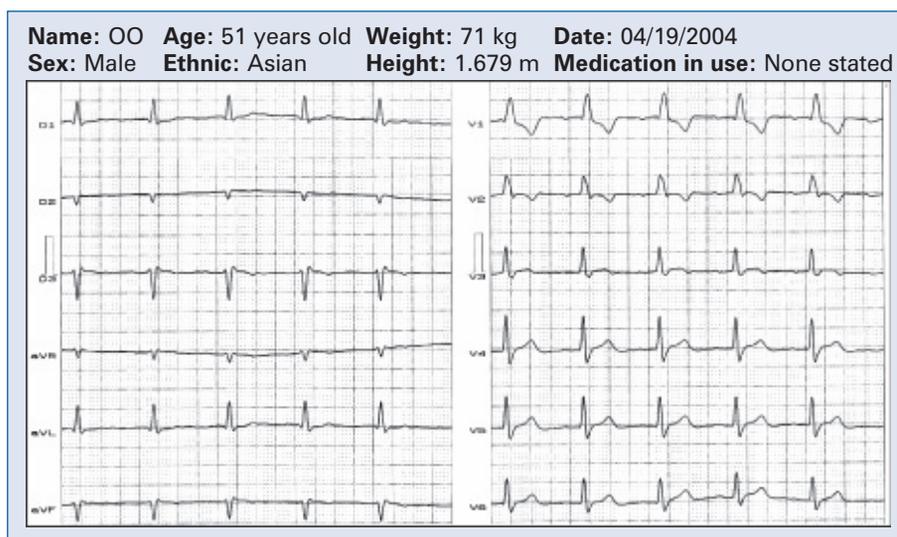


Figure 3. Clinical diagnosis: chronic Chagasic heart disease, dromotropic form.

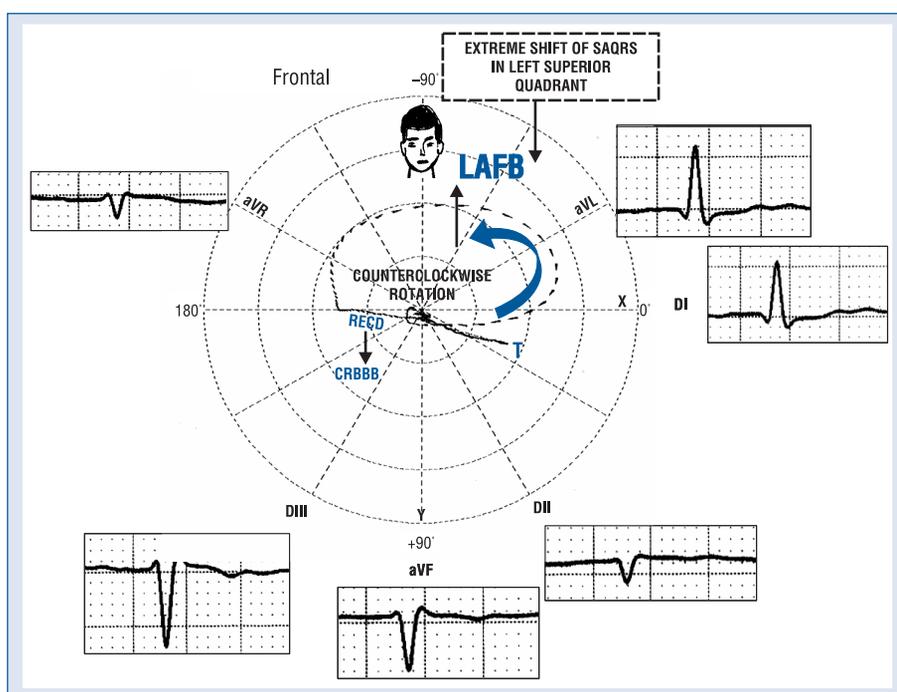


Figure 4. ECG/VCG correlation — frontal plane; CRBBB — complete right bundle branch block; LAFB — left anterior fascicular block; RECD — right end conduction delay.

- **Ejection fraction:** 73%;
- **ECG diagnosis:** heart rate: 77 bpm, P wave difficult to visualize in the frontal plane. The difficult visualization of P wave in the FP may indicate a certain degree of atrial wall fibrosis (sinoventricular conduction); PR interval: 200 ms; SAQRS -70° ; QRS duration: 150 ms; Rs pattern from V2 to V6.
- **Conclusion:** complete RBBB + LAFB + prominent anterior forces (PAF) (Fig. 3)

**ECG/VCG correlation:
Frontal plane (Fig. 4)**

- QRS loop with counterclockwise rotation and extreme left axis deviation;

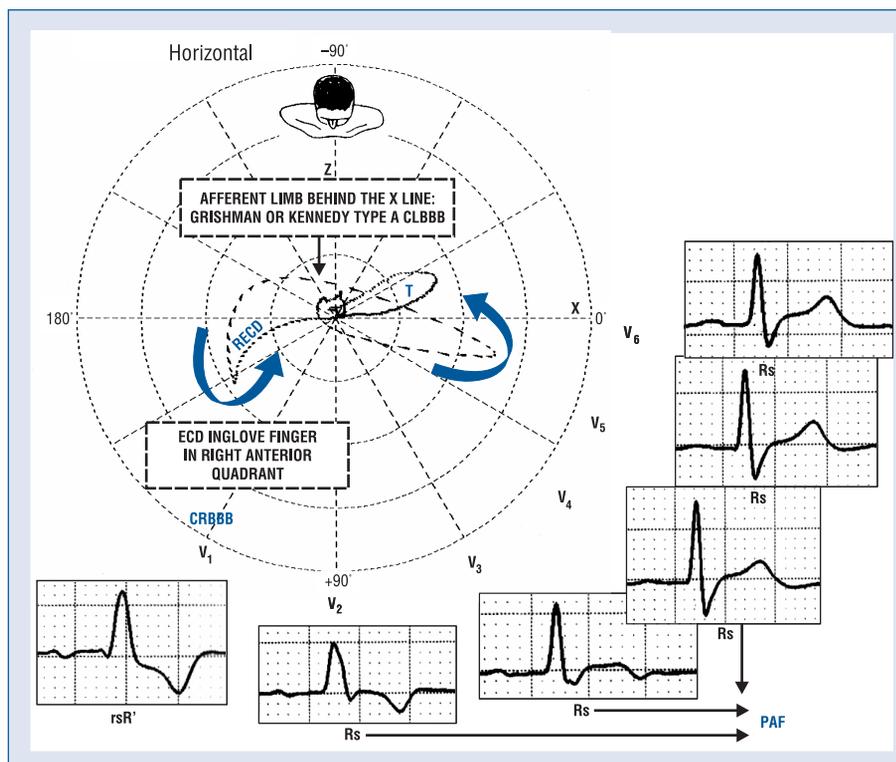


Figure 5. ECG/VCG correlation — horizontal plane; PAF — prominent anterior forces; CRBBB — complete right bundle branch block; LAFB — left anterior fascicular block; RECD — right end conduction delay.

- rS or rSr' pattern in inferior leads with SIII > SII: LAFB;
- End conduction delay located near right portion ($\pm 180^\circ$) of X orthogonal leads: complete RBBB.

**ECG/VCG correlation:
Horizontal plane (Fig. 5)**

- Typical pattern of complete RBBB Grishman type; right end conduction delay located on right anterior quadrant with “glove finger” shape;
- PAF form V1 to V4;
- T loop directed backwards and leftwards.

Prognosis

Independent prognostic factors identified in chronic Chagas cardiomyopathy:

- depressed left ventricular ejection fraction < 50%;
- VT at Holter monitoring or stress testing;
- SAECG: prolonged (> 150 ms) filtered QRS complex duration [34];

In patients with chronic systolic heart failure in the course of Chagas' disease predictors of all-cause mortality include:

- New York Heart Association (NYHA) class IV on admission;
- lack of beta-blocking agent use;
- serum sodium levels;
- digoxin treatment [35].

Chagas' risk index (Table 2) [36]

A systematic review of published studies indicates that impaired left ventricular function, NYHA class III/IV, cardiomegaly on the chest radiography, and NS-VT indicate a poor prognosis in patients with chronic Chagas' disease [37].

Five-year mortality of chronic Chagas' disease patients with cardiac dysfunction is above 50%.

Management

Therapeutic armamentarium in cardiac Chagasic disease:

- etiological approach: antiprotozoal;
- hygienic dietetic approach;
- medical treatment of chronic Chagasic heart failure;
- anticoagulant treatment;
- pharmacological treatment of ventricular arrhythmias with class III drugs;

Table 2. Chagas' risk index.

Risk factor	Points
NYHA class III or IV	5
Cardiomegaly \geq +++ chest X-ray	5
Wall motion abnormalities	3
Non-sustained ventricular tachycardia (NS-VT)	3
Low voltage on ECG	2
Male gender	2
Total points	Risk of death in 10 years
0–6	10%
7–11	40%
12–20	85%

- permanent pacemaker implantation;
- ICD;
- radiofrequency ablation;
- orthotopic heart transplantation.

Etiological approach: Antiprotozoal

Etiological treatment of Chagas disease is a controversial issue because the available drugs are highly toxic. Treatment for Chagas disease is recommended for all people diagnosed with an acute infection, congenital infection, and for those with suppressed immune systems. Other chronically infected people (especially children) may benefit from treatment. The antiparasitic drug, benznidazole (5 mg/kg/day), is effective when given for the initial infection and may also be beneficial for the chronic phase (recently acquired). Recent data indicate that parasite persistence plays a pivotal role in the pathogenesis of chronic Chagas' cardiomyopathy. However, the efficacy of trypanocidal therapy in preventing clinical complications in patients with preexisting cardiac disease is unknown.

The BENEFIT Trial (Evaluation of the Use of an Antiparasitic Drug [Benznidazole] in the Treatment of Chronic Chagas' Disease) was designed to determine if 60 days of treatment with benznidazole could prevent the progression of cardiac disease in patients with Chagas disease.

The BENEFIT study is being conducted by the Population Health Research Institute (in Hamilton, Canada) and the Institute Dante Pazzanese de Cardiologia (Sao Paulo, Brazil) together with an independent Steering Committee. The study is an interventional one and it is a randomized, double-blind, placebo-controlled, single group assignment, safety/efficacy study. Up to date, this is the first trial

investigating the use of antiparasitic drugs in patients that are in the chronic phase.

It will be conducted in 75 study centres in Argentina, Brazil, Colombia, Venezuela, Peru and Bolivia — countries with high incidence of Chagas disease and will include 3,000 patients.

The primary outcome is:

- the composite of death and hospitalization;
- resuscitated cardiac arrest;
- documented S-VT requiring cardioversion;
- insertion of pacemaker or ICD;
- cardiac transplantation;
- new development of symptomatic congestive heart failure;
- new development of stroke;
- any new thromboembolic event in patients with no prior thromboembolic phenomena;
- new development of systemic or pulmonary hypertension.

The study started on November 2004, with an average follow-up time of 5 years, and the trial has a 90% power to detect a 25% relative risk reduction. The estimated study completion date is December 2010.

Medical treatment of chronic Chagasic heart failure

In patients with chronic Chagas' cardiomyopathy, optimization of treatment with angiotensin-converting enzyme inhibitors, furosemide, spironolactone and subsequent addition of carvedilol are safe and associated with benefits in cardiac function and clinical status. Larger trials are needed to show effects on mortality and/or hospitalization [38].

Pharmacological approach of ventricular arrhythmias with class III drugs

The antiarrhythmic drug amiodarone, frequently prescribed for the symptomatic treatment of Chagas' disease patients, has also recently been shown to have antifungal activity. Amiodarone has direct activity against *T. cruzi*, both *in vitro* and *in vivo*, and it acts synergistically with posaconazole. In patients with chagasic cardiomyopathy and S-VT, electrophysiologic testing can predict long-term efficacy of class III antiarrhythmic drugs. This may help in the selection of patients for ICD therapy [39, 40].

Permanent pacemaker implantation

Pacemaker implantation may contribute to a better survival in selected chronic Chagas' disease

Table 3. Differences between Chagas and non-Chagas patients in pacemaker recipients.

	Chagas' s disease patients with permanent pacemaker	Non-Chagas' disease patients with permanent pacemaker
Age	Younger	Older
Left ventricular ejection fraction	Lower	Higher
Ventricular arrhythmia during Holter monitoring	More frequent	Less frequent
Prognosis	Worse	Better
Chest X-ray	Similar	Similar
Ventricular stimulation threshold	Similar	Similar

patients with cardiac involvement [41]. Chronic Chagas disease patients require pacemaker implantation at a younger age in contrast with patients with other cardiac pathologies [42].

Comparison between Chagas and non-Chagas' disease patients using single or dual-chamber pacemaker in relation to the left ventricular ejection fraction, the ventricular stimulation threshold and the occurrence of ventricular arrhythmia show that these patients are not similar (Table 3) [43].

The principal causes of pacemaker implantation in this pathology are:

- sinus node dysfunction 57%;
- second and third degree AV block 26%;
- atrial fibrillation with AV block or trifascicular block [43].

The proportion of implants of single-chamber devices is bigger than dual-chamber. Frequently the decision is based on the price of the devices and not on medical reasons. Anyway, it is necessary to consider that the evolution toward the dilated cardiomyopathy is common in these patients. In this case the use of the atrial electrode is crucial. In the selection of the pacemaker type it is necessary to take into account the autonomic alterations frequently present in this pathology such as syncope and chronotropic incompetence. The implantation of a DDD-R system is then mandatory.

Cardiac resynchronization therapy could be useful in selected cases but since the right bundle branch block is the most frequent intraventricular disorder the possibility of improving the ventricular function has not been completely explored.

On the other hand, Rassi et al. [44] underlined the importance of rate response function to obtain a better functional class and reduce the incidence of ventricular arrhythmias.

This author also suggested that the pacemaker change the natural evolution of this pathology and reduce the incidence of sudden death. In the evaluation of risk for sudden death the severe bradyar-

rhythmia due to AV block and/or sinus node dysfunction are the major predictors together with left ventricular dysfunction, sustained or non sustained ventricular tachycardia and syncope.

Recommendations for permanent cardiac pacing in chronic Chagasic cardiomyopathy are similar to other diseases and where previously published.

Implantable cardioverter-defibrillators (ICD)

ICD have sporadically been used in the treatment of either S-VT or VF in Chagas' disease patients. The ideal programming of ICD shock energy should be at least 10 J above the defibrillation threshold requiring alternative techniques when the defibrillation threshold is elevated. The occurrence of elevated defibrillation threshold (> 25 J), leading to alternative therapies, is low. There is an association with severe ventricular dysfunction, although without correlation to the causes of death [45].

Patients with chronic Chagas' heart disease recovered from cardiac arrest have an arrhythmogenic profile characterized by a high frequency of VF and no left ventricular systolic dysfunction and a short period of time to the first shock [46].

The predictors of all-cause mortality for Chagas' disease patients receiving ICD therapy are the number of shocks per patient per 30 days [47].

In Latin America, the experience in secondary prevention of sudden cardiac death is evaluated by means of an ongoing registry involving seven Latin American countries and 770 patients, the ICD-LABOR. Despite the differences in terms of pathologies between this trial and randomized ICD trials, a parallel evolution in all cause mortality and cardiac mortality was observed. Independent risk factors for mortality included age > 70 years, male gender, NYHA III/IV, and ejection fraction < 0.30. The etiology of heart disease (Chagas disease 26.1% vs. coronary disease 39.7%) was not found to be a risk factor [48].

Radiofrequency ablation

Ventricular tachycardia (VT) is common among patients with Chagas heart disease but the intrinsic mechanisms responsible for its sustained and nonsustained forms are not completely known. Sarabanda showed that a scar-related reentry was observed in all patients who underwent endocardial mapping for attempted radiofrequency ablation. The localization of the arrhythmia was related to left ventricular inferolateral scar in most cases (82%). They also found a significantly higher prevalence of wall motion abnormalities and myocardial perfusion defects in basal segments more frequent in patients with sustained ventricular tachycardia than in non sustained. In conclusion VT may arise from various regions in both ventricles, but left ventricular inferolateral scar is the main source of sustained VT reentrant circuits [49–50]. The subxyphoid pericardial mapping approach can be used to facilitate catheter ablation of Chagasic ventricular tachycardia. Nonsurgical epicardial transthoracic catheter ablation is a minimally invasive procedure that has proven to be efficacious for the treatment of VT. The usefulness of this technique depends on the prevalence of epicardial circuits, which seem more frequent in Chagasic than post-myocardial infarction VT [51].

For ablation indication, VT must be monomorphic, incessant, frequent, refractory to medical treatment with good hemodynamic tolerance. The technique is better indicated in patients with a ICD implantation and frequent episodes of ventricular tachycardia or electric storms. Sosa et al treated 173 patients with this technique, in 65% of them the approach was endocardial and in 35% epicardial. The event free survival, around 40% in 5 years, was better with the combination of epi- and endocardial mapping [51, 52].

Orthotopic heart transplantation

It is a therapeutic option for patients with end-stage Chagas' cardiomyopathy. Reactivation may occur after transplantation, leading to higher morbidity and graft dysfunction. Events resulting in greater immunosuppression status contribute to Chagas' disease reactivation episodes after heart transplantation and should alert physicians to make an early diagnosis and perform pre-emptive therapy. Although reactivation leads to a high morbidity rate, a low mortality rate is observed [53].

Although Chagas' patients have several different implications when submitted to the transplan-

tation comparing to other etiologies, actually these difficulties are well known, so treatments and preventive strategies are also better established. The most important care is with the immunosuppressive dosages, which must be different and lower than used in other pathologies [54].

Acknowledgments

The authors want to acknowledge Maribel Ayala and Karolina Dorniak for their assistance in reviewing and correction of the English version of this manuscript.

The authors do not report any conflict of interest regarding this work.

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