

## CLINICAL MANAGEMENT OF CHRONIC CHAGAS CARDIOMYOPATHY

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### 1. ABSTRACT

Chagas disease is caused by a protozoan parasite, *Trypanosoma cruzi*, and infects over 15 million people worldwide. New cases of the disease are now uncommon, mainly due to national control programs in Latin America. However, there is a large reservoir of chronically infected patients, many of whom will develop chagasic cardiopathy. Here, the clinical diagnosis and management of Chagas cardiopathy are discussed. Particular emphasis is placed on the clinical staging of patients and the use of various diagnostic tests that may be useful in individualizing treatment of the two most relevant clinical syndromes, ie. heart failure and arrhythmias. Finally, the relevance of specific treatment is discussed, stressing the important role of parasite persistence for disease pathogenesis.

### 2. INTRODUCTION

Chagas disease is an endemic illness caused by the protozoan parasite *Trypanosoma cruzi* that occurs in South and Central America. It is estimated that 16 to 18 million people are infected with *T. cruzi*, many of whom will develop advanced chronic disease, especially cardiac involvement and will eventually die of Chagas disease. Approximately 45,000 Chagas related deaths are thought to occur every year in Latin America (1). The social impact of Chagas disease in Latin America is much greater than the other major tropical diseases and is fourth, when considering all infectious diseases (2). Moreover, Chagas disease treatment is very costly and frequently affects patients in their most productive working years.

At present, vector transmitted infection by *T. cruzi* has been the target of several national control programs and this has led to a significant drop in the

incidence of new cases in places where programs are active (3). In regard to the latter aspect, 10 of the 14 Brazilian states, where transmission had been previously detected, have been declared free of new cases of Chagas disease, according to the World Health Organization. However, transmission via blood transfusion is still a matter of concern in many places, including developed countries with large immigrant populations, such as the USA (4). A community-based serologic survey carried out in 205 Salvadorans and Nicaraguans who resided in the Washington D.C. area showed that 10 people (4.9%) had clear evidence of infection, but none had clinically apparent Chagas' disease (5). If this prevalence rate was extrapolated to the whole population of immigrants from endemic countries, i.e. around two to three million people, perhaps 100,000 to 150,000 *T. cruzi* infected individuals resided in the United States in the early 1990's. Finally, it is estimated that around 5,000 to 18,000 new cases per year may occur as consequence of maternal-fetal transmission.

The main pathological finding in the heart of infected patients is that of a chronic progressive and fibrosing myocarditis (see review by Rossi in this series). Interestingly, focal myocarditis is found even in the indeterminate form of the disease and is more intense as disease progresses to the more severe clinical stages. In the chronic stages of the disease, tissue parasitism and blood parasitemia are scanty. The loss of cardiomyocytes and substitution of lost cells by fibrotic tissue appears to induce disruption of muscle fibers and fascicles. This architectural disarrangement causes mal-functioning of the electrophysiological syncytia and is important for the tendency of chagasic patients to develop heart failure and ventricular arrhythmias (6,7).

The host and/or parasite-related factors that determine the outcome of *T. cruzi* infection in infected people have not been identified. Several hypothesis have been raised trying to explain the pathogenesis of Chagas heart disease, including (i) an essential role of parasite persistence; (ii) a role for auto-immune process; (iii) the participation of structural and functional lesions to the microvasculature and (iv) the role of cholinergic and adrenergic organ denervation. Recent studies using more sensitive techniques for parasite detection (PCR and immunohistochemistry) have suggested that the association of chronic chagasic lesions, inflammation and parasite products (DNA and protein) occur much more often than previously thought (8,9). Indeed, there is now good evidence to indicate that parasitism of heart tissue is both necessary and sufficient to induce inflammation and tissue damage in Chagas disease (10). Thus, it is suggested that the chronic inflammatory infiltrate observed in the heart of chagasic patients may be the result of a continuous release of inflammatory mediators by tissue cells in response to *T. cruzi* and/or its products. In addition, there is also evidence to suggest that auto-immunity may contribute significantly to the inflammatory damage to heart cells and conduction system of the heart (11,12). The realization that parasites play an essential role in driving tissue inflammation in the chronic phase of the disease has obvious implications in the treatment of patients (see below).

### 3. NATURAL HISTORY

In endemic areas, the great majority of acute Chagas disease is unapparent, and most symptomatic patients present slight clinical manifestations. Classical acute cases are found primarily among children up to 10 years of age, and the mortality depends basically on the presence of acute myocardopathy and/ or meningoencephalitis. Untreated acute disease has duration of about 4 to 12 weeks, with a progressive decrease of blood parasitism (13).

Most untreated acute cases evolve into the so-called indeterminate form of chronic Chagas disease. This is defined by the presence of infection, confirmed by either serologic or parasitological tests, the absence of symptoms and of electrocardiographic and radiologic abnormalities (comprising heart, esophagus and colon evaluation) (14). Patients with the indeterminate form constitute the majority of infected people in endemic areas, and around 40% of these patients may persist forever in this clinical situation (15-19).

The evolution from the indeterminate to a "clinical" form (cardiomyopathy and the mega-syndromes) of chronic Chagas disease generally occurs 10 to 20 years after the acute phase in a slow and progressive fashion. Epidemiological studies in the endemic area have shown that 2 to 3% of patients will evolve each year from the indeterminate to a clinical form of the disease (16,17,20,21). In Brazil, about 20 to 30% of patients develop a cardiac form, 5 to 8% chronic esophagopathy, and 4 to 6 % chronic colopathy (15,16). From the epidemiological and clinical points of view, chronic cardiopathy is the most important chronic form of Chagas

disease, because of its associated morbidity and mortality and the consequent medical and social impact. When heart failure and/or severe arrhythmias occur, the prognosis is ominous, with high and premature mortality rates, chiefly among male patients in age groups between 30 and 50 years (16,22).

From the epidemiological point of view, morbidity and mortality associated with Chagas disease are related with the presence of electrocardiograph abnormalities, male gender, myocardial dysfunction and the occurrence of complex arrhythmia during exercise testing (13,16). The most important prognostic factor in established Chagas cardiopathy is the degree of myocardial dysfunction (23). For example, a mortality rate of 82 percent was seen in the group of patient with signs of heart failure at the beginning of the study. On the other hand, a 65 percent 10-year survival was verified in those patients with ECG abnormalities but without any signs of heart failure (23,24).

Patients classified as possessing the indeterminate form of the disease according to the World Health Organization (14) have the best prognosis and deaths due to the infection are not thought to occur in these patients (3,16). Nevertheless, 25 percent of indeterminate form patients may present significant structural and/or functional abnormalities when they are fully evaluated by more sensitive diagnostic methods, such as ergometry, dynamic ECG, autonomic tests or echocardiography (13,25-27). The exact meaning of these abnormalities is not known. We are not currently able to predict who will progress to the more severe forms of disease and would, therefore, benefit the most from specific treatment. Moreover, in any given group of patients, however strict the classification is, remarkable functional individual differences among the constituents of the same clinical group will be found. Chagas disease is a notable entity not only for its clinical pleomorphism, but also for the striking individuality among chagasic patients. Thus, although patients with more severe disease have a worse prognosis as a group, there is much individual variation. This great individual variation makes it essential that patients are stratified and followed-up carefully, as we suggest below.

### 4. DIAGNOSIS

In a patient with appropriate epidemiological background, the detection of serum antibodies against *T. cruzi* or its components by at least two different methodologies is sufficient to support the diagnosis of Chagas disease. There are several techniques available to detect anti-*T. cruzi* antibodies, including indirect immunofluorescence, indirect hemagglutination and immunoenzymatic assays (28). At present, well-standardized commercial kits are available and largely employed in Latin America, mainly for screening of blood donors and for sero-epidemiological surveys. One source of such kits is Bio-Manguinhos, a foundation part of Oswaldo Cruz Foundation (<http://www.bio.fiocruz.br/reagents.htm>).

The parasitologic diagnosis of Chagas disease is important in the acute phase and is based on detection of *T.*

*cruxi* trypomastigote forms by microscopic examination of fresh blood samples or by using indirect methods, such as xenodiagnosis and hemoculture. These tests are not essential during chronic Chagas disease as parasitemia is often absent and repeated parasitologic tests are usually necessary to demonstrate the parasite (29,30).

### 5. CLINICAL FINDINGS AND STAGING

The description below derives from our experience with a group of approximately 2000 chagasic patients comprising all chronic forms of the disease, from the indeterminate form to very severe cardiomyopathy, at a tertiary referral center (Chagas Disease Outpatients Clinic, Centro de Tratamento e Referência em Doenças Infecciosas e Parasitárias, Belo Horizonte, MG, Brazil). Detailed longitudinal clinical history, serology, blood testing, electrocardiogram, X-rays (chest, esophagus and colons), echocardiogram, exercise testing and Holter exams were available for a large proportion of these patients.

Heart disease secondary to a progressive and frequently late chronic myocarditis is the most important clinical manifestation of Chagas disease. In the early stages of the infection, only small numbers of patients display the clinical signs of the disease. In fact, most of the infected subjects enter silently into the chronic phase. Clinical presentation varies widely according to the degree of myocardial damage and most patients present with a milder form of heart disease. The adaptation and tolerance of the heart varies with the speed and quality of the pathogenetic process, especially if the damage of myocardium develops rapidly or gradually over the course of many years. On average, the heart involvement is fully developed around 20 years after the primary infection, although this takes place earlier in some subjects, and later, in others. Clinical manifestations of severe chronic chagasic heart disease comprise three basic syndromes: heart failure, cardiac arrhythmia and thromboembolism.

Heart failure is usually biventricular, although the right-sided manifestations, like increased jugular venous pressure, peripheral edema and liver enlargement, are usually more pronounced than those of left-sided failure. The severity of ventricular arrhythmias tends to correlate with the degree of left ventricular dysfunction. However, it is not uncommon to have patients with ventricular tachycardia or complete atrioventricular block who have well preserved global ventricular performance. Once congestive heart failure or complete heart block supervenes, life expectancy is reduced to a few years and this is in agreement with findings in field studies (16,20). Sudden unexpected death may occur even in patients previously asymptomatic, although rarely (13,31). It is usually precipitated by physical exercise or by Valsalva's maneuvers physiologically performed in the daily life. The final event in these patients is presumed to be to ventricular tachycardia and fibrillation, but bradyarrhythmias may also occur. Patients with ventricular dysfunction, ventricular tachycardia during Holter monitoring, a previous history of recovery from cardiac arrest, severe bradyarrhythmia and syncope are at greater risk of developing sudden death.

Chronic Chagas heart disease is characterized by a wide variety of anatomical and electrophysiologic alterations that lead to many kinds of atrial and ventricular arrhythmias. Ventricular premature contractions and intraventricular conduction disturbances are usually the earliest manifestation of ventricular involvement in Chagas disease. When ambulatory ECG monitoring is performed, ventricular premature beats can be detected in about 10% of chagasic patients without evidence of cardiac involvement. However, in patients with intraventricular conduction disturbances and ventricular dysfunction, although without clinical evidence of heart failure, the prevalence of ventricular premature contractions increases significantly (32). Moreover, virtually all patients with heart failure have frequent monomorphic or polymorphic ventricular premature beats and runs of non-sustained ventricular tachycardia. Episodes of malignant ventricular arrhythmia seem to be much more frequent in chagasic patients than those with other types of underlying heart disease (33).

Systemic and pulmonary embolism, arising from mural thrombi in cardiac chambers and from deep venous thrombosis due to low cardiac output, is a common complication of Chagas disease. The presence of apical aneurisms in over 50% of patients with Chagas cardiomyopathy may be a contributing factor (34). Evidence from postmortem studies suggests that emboli are often overlooked in daily medical practice (35).

To take into account the great clinical pleomorphism of Chagas disease and in order to plan clinical cohorts of patients, we have developed a clinical classification system displaying a spectral range of the disease, from the indeterminate form through chagasic cardiomyopathy (table 1).

The potential evolution of the indeterminate form, depending on as yet ill-defined factors, is shown by longitudinal cohort studies in endemic areas. A one to three percent per year rate of appearance of heart damage has been observed in several studies. Nevertheless, the results of these studies indicate that, as long as the patients remain in the indeterminate form, their overall prognosis is good. In fact, it is important to point out that after 10 years, almost 80 percent of the patients remain in the indeterminate form.

Although seropositive adults with normal ECG and X-rays show a favorable prognosis in several studies (16-18), sensitive techniques can detect abnormalities of variable severity in many such patients (CCC1). Patients with these characteristics should be set in a different group, as they appear to represent a group with a subclinical cardiomyopathy. It is worth noting that patients with the indeterminate form of Chagas disease often have pathological findings on necropsy. These (CCC1) patients are of special interest for studies involving the natural development of the disease, the possible determinants of clinical outcome, and indications for specific treatment. If these are the patients who will evolve, they will certainly be those who will gain the most from specific therapy.

**Table 1.** Clinical classification of chagasic cardiomyopathy

Clinical group	Characterization
Chronic Indeterminate Form	Asymptomatic, no significant alteration on physical examination, ECG, chest X-ray, esophagogram and barium enema. No change on evaluation by sensitive techniques (echocardiogram, exercise testing, Holter).
CCC 1	Asymptomatic, no significant alteration on physical examination, ECG, chest X-ray, esophagogram and barium enema. Sensitive techniques can detect abnormalities of variable severity.
CCC 2	Asymptomatic patients or ones presenting NYHA functional class I, without clinical and radiological signs of heart enlargement, but with minor ECG alterations, such as low voltage of QRS complexes in the standard leads, block of the anterosuperior division of the left branch, minor changes in the ST segment and in the T wave.
CCC3	Patients without manifestations of heart failure or in NYHA functional class II and without enlargement of the cardiac silhouette. These patients must display considerable ECG alterations, such as right bundle branch block, or uniform ventricular premature contractions.
CCC 4	As in the previous group, these patients do not show signs of cardiac enlargement. However, the ECG abnormalities displayed by this group are significantly more severe and include right bundle branch block associated with left anterior hemiblock, abnormal Q waves, diffuse negative symmetric T waves, left bundle branch block, second degree atrioventricular block Mobitz type II and complete AV block.
CCC 5	Patients with clinical, radiological and, especially, echocardiographic signs of heart enlargement, with or without manifestation of cardiac insufficiency.

CCC: chronic chagasic cardiomyopathy

The ECG abnormalities in patients with CCC 2 and CCC 3 are indicative of chagasic heart damage. Patients with conduction defects are at high risk for developing progressive myocarditis, although years may elapse before the appearance of symptoms. Those with ventricular extrasystoles in combination with conduction defects are at high risk of sudden death (32) and should be considered for anti-arrhythmic therapy.

Patients classified as CCC 4 and CCC 5 represent the most severe forms of Chagas heart disease. The separation of the severe groups into those individuals with severe conduction defects or ECG abnormalities only (CCC4) and those who have ventricular enlargement (CCC5) with or without conduction defects and significant ventricular dysfunction is important. The damage to the heart is to different structures, that is, mainly conduction system (CCC4) versus muscle (CCC5). Moreover, their prognosis is different, being worse in those with ventricular enlargement (CCC5) and/or severe ventricular impairment. Whether the immune responses and the infecting parasite strains differ within these two groups deserves further investigation.

## 6. THE RELEVANCE OF VARIOUS DIAGNOSTIC METHODS

The electrocardiogram is the single most important exam in Chagas disease patients (table 1). Numerous epidemiological studies have shown that patients with a normal ECG have an excellent medium-term survival (16,32). Moreover, severe global left ventricular dysfunction, the main prognostic marker in Chagas disease, is rare in such patients. The greater the number and severity of ECG alterations registered in a same tracing, the more advanced the myocardial damage possibly is, and the worse the prognosis should be. Although rarely sudden death may occur in patients with a normal ECG, as the initial manifestation of the disease, it is generally a complication of late advanced disease (36).

Echocardiography is the best non-invasive technique used in the assessment of cardiac function and represents an important method in the evaluation of Chagas cardiomyopathy. Variables usually employed in the clinical evaluation of and in the clinical research on chagasic patients are: the ejection fraction, left ventricular diastolic and systolic diameters, left atrium diameter, the estimate of right ventricular size, the evaluation of global and segmental myocardial contractility and the assessment of diastolic function.

Global systolic left ventricular dysfunction is the strongest predictor of morbidity and mortality in Chagas disease (22-24,31,37), although asymptomatic left ventricular systolic dysfunction is, at least, as common as symptomatic heart failure as defined by clinical criteria. Identification and treatment of patients with left ventricular global systolic dysfunction can improve survival and reduce morbidity. Since it is costly to submit all patients with Chagas disease to echocardiographic evaluation, it is desirable to develop screening methods to indicate which patients should be submitted to complete left ventricular evaluation. Enlarged heart silhouette at the Chest X-ray, although a specific sign for cardiac dilatation, lacks sensitivity and has an overall poor diagnostic performance (38). Elevation of brain natriuretic peptide (BNP) levels in blood, a reliable indicator of systolic left ventricular dysfunction in different clinical and epidemiological settings, is a promising screening method. In patients with abnormal ECG and/or Chest X-Ray, BNP elevation has a positive predictive value of 80% and a negative predictive value of 97% (39).

One of the most interesting findings in the study of the heart in Chagas cardiomyopathy is the pattern of segmental myocardial contractility disturbance that makes this disease closer to ischemic rather than idiopathic cardiomyopathy. The segments predominantly involved are the apex and the postero-inferior wall of the left ventricle (26,27). These latter changes appear even in the

indeterminate form of Chagas cardiomyopathy (about 20-30 % of cases) and are universally present in cases of severe heart failure (26,27). Echocardiography allows the identification of almost all apical lesions, even small ones. It is important to note that the apical lesion in Chagas disease generally is not associated with contractile dysfunction in the anteroapical segment of the left ventricle, which distinguishes Chagas disease from patients with coronary artery disease complicated with infarction where contractile dysfunction is observed. The involvement of other segments of the left ventricle in Chagas disease is almost impossible to differentiate from coronary artery disease and the clinical and epidemiological aspects are essential for the differential diagnosis.

The use of transesophageal echocardiography allows the identification of possible cardiac sources of emboli with high accuracy. As Chagas disease is frequently complicated by embolic accidents transesophageal echocardiography can be important in deciding the benefit of anticoagulant therapy.

The assessment of left ventricular diastolic function in Chagas disease has shown that diastolic dysfunction may occur early in the disease. Studies by our group have demonstrated a relationship between systolic and diastolic function, so that the presence of abnormal relaxation and compliance is generally associated with poor ejection fraction of the left ventricle in chagasic patients (26,27). Recent studies using Tissue Doppler Imaging have shown subtle and early abnormalities in segmental contractility and relaxation of the right and left ventricles (26,27). Moreover, this innovative technique may help in the detection of pseudonormal pattern of diastolic dysfunction, which is harder to diagnose with conventional Doppler analysis (26,27).

Both exercise testing and 24-hour electrocardiographic monitoring (Holter monitor) are important diagnostic tools for Chagas disease-associated arrhythmias and risk of sudden death. A comparative study of exercise testing and ambulatory monitoring showed that, although complex ventricular arrhythmia was more readily detected by means of 24-hour monitoring, exercise testing detected more severe abnormalities in approximately 15% of patients. Both methods detected the same maximum grade of ventricular arrhythmias in 40% of cases and ambulatory monitoring was superior in the remaining 45 % (33).

Dynamic ECG recording is especially important in Chagas disease because of the relatively frequent occurrence of asymptomatic transitory arrhythmias. Identification of complex forms of ventricular arrhythmias, such as couplets, bigeminy and ventricular tachycardia is prognostically important. The detection of potentially lethal arrhythmias, as prolonged ventricular tachycardia or transient advanced heart blocks may indicate the necessity of specific antiarrhythmic therapy or devices. Sick sinus syndrome is also frequent in Chagas disease patients and can be recognized by Holter monitoring. The lack of significant ventricular arrhythmia in 24hr ECG does not

however, preclude risk of death due to arrhythmia. Ambulatory monitoring may also be used in the investigation of palpitations and syncope and to assess the efficacy of antiarrhythmic drugs.

In selected patients, invasive electrophysiologic study may be useful to identify the cause of syncope (when non-invasive tests are inconclusive) or to guide the use of anti-arrhythmic devices, as cardiac pacemakers and implanted defibrillators. Moreover, induction of SMVT during programmed ventricular stimulation is a predictor of arrhythmia occurrence cardiac death and general mortality in patients with Chagas cardiopathy and non-sustained ventricular tachycardia.

Maximal exercise testing is usually assessed with use of a standard Bruce protocol and can be conducted safely in patients with Chagas disease. Exercise testing enables the assessment of the influence of the exercise in provoking arrhythmias and also plays a role in defining the type of work a patient may perform. Chronotropic insufficiency and abnormal blood pressure response are more frequent in Chagas disease patients and may also hamper the effort capacity of Chagas disease patients. Sick sinus syndrome, autonomic impairment and left ventricular dysfunction are putative causes of these abnormalities, but it is also well known that some patients with advanced cardiopathy may retain an excellent exercise capacity. Indeed, as many other aspects of Chagas disease physiopathology, the response to exercise cannot be predicted by other means and stress testing is an essential tool in the evaluation of Chagas cardiopathy patients. Exercise testing may also be useful in the evaluation of the efficacy of antiarrhythmic therapy.

Radioisotopic techniques, such as myocardial scintigraphy with Thallium-201, has been performed in combination with exercise testing in order to study the myocardial perfusion pattern in the following clinical situations: 1) patients with precordial pain; 2) left ventricular segmental hypocontractility; and 3) ischemic T wave changes. Both transient and irreversible perfusion defects may be detected by myocardial perfusion scanning in these patients. In patients who complain of angina-like pain, perfusion disturbances may occur, usually in the presence of normal coronary arteries. This finding probably represents microvascular abnormalities or areas of myocardial fibrosis. Occasionally cardiac and coronary catheterization are required to exclude the presence of epicardial obstructive coronary artery disease.

## 7. TREATMENT

### 7.1. Specific treatment

Two drugs are indicated for the specific treatment of Chagas disease, namely benznidazole and nifurtimox, although only the former is currently available in Brazil and, the latter, in the United States (40). Benznidazole is administered in a daily dose of 5 to 10 mg/kg of body weight for children, and in a daily dose of 5 mg/kg for adults, both to be taken twice a day. The recommended duration of therapy is 60 days. Nifurtimox is prescribed in a total daily dose of 15 mg/kg for children, and of 8 to 10

**Table 2.** Recommendations for specific treatment in Chagas disease

- Acute phase of the disease, whatever the mechanism of transmission –vectorial, transfusional, congenital, laboratory accidents or organ transplant;
- As a preventive measure, in cases of organ transplantation, both to the donor and to the receptor
- Cases of reactivation of the disease, as it can occur in immunosuppressed patients
- Patients with “recent” chronic infections, specifically all children infected by *T. cruzi*
- Patients with the indeterminate form or with slight heart damage, provided the treatment is done under an investigative protocol, with systematic clinical, parasitological, immunological and laboratorial evaluation
- To young patients already displaying significant conduction disturbance or arrhythmia, also under an investigative protocol, in the hope of preventing a possible clinical deterioration
- To patients showing a tendency to clinical worsening, also under an investigative protocol

Benznidazole, 5 to 10mg/kg for children and 5mg/kg/day for adults twice daily for 60 days. Nifurtimox, 15mg/kg for children and 8 to 10 mg/kg for adults three times daily for 90 days.

mg/kg for adults, both taken three times a day, for a period of 90 days. Our experience with benznidazole shows that an allergic rash of variable intensity, usually appearing around the ninth day of treatment is the most common side effect and is usually a reversible disorder. Nevertheless, treatment should be interrupted when the eruption is intense or followed by fever and lymphadenopathy. Neutropenia and agranulocytosis may occur sometimes, while the occurrence of severe thrombocytopenia is rare. Hematologic alterations tend to occur early and require the interruption of treatment. A complete hematologic evaluation should be performed in the first three weeks of treatment. A sensory neuropathy is a later, toxic, dose-related manifestation that can be prevented by not exceeding using only the recommended dose of the drug, especially for adults. The side effects of nifurtimox are mainly a severe anorexia, abdominal pain, emaciation, a peripheral sensory neuropathy, insomnia, mental disturbances and also an allergic dermatopathy.

The indications for specific treatment are shown in table 2. The relevance of specific treatment for the control of Chagas disease has recently gained interest since findings suggest that chronic parasitism is essential for disease to occur. Moreover, it is clear that specific treatment is beneficial in acute or recently infected chagasic patients. It is estimated that treatment with benznidazole can lead to 70 % of parasitological cure if chagasic patients are treated during the acute infection (40). The Pan American Health Organization has issued a recent statement suggesting that all patients with chronic Chagas disease should be treated. This recommendation finds support in studies that show a benefit of treatment in the early stages of chronic Chagas disease (41,42). Some studies have suggested a benefit of treatment for older patients (see for example ref. 43) but most of these are small, non-randomized, non-controlled trials. However, other studies have failed to show benefit (44). Thus, no studies to date have provided definitive proof that treatment is beneficial for chronic Chagas disease in adults with stable disease and in the most advanced clinical pictures. Nevertheless, the approach suggested by the Pan American Health Organization is an important modification in the guidelines for the way physicians should handle chronic Chagas disease. There are, however, important issues that need to be addressed if therapy is to be of true benefit. First, there are important and unsolved concerns about the

long-term safety (especially, a possible risk of treatment-associated malignancies) of the currently available medication (45). Second, the early detection and proper management of the common side-effects associated with the use of imidazole-containing compounds are rarely performed in endemic areas without close medical supervision. Also, in face of the low efficacy of currently available medication for specific treatment (nifurtimox and benznidazole), it would be useful to define those patients that show a tendency for clinical worsening and those at most risk of developing severe disease, as the latter could be targeted in clinical trials with more effective (and, perhaps, more expensive) drugs. In addition, the definition of a simple but effective criterion of cure would be very useful not only in larger epidemiological studies evaluating the effect of mass treatment but also in case of individual specific treatment.

The criteria of cure in Chagas are a matter of greater controversy. Clinical criteria are of limited value either in the acute or in the chronic phase of Chagas' disease. Even in the absence of any treatment, symptoms usually subside within one or two months in the acute phase. In the chronic phase these criteria are even less important. Chronic patients are usually symptomless and visceral lesions already present are not reversible. In long-term longitudinal studies, suitable, specific markers for the development or worsening of the pathological picture of Chagas disease need to be chosen but this has proven a very difficult task. For instance, the development of ECG signs of left anterior hemiblock in a given treated or untreated patient may result from Chagas disease-related pathogenetic mechanisms, but may also be related to other morbid processes, such as arterial hypertension. Indicators of cardiac normality or enlargement, such as the cardiothoracic ratio measured using a chest X-ray, have similar pitfalls (38). Nevertheless, such unspecific and variable markers have been employed as morbidity indicators in some recent studies of specific treatment of Chagas disease. As a consequence, the meaning of these alterations in long-term prospective studies is of doubtful nature.

Serological tests may demonstrate a fall in titers or negatization of the test in cases where treatment was successful. Most studies show that negatization of serological test is uncommon but a drop of titers may occur

(41,42,46). One of the hypotheses raised to explain the lack of seroconversion to negative of these tests, even after the confirmed elimination of parasitism, stem from the experimental work of Andrade and co-workers (47) who demonstrated the persistence of parasite antigens in dendritic cells of the lymphoid follicles of the spleen. The actual meaning of the drop of titers commonly observed in many treated patients has not been fully appreciated.

Lytic antibodies and trypomastigote glyconjugates have been used as alternative to serological tests, which mainly use parasite lysates. The overall impression is that the use of certain specific antigens or a small group of specific antigens results in maintained specificity and sensitivity but with a more pronounced and detectable fall of titers after specific treatment (46). PCR-based strategies offer the possibility of a high degree of sensitivity and specificity. A few uncontrolled studies have evaluated the ability of parasite-specific PCR to detect cure after treatment. In addition, the results of PCR correlates well with studies evaluating lytic antibodies, again suggesting the possible use of this methodology as a criterium of cure. Although parasitological techniques (hemoculture and xenodiagnosis) are essential for isolation of parasite strains, these tests are often negative due to the low number of circulating parasite in chronic Chagas' disease. Although one study by Luz and others (30) mention a positive hemoculture in over 90 % of infected patients, most studies suggest that only 50% of patients possess a positive result.

Thus, it is clear that the definition of cure in chronic Chagas disease is not simple as there is no single laboratory test that unequivocally diagnoses cure in treated patients. However, if we are to compare the effects of specific treatment on immune responses of treated chagasic patients, proper criterium of cure must be devised. In addition, a simple method to evaluate cure must be devised if we are to conduct large trials to demonstrate the clinical efficacy of specific treatment.

### 7.2. Treatment of heart failure

The prognosis of the patients with chronic chagasic cardiopathy and heart failure is poor, as the great majority die within six years of diagnosis (13,23). As most patients in endemic regions are from the hinterland and from poor economic backgrounds, cost is a very important limiting factor in the management of chagasic patients with heart failure. In Brazil, most of the drugs used in the pharmacological therapy of Chagas disease - namely enalapril, captopril, digoxin, furosemide, thiazides and amiodarone - has been provided by the Brazilian Ministry of Health and distributed to National Health Service Clinics, although in a non systematic way.

Heart failure in chagasic patients is probably associated with higher rates of morbidity and mortality when compared with other cardiomyopathies. At any given time, around 30 % of the whole population with heart failure falls into New York Heart Association functional class III or IV, compatible with an advanced degree of disability. Although very few clinical trials have been

carried out with patients with chagasic heart failure, the treatment of the condition in the chagasic population follows the general guidelines for the treatment of heart failure due to other conditions. A few studies demonstrated a beneficial effect of angiotensin converting enzyme (ACE) inhibitors (e.g. enalapril and captopril, for the treatment of Chagas disease associated cardiopathy (48,49). It remains to be determined whether pharmacological treatment with ACE inhibitors (either alone or in combination with any other therapy) actually prolongs survival in chagasic patients, as it has been determined for other conditions.

The use of digitalis in the chagasic population may be cumbersome and no large studies have evaluated the use of drug in this group of patients. Patients with heart failure commonly have associated sinus node disease, intraventricular conduction defects and heart blocks. Moreover, Chagas heart disease is characterized by a great degree of excitability and digitalis may enhance ventricular arrhythmias in these patients. Thus, it is our opinion that digitalis should only be used in chagasic patients when there is a clearly measurable benefit of its use and with careful follow-up. The use of betablockers, e.g., metoprolol and carvedilol, as well as the diuretic spironolactone, now a routine in the treatment of heart failure due to other conditions, has not been specifically tested in Chagas disease.

Pacemaker biventricular resynchronization, which benefits mainly patients with left bundle branch block and severe systolic left ventricular dysfunction, has been used in Chagas disease patients with success. The high cost of such treatment, as well as the unknown efficacy in those patients with right bundle branch block (which is much more common in Chagas disease) limits its use in this setting. Heart transplantation for advanced Chagas heart disease should be regarded as a valuable treatment option, although often unavailable at the endemic region (50). The identification and the treatment of the reactivation of the *T. cruzi* infection poses additional challenges in the post transplantation follow up. Finally, partial left ventriculotomy has met with success in some patients and is currently receiving increased attention (55,56).

### 7.3. Treatment of arrhythmias

Treatment of ventricular arrhythmia in chagasic patients is essentially empirical and not supported by large randomized controlled trials. This is to say that there are no properly designed prospective trials in larger groups of chagasic patients to ascertain whether pharmacological control of potentially malignant ventricular arrhythmias prevents sudden cardiac death. Patients with asymptomatic ventricular premature beats or nonsustained ventricular tachycardia, without significant ventricular dysfunction, usually do not require any anti-arrhythmic therapy (table 3).

Amiodarone has been reported to be the best and safest antiarrhythmic drug in chagasic patients, and has a low incidence of ventricular arrhythmogenic side effects (33,51). There is some evidence that low-dose amiodarone

**Table 3.** Indication for specific therapy of ventricular arrhythmias in Chagas disease.

	Clinical conditions			
	Normal LV function		Depressed LV ejection fraction	
	Asymptomatic or minor symptoms	Major symptoms (hemodynamically significant)	Asymptomatic or minor symptoms	Major symptoms (hemodynamically significant)
Complex ventricular arrhythmia and/or non-sustained ventricular tachycardia	None	Check if symptoms are related to ventricular arrhythmias; consider amiodarone	Consider amiodarone, which may prevent sudden death	Evaluate with electrophysiological study, if available; amiodarone, consider ICD
Sustained ventricular tachycardia	Amiodarone	Amiodarone and ICD	Amiodarone and/or ICD	Amiodarone and ICD; consider other invasive alternatives

Modified from Mendoza and colleagues (53), considering the American College of Cardiology/American Heart Association (ACC/AHA) task force updated guidelines for the implantation of cardiac pacemakers and antiarrhythmia devices, published in 1998 (Gregoratos et al.). LV = left ventricular, ICD = Implantable cardioverter - defibrillators.

**Table 4.** Indication for the use of pacemaker in Chagas disease cardiomyopathy

Issue	Class	Recommendation
Permanent pacing in acquired AV block	I	Third-degree AV block with any one of the following conditions: <ul style="list-style-type: none"> <li>Bradycardia with symptoms presumed to be due to AV block</li> <li>Arrhythmias and other medical conditions that require drugs that result in symptomatic bradycardia (as amiodarone)</li> <li>Documented periods of asystole of &gt; 3.0 sec or any escape rate of &lt; 40 beats/min in awake, symptom-free patients</li> </ul>
	IIa	Second-degree AV block, regardless of the type or site of block, with associated symptomatic bradycardia Asymptomatic third-degree AV block at any anatomical site with average awake ventricular rates of 40 beats/min or faster Asymptomatic type II second-degree AV block Asymptomatic type I second-degree AV block at the intra- or infra-His levels found incidentally at electrophysiological study
	IIb	First-degree AV block with symptoms suggestive of pacemaker syndrome and documented alleviation of symptoms with temporary AV pacing Marked first-degree AV block (> 0.30 sec) in patients with LV dysfunction and symptoms of congestive heart failure in whom a shorter AV interval results in hemodynamic improvement, presumably by decreasing left atrial filling pressure
	I	Intermittent third-degree AV block Type II second-degree AV block
Permanent pacing in chronic bifascicular and trifascicular block	IIa	Syncopal not proved to be due to AV block when other likely causes have been excluded, specifically VT Incidental finding at electrophysiological study in asymptomatic patients of markedly prolonged H-V interval (> 100 msec) or of a pacing-induced infra-His block that is not physiological
	I	Sinus node dysfunction with documented symptomatic bradycardia (including frequent sinus pauses)
	IIa	Symptomatic chronotropic incompetence Sinus node dysfunction occurring spontaneously or as a result of necessary drug therapy, with a heart rate of <40 beats/min when a clear association between typical significant symptoms and the actual presence of bradycardia has not been documented
Permanent pacing in sinus node dysfunction	IIb	In minimally symptomatic patients, chronic heart rate of less than 30 beats/min while awake

Adapted from Gregoratos and colleagues (54). Class I means general agreement that the device or therapy is indicated. Class II indicates a divergence of opinion with respect to their usefulness, with Class IIa favoring and Class IIb not favoring usefulness. AV = atrioventricular; LV = left ventricular; VT = ventricular tachycardia.

is effective in reducing mortality and hospital admission in patients with severe heart failure, independent of the presence of complex ventricular arrhythmia. Sinus node dysfunction, atrioventricular nodal delay and intraventricular conduction delay frequently complicate the use of amiodarone, as severe bradyarrhythmias may occur. In these situations, a permanent pacemaker may be implanted (see below). Extra-cardiac toxicity, as thyroid dysfunction and dermatological abnormalities, are not uncommon, although life-threatening pulmonary toxicity appears to be rare. In patients with significant left ventricular dysfunction and asymptomatic, frequent and/or complex ventricular arrhythmia, a significant reduction in the incidence of sudden death was observed following treatment with amiodarone (33,51). Patients with unstable or sustained ventricular tachyarrhythmia and those resuscitated from sudden death would probably benefit from a portable cardioverter-defibrillator, but the widespread use of this procedure is also hindered by socio-economical factors in endemic areas (52). Alternative

therapies, as surgery and catheter ablation, are restricted to selected cases and tertiary referral centers.

Treatment of symptomatic bradyarrhythmias does not differ from that recommended for other cardiomyopathies and is usually performed by permanent pacemaker insertion. Main indications for pacing are atrioventricular block and sinus node dysfunction (table 4). A very important situation commonly observed in chronic chagasic patients is the association of atrioventricular disturbances and frequent, complex ventricular arrhythmia. In these cases, an effective pharmacological antiarrhythmic therapy may require a "prophylactic" artificial pacemaker implantation in order to prevent the harmful consequences of an eventual complete atrioventricular block.

## 8. PROSPECTS

Although the number of new cases of Chagas disease has dropped markedly in the last few years, due to



effective control programs, there is a large population of individuals who will clearly benefit from adequate clinical management. The identification of early markers of worse prognosis would be an important advance, as these markers may identify a group of patients who would benefit the most from early and, perhaps, more aggressive intervention. It is essential that we define whether specific treatment with currently available or new drugs will modify the ominous evolution of the disease observed in a significant proportion of individuals. However, in order to evaluate the effectiveness of specific treatment, it is imperative that we define adequate criteria of cure. Moreover, large multicenter trials are needed if we are to demonstrate the clinical benefit for chagasic patients of the drugs currently used for the treatment of arrhythmias and heart failure due to other causes. Chagas disease has many characteristics and response to treatment that need to be understood if we are to use evidence-based therapies.

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