e37 Chagas' Disease: Advances in Diagnosis and Management

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INTRODUCTION

Chagasic cardiomyopathy is the major complication resulting from infection by *Trypanosoma cruzi,* occurring in up to 30% of individuals who have a positive specific serology. The *T. cruzi* infection is related to the close proximity between humans and triatomines carrying *T. cruzi* and extends from the Southern United States[11] and Mexico to the south of Argentina. According to the World Health Organization Technical Report, among individuals living in Latin American countries, 5–6 million are infected and 25 million are at risk of contracting the infection (Chap. 206).

It usually takes 10–20 years for the infection to manifest the disease in a broad range of clinical presentations including heart failure, cardiac arrhythmias, thromboembolism, and sudden death. Once established, the signs of heart failure result in life expectancy being reduced to ≤5 years. Therefore, strategies to identify the disease in the early phase and characterize predictive signs and potential therapeutic targets have been intensely pursued. In this chapter, we discuss the results from recent, novel research on the diagnosis and management of Chagas' disease.

LABORATORY DIAGNOSIS

Parasitemia During the acute phase of the disease, parasites can easily be found by microscopic observation of fresh blood. Morphologic characteristics of the parasite and differentiation from *T. rangeli* can also be determined by staining the blood smears. When parasitemia is low, procedures for parasite concentration or indirect methods (xenodiagnosis and hemoculture) can be used instead. Parasite concentration could be obtained either by microhematocrit or by the Strout method. In the microhematocrit, blood is centrifuged and the buffy coat examined by microscopy to visualize trypomastigote movements. In the Strout method, blood cells are first eliminated by precipitation and centrifugation. The supernatant is then submitted to a second centrifugation and the precipitate is examined as fresh blood.

The xenodiagnostic method consists of feeding uninfected triatominae with blood from the patient under examination and then investigating the intestinal contents of the insects some days later to search for metacyclic trypomastigotes. Artificial xenodiagnosis is preferred to avoid inconveniences from direct contact between the triatomines and patients' skin. Recently, amplification of *T. cruzi* DNA target sequences by polymerase chain reaction (PCR) has become a preferred method for the detection of parasites in blood and tissues. Such PCR techniques are especially helpful for the follow-up of chemotherapy for *T. cruzi*. However, despite being more sensitive than xenodiagnosis and hemoculture, this sensitivity is equally dependent on the magnitude of the parasitemia.

Immunodiagnosis Infected individuals soon develop antibodies, initially IgM and later IgG, against several epitopes of *T. cruzi* allowing the indirect diagnosis of Chagas' disease. Conventional immunodiagnostic tests are available worldwide and are based on three main techniques: hemagglutination, immunofluorescence, and ELISA. Nonconventional tests using recombinant chimeric proteins, synthetic peptides, or purified antigens have been developed to increase specificity and reduce cross-reactivity with other infections and with autoimmune diseases. In general, conventional tests have elevated sensitivity, and a positive result in two conventional tests is sufficient to diagnose the infection. In parallel with PCR for detecting *T. cruzi* parasitemia, conventional serologic tests could also be used for the follow-up of patients undergoing chemotherapy.

ANATOMIC DIAGNOSIS

Myocardial Fibrosis and Inflammation *T. cruzi* can be easily detected in muscle cells and interstitial histiocytes of individuals in the acute phase of Chagas' disease. However, such a finding is rare in the chronic phase of the disease. Hence, the main finding in the hearts of patients with chronic Chagas' disease is the presence of inflammatory infiltrates. Chagas' myocarditis lesions are spread out over both ventricles and in a large spectrum of severity, transforming myofibers into fibrous tissue and featuring the changes in heart structure and function. Accordingly, myocardial fibrosis caused by Chagas' disease is a strong marker of clinical impairment and ventricular dysfunction.

The histopathologic evaluation of myocardial fibrosis and inflammation can be obtained through a percutaneous and transvenous endomyocardial biopsy of the right ventricle. This diagnostic procedure has been proved to be a powerful tool for both the prediction of clinical outcome and estimation of the severity of myocardial damage in Chagas' disease and in other primary and secondary cardiac diseases. In patients with Chagas' disease who undergo heart transplantation, endomyocardial biopsy is considered the "gold standard" technique in the differentiation between allograft rejection and reactivation of the disease. In such patients, however, the use of endomyocardial biopsy has been limited by the mild, albeit significant, intrinsic risk of the procedure and the lack of evidence-based parameters that may guide clinical decisions. Consequently, noninvasive methods have been developed to explore potential clinical benefits from assessing the degree of myocardial inflammation and fibrosis in patients with Chagas' disease. In our group, the histopathologic findings of myocardial inflammation via endomyocardial biopsy were compared with two noninvasive techniques, gallium-67 myocardial uptake scintigraphy and MRI. Despite both noninvasive techniques detecting Chagas' myocarditis, MRI was more accurate due to the higher spatial resolution.

Myocardial delayed enhancement by MRI has been proved to be efficient in detecting myocardial fibrosis in ischemic and nonischemic myocardial disease. In Chagas' disease, delayed enhanced MRI can detect even traces of myocardial fibrosis in individuals in the indeterminate phase, that is, the period before presentation of cardiac electrical or mechanical abnormalities.[3] Such refined accuracy would potentially be helpful for characterization and treatment of arrhythmogenic foci in patients with Chagas' disease. Moreover, the severity of myocardial fibrosis detected by MRI is proportional to the severity of myocardial dysfunction and clinical symptoms.

In patients in the chronic phase of the disease, myocardial fibrosis is found particularly at the apex and inferolateral regions of the left ventricle. Ischemia, inflammation, mechanical factors, and parasympathetic nerve cell destruction are considered among potential underlying mechanisms for these lesions. In these affected regions, ventricular wall aneurysms would develop in a later stage of Chagas' cardiomyopathy, constituting a classic sign of the disease. **Figure e37-1** shows the typical apex lesion with severe myocardial fibrosis in a heart examined at autopsy.

Myocardial Perfusion Myocardial ischemia has been frequently reported in patients with Chagas' disease and normal coronary angiograms. In fact, these patients have chest pain associated with electrocardiographic signs of ischemia simulating obstructive coronary artery disease. From a pathophysiologic standpoint, vascular dysautonomia due to denervation and inflammatory damage of the microcirculation is considered the leading cause of myocardial ischemia in these patients. **Figure e37-2** shows myocardial denervation and ischemia by scintigraphic imaging; the denervation demonstrated by the reduced cardiac uptake of ^{123}I-metaiodobenzylguanidine (MIBG) is concordant with the perfusion deficit, but is much larger, suggesting that denervation is the initiating event.

In angiographic studies, endothelium-dependent and -independent impairment in coronary vasodilation have been observed in patients with Chagas' disease.[4] With scintigraphic perfusion imaging using thallium-201, transient and permanent myocardial perfusion abnormalities have been described in patients with the disease (Chaps. 222

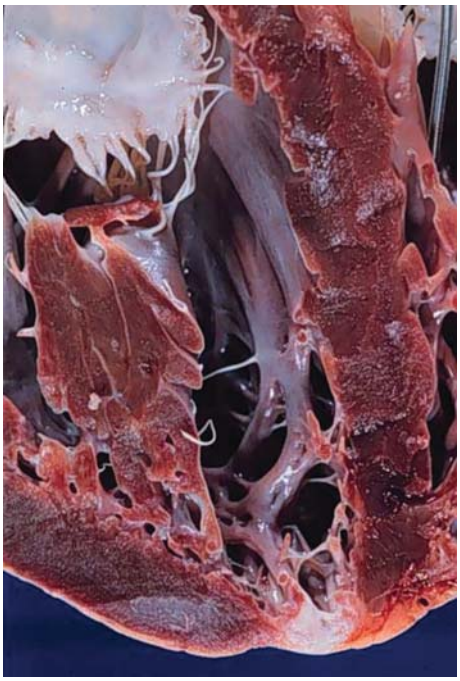

FIGURE e37-1 Photo of a heart from a patient with chronic chagasic cardiac disease, exhibiting a typical lesion at the left ventricle.

and e20). These studies demonstrate an elevated topographic correlation between perfusion and wall motion abnormalities. Even though prospective cohorts demonstrating a temporal association between perfusion defects and the development of wall motion dysfunction are lacking, it is plausible to consider that such perfusion defects would represent an early sign of Chagas' cardiomyopathy. In addition, these radionuclide studies also indicate that the perfusion defects are predominantly in the apex and inferolateral regions, which are those most affected by the inflammatory damage and the autonomic denervation.

From a clinical perspective, caution must be taken to interpret the presence of perfusion defects detected by either scintigraphy or MRI as an indication of epicardial coronary disease in patients with Chagas' disease. Actually, both the endothelium-dependent and -independent vasodilatory responses of coronary resistance vessels are also affected in patients with idiopathic dilated cardiomyopathy and angiographically normal coronary arteries. These patients have impairment of the vasodilator responses to both metabolic and pharmacologic stimuli and an increased sensitivity to vasoconstrictors. Such evidence indicates that the segmental microvascular dysfunction observed in patients with Chagas' disease is unlikely to be pathogen-dependent but rather an early sign of ventricular wall disease. Whether such perfusion disturbances also contribute to the detriment of ventricular wall motion is presently unknown.

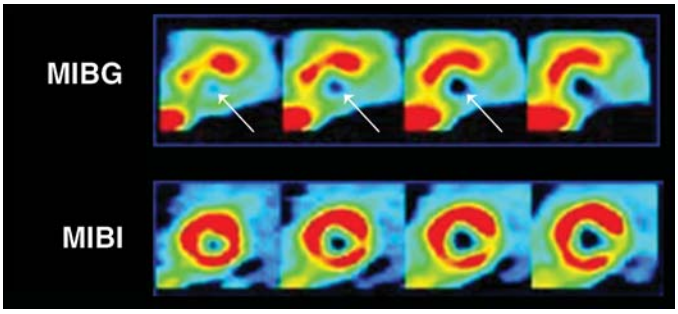

FIGURE e37-2 Myocardial denervation and ischemia detected by scintigraphic imaging. *Above.* The denervation is demonstrated by the reduced cardiac uptake of ^{123}I-metaiodobenzylguanidine (MIBG) (*arrows*). ***Below.*** A permanent perfusion deficit with smaller size as compared with the denervation is demonstrated by scintigraphic perfusion with ^{99m}Tc-sestamibi (MIBI).

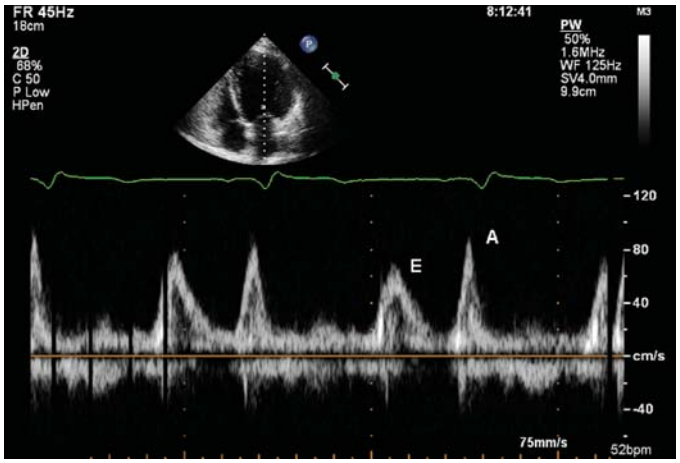

FIGURE e37-3 Echocardiographic analysis of mitral inflow by pulse-wave Doppler showing diastolic function in a patient with Chagas' disease. Normally, the early flow velocity (E) is higher than the late flow velocity (A), which is related to atrial contraction. In this case, there is an inverted E/A relation, indicating the impairment of left ventricular relaxation.

Myocardial Wall Motion In the acute phase of the disease, pericardial effusion and occasionally myocardial wall motion abnormalities have been described. By definition, in the indeterminate phase, chronically infected individuals remain a parasite reservoir without being affected by the disease and consequently have a normal life expectancy. Hence, the appearance of an abnormality of the ventricular wall reflects progression of the disease and must be considered, accordingly, as the onset of the chronic phase of Chagas' disease.

In the chronic phase, thinning, aneurysm formation, and wall motion dysfunction are the most frequent findings detected on echocardiography. In keeping with necropsy, scintigraphic, and MRI studies, these echocardiographic findings are mostly observed in the apex and inferobasal regions of the left ventricle. The segmental thinning of the ventricular wall, particularly at the apex, promotes remodeling of the left ventricle, which may increase mechanical tension and contribute to aneurysm formation in this area. Nevertheless, abnormalities of other left ventricular segments can also be found.

As the disease progresses, the affected segments of the ventricular wall become hypokinetic, akinetic, or even dyskinetic. Frequently, diastolic dysfunction occurs in an early phase of the disease, as shown in Fig. e37-3. The thinning of the apex becomes an aneurysm, and the global systolic function of the left and right ventricles deteriorates. Initially, the systolic dysfunction may be apparent only under pharmacologic stress by dobutamine or phenylephrine, characterizing the reduction of systolic reserve. Echocardiography or MRI can accurately detect these characteristics.

The right ventricle is first and predominantly affected in the majority of patients with Chagas' disease. This may occur even in the absence of any detectable abnormality in the left ventricle. Accordingly, in these patients, the development of heart failure is typically manifested with a predominance of systemic over pulmonary congestion. Because echocardiography has a low accuracy for detecting right ventricular dysfunction, radionuclide angiography or MRI is preferred for evaluation of this chamber.

Rx CHAGAS' DISEASE

ETIOLOGIC TREATMENT Nitrofurans and nitroimidazole derivatives (nifurtimox and benznidazole respectively) have been the cornerstones of trypanosomicidal treatment in recent decades. These compounds seem to exert their trypanosomicidal action by the generation of superoxide radicals causing oxidative stress and cell death in susceptible parasites.

From the clinical point of view, the activity of treatment with both compounds is evident in terms of parasite load reduction and serologic conversion to negative in the acute phase of Chagas' disease and in congenital

infection. In the indeterminate phase, new promising findings have been reported particularly in children and young adults, showing long-lasting disappearance of specific antibodies in 58–98% of treated individuals together with a 10–20% rate reduction of side effects. In general, treatment with nitroimidazole derivatives, especially benznidazole, has been shown to be effective more frequently in reducing parasitemia and specific antibody titers in individuals in the indeterminate phase. Whether this treatment will prevent the development of cardiac or digestive complications of the disease is still unclear. Large randomized controlled trials are required to define this issue.

The effect of trypanosomicidal therapies on parasite load or disease progression in patients in the chronic symptomatic phase of Chagas' disease is even less clear. The disappearance of specific antibodies is uncommon in the chronic phase and may take up to 10–20 years. Parasite DNA is present in several tissues and may induce immune response and perhaps disease progression. Hence, the ideal therapeutic schema or duration for such chronic patients is unknown. In addition, several adverse reactions, such as peripheral neuropathy and skin disorders, have been reported in a large proportion of patients treated with both nifurtimox and benznidazole. Thus, there is insufficient evidence to demonstrate the clinical benefit for trypanosomicidal treatment in patients in the chronic phase of Chagas' disease.

Novel potential targets for trypanosomicidal treatment have been investigated to reduce side effects and increase treatment efficacy. Sterol biosynthesis inhibitors, protein prenylation inhibitors, protease inhibitors, and phospholipid analogues are among potential chemotherapeutic agents for this purpose. Although some of these compounds have already demonstrated potent inhibitory activity in vitro against *T. cruzi*, clinical benefits have not been proved thus far.

COMPLEMENTARY TREATMENT In the acute phase, symptoms disappear in up to 2 months. In rare cases of severe acute myocarditis, an empirical combination of corticoid and trypanosomicidal treatments has been attempted. In animal models, immunosuppressive therapy in combination with benznidazole has been demonstrated to be effective in attenuating the inflammatory response. However, insufficient studies in humans have been done to define the ideal approach in these cases.

The aim of treatment in the chronic phase of Chagas' disease is to attenuate symptoms and prevent complications. The most relevant cardiac complications in the late chronic phase are heart failure and life-threatening arrhythmias. The mortality attributable to Chagas' disease is fundamentally related to these two disorders. Even though few studies have compared the efficacy of the treatment for heart failure in patients with and without Chagas' disease, the standards of clinical treatment are mostly the same. Heart failure in both classes of patients responds equally to digitalis, diuretic, and vasodilator therapy (Chaps. 227 and 231). The use of angiotensin-converting enzyme (ACE) inhibitors has been reported to reduce neurohormonal activation, improving heart failure symptoms and nonlethal arrhythmias. In an animal model, there is evidence that aldosterone blockade with spironolactone attenuates myocardial remodeling and inflammatory infiltration and may reduce mortality in Chagas cardiomyopathy.[8]

As is the case for nonchagasic heart failure, the use of beta blockers is also believed to be beneficial in patients with Chagas' disease. In addition, beta blockers may reduce the transmyocardial pressure gradient and attenuate subendocardial ischemia, which is supposed to participate in the deterioration of ventricular function in Chagas' disease. The blockade of sympathetic activity, which is typically augmented in these patients, may help to attenuate ventricular remodeling and arrhythmias. Thus, despite the lack of specific trials to verify this assumption, beta blocker use in patients with Chagas' disease who also have heart failure is indicated.

There is some evidence that amiodarone can prevent complex arrhythmias in patients with heart failure irrespective of the cause. In small studies in patients with Chagas' disease with sustained ventricular tachyarrhythmias, amiodarone provided longer intervals free of arrhythmic events compared with other antiarrhythmic drugs. The efficacy of amiodarone in preventing ventricular tachyarrhythmias seems to be reduced in patients with severe systolic dysfunction. In these patients, percutaneous catheter ablation, implantation of implanted cardioverter/defibrillators (ICD) or surgical procedures may be attempted.

Reentry is considered to be the major arrhythmogenic mechanism of ventricular tachyarrhythmias in Chagas' disease, it is usually in the perianeurysmatic zone or in focal areas of fibrosis in the inferolateral region of the left ventricle. Surgical treatment consists of conventional aneurysmectomy associated with endocardial or myocardial resection and/or isolation of critical sites of reentry by endocardiectomy or cryoablation guided by electrophysiologic mapping. Alternatively, interpapillary endomyocardial cryoablation without electrophysiologic mapping has been attempted in patients with sustained ventricular tachycardia and akinesia or dyskinesia of the inferolateral region of the left ventricle, with efficacy in nearly 60%. Because the mortality of the procedure is high, surgical ablation should be considered only when systolic dysfunction is not severe, the overall surgical risk is low, and when other surgical procedures, such as aneurysmectomy, are not indicated.

Nonsurgical simultaneous epicardial and endocardial catheter ablation has been introduced recently as an alternative approach in the treatment of patients with Chagas' disease and recurrent ventricular tachycardia.[10] Because critical sites of reentry may be endocardial, intramural, or epicardial, this combined approach provides a higher efficacy for treating recurrent ventricular tachycardia. For patients with severe systolic dysfunction, however, the insertion of an ICD is the treatment of choice, particularly in those with left ventricular ejection fractions <30%. Symptomatic or high-risk bradyarrhythmia is frequently manifested in these patients. Thus, implantation of an ICD with pacing capability is often indicated. ICDs are effective in preventing death due to ventricular tachyarrhythmias, but frequent shocks triggered by tachycardias, life-threatening or not, can lead to a reduced quality of life. Therefore, a combination of ICD, antiarrhythmic therapy, and catheter ablation appears to be ideal in these patients.

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