

Chagas heart disease: pathophysiologic mechanisms, prognostic factors and risk stratification

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Chagas heart disease (CHD) results from infection with the protozoan parasite Trypanosoma cruzi and is the leading cause of infectious myocarditis worldwide. It poses a substantial public health burden due to high morbidity and mortality. CHD is also the most serious and frequent manifestation of chronic Chagas disease and appears in 20-40% of infected individuals between 10-30 years after the original acute infection. In recent decades, numerous clinical and experimental investigations have shown that a low-grade but incessant parasitism, along with an accompanying immunological response [either parasite-driven (most likely) or autoimmune-mediated], plays an important role in producing myocardial damage in CHD. At the same time, primary neuronal damage and microvascular dysfunction have been described as ancillary pathogenic mechanisms. Conduction system disturbances, atrial and ventricular arrhythmias, congestive heart failure, systemic and pulmonary thromboembolism and sudden cardiac death are the most common clinical manifestations of chronic Chagas cardiomyopathy. Management of CHD aims to relieve symptoms, identify markers of unfavourable prognosis and treat those individuals at increased risk of disease progression or death. This article reviews the pathophysiology of myocardial damage, discusses the value of current risk stratification models and proposes an algorithm to guide mortality risk assessment and therapeutic decision-making in patients with CHD.

Key words: Chagas disease - Chagas heart disease - pathophysiology - pathogenesis - prognostic factors - risk stratification

A century after its discovery, Chagas disease continues to be a serious health and economic problem in most Latin American countries. Moreover, due to growing population movements, an increasing number of imported Chagas disease cases have now been detected in non-endemic areas, such as North America and many parts of Europe, Asia and Oceania (Schmunis 2007). Recent estimates indicate that at least 8-10 million people are chronically infected with *Trypanosoma cruzi* (OPS 2006, Remme et al. 2006) and around 50,000 new cases occur each year (Dias et al. 2008).

Chagas disease has two successive phases: acute and chronic. Acute infection is often asymptomatic or may manifest as a self-limited febrile illness that lasts 4-8 weeks. Clinical manifestations of chronic Chagas disease are related to the pathologic involvement of the heart, oesophagus and/or colon (Coura 2007).

Cardiac involvement is the most serious and frequent manifestation of chronic Chagas disease and affects 20-40% of individuals, typically years or decades after the initial infection. Chagas heart disease (CHD) is also the most common cause of cardiomyopathy in Latin America and, in endemic areas, it is the leading cause of

cardiovascular death among patients aged 30-50 years (Rassi Jr et al. 2000).

Chronic Chagas cardiomyopathy presents as three major syndromes, which may coexist in the same patient: cardiac dysrhythmia, heart failure and thromboembolism (systemic and pulmonary). Clinical presentation varies widely according to disease duration and the extent and location of cardiac lesions (Rassi Jr et al. 2000).

Pathophysiology of myocardial damage in chronic CHD

CHD is an acquired inflammatory cardiomyopathy characterised by a chronic fibrosing myocarditis (varying from focal or multifocal to diffuse) and a progressive impairment of myocardial contractile function (Rossi 1991). Numerous contributing mechanisms have been suggested to explain the pathogenesis of CHD (Marin-Neto et al. 2007). A consensus is now emerging that parasite persistence and the parasite-driven immune response play a pivotal role (Tarleton 2003a, b, Kierszenbaum 2007, Bonney & Engman 2008). In contrast, whether one or more of the autoimmune events described in experimental models and human cases of Chagas disease can contribute to, or aggravate, this pathology, has been more controversial and difficult to validate (Tarleton 2003a, b). The evidence supporting this viewpoint can be summarised as follows: (i) in recent years, more powerful and sensitive methods of parasite detection, such as immunohistochemistry and polymerase chain reaction (PCR), have demonstrated a higher frequency of *T. cruzi* antigens and parasite DNA in chronic lesions;

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also, a significant correlation between parasite persistence and tissue inflammation has been clearly documented; therefore, the supposed absence of parasites at or near sites of disease (the mainstay of the autoimmune theory), probably reflects the use of insensitive histological techniques in past decades (Tarleton & Zhang 1999); (ii) interventions that lessen the parasite burden, such as aetiologic treatment with benznidazole or nifurtimox, reduce clinical disease in humans (Viotti et al. 2006, Fabbro et al. 2007) and experimental animals (Andrade et al. 1991, Garcia et al. 2005), in contrast to immunosuppressive treatments/situations that clearly increase *T. cruzi* parasitemia (Rassi et al. 1997) and usually aggravate the inflammatory response (Sartori et al. 2007); (iii) reinfection or continued exposure (due to continued residence in areas of active transmission) seems to increase the parasite load and disease severity in experimental models and in human cases (Bustamante et al. 2002, Storino et al. 2002); (iv) although anti-self responses are encountered in *T. cruzi* infection, the nature of anti-self antibodies in experimental and human chronic Chagas disease is heterophilic, with a poor correlation with the heart lesions (i.e., there is no direct and definitive evidence that the immune reactions against the mimicked auto-antigens are actually pathogenic) (Tarleton 2003a, b); and (v) data supporting the direct involvement of either molecular mimicry or polyclonal activation in the pathogenesis of myocardial lesions ascribed to *T. cruzi* infection are sparse and inconclusive.

The release of intracellularly replicated trypanosomes followed by parasite-driven myocyte necrosis and inflammation not only contributes decisively to pathogenesis, but may also trigger additional mechanisms of cardiac damage (Bonney & Engman 2008). Several coronary microvascular abnormalities, including increased platelet activity, microthrombi, microvascular spasm and endothelial dysfunction have been reported in animal models (Rossi 1990) and in some studies in humans (Marin-Neto et al. 1992, Simões et al. 2000). These phenomena could be explained by vascular endothelial cell damage caused either by *T. cruzi* or immune effector cells directly, or could result from the underlying inflammatory process (Rossi 1990). Abnormal reactivity to vasodilating and vasoconstricting stimuli has also been reported in the epicardial coronary arteries of chagasic patients (Torres et al. 1995). It is possible that such derangements contribute to the exacerbation of myocardial cell damage and fibrosis and participate in the genesis of ischemic-like symptoms, electrocardiographic changes and perfusion defects described in chagasic patients with angiographically normal coronary arteries (Marin-Neto et al. 1992).

Intense neuronal depopulation has been demonstrated in several independent pathologic studies since the early 1920s (Chagas & Villela 1922). In the 1950s, studies using standardised methods of counting intramural neurons showed a strikingly diminished number of cardiac ganglion cells in chagasic hearts. Because the intramural cardiac ganglia are mostly parasympathetic, a neurogenic ("parasympathicopriva") hypothesis was postulated

(Köberle 1959). According to this theory, a long-lasting autonomic imbalance leads to a catecholamine-induced cardiomyopathy characterised by myocardial hypertrophy and cardiac dilation, whereas myocardial inflammation is not considered to be an important element for cardiac damage. Consistent with anatomic parasympathetic denervation, abnormal autonomic cardiac regulation has been shown in many functional investigations, even before the development of ventricular dysfunction (Ribeiro et al. 2001). Because of the dysautonomia, chagasic patients are deprived of the tonic inhibitory action normally exerted by the parasympathetic system on the sinus node and they also lack the vagally mediated mechanism to respond to transient changes in blood pressure or venous return by using quick-onset bradycardia or tachycardia (Amorim & Marin-Neto 1995). However, several conceptual obstacles have challenged the applicability of the neurogenic theory (Marin-Neto et al. 2007). These include the subtleness and variability of the intensity of cardiac denervation in CHD patients and the lack of correlation between parasympathetic denervation and the extent of myocardial dysfunction. Moreover, sympathetic denervation has also been shown at the sinus node level and in myocardial regions during the early stages of disease (Marin-Neto et al. 1980, Simões et al. 2000).

Nevertheless, neurogenic disturbances may play a contributing role in the complications of the chronic phase of Chagas disease by triggering malignant arrhythmia and sudden death and by disturbing the coronary microcirculation control (Maturri 1996). A schematic overview of the pathogenesis of chronic CHD is shown in Fig. 1.

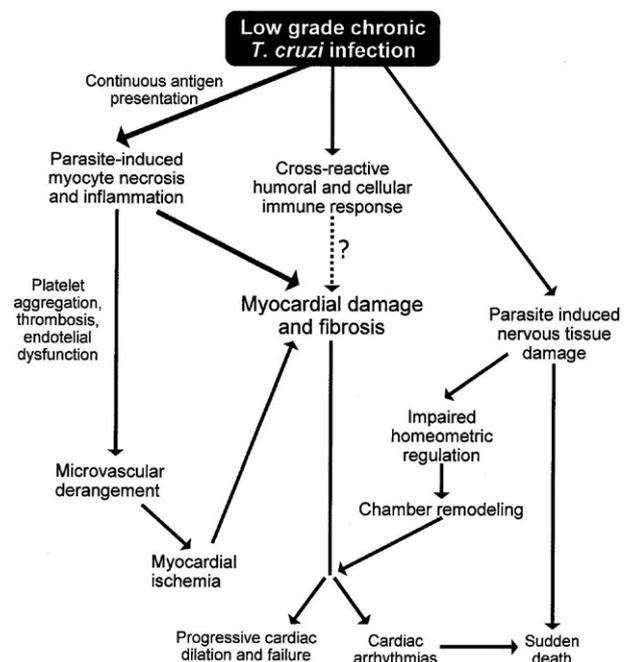


Fig 1: schematic view of main pathogenetic mechanisms in chronic Chagas heart disease (modified from Marin-Neto et al. 2007).

Since parasite persistence is required for the development of myocardial damage in Chagas disease, the next step is to try to understand why a subset of individuals chronically infected with *T. cruzi* develops disease, whereas others do not. It is quite possible that factors such as parasite burden, parasite strain and tissue tropism, time of infection and the host's genetic background all play some role. However, it seems that the effectiveness of the host immune response in controlling parasites in specific tissues plays the most important role. According to this hypothesis, when the immune control is inefficient, parasite load and inflammation increase. In contrast, a well-executed immune response, capable of reducing parasite burden and limiting its inflammatory consequences, results in less tissue damage. Some in-depth overviews of the immunoregulation and pathology of the heart in Chagas disease have been published during the current decade (Higuchi et al. 2003, Tarleton 2003a, b, Marin-Neto et al. 2007, Dutra & Gollob 2008).

A variety of structural and functional cardiovascular changes have been described in patients with CHD. Normal myocardium is composed of various cell populations: (i) cardiac myocytes tethered within an extracellular scaffolding of fibrillar collagen and (ii) non-cardiac myocytes, which include endothelial and vascular smooth muscle cells of the intramural coronary circulation and fibroblasts located in the interstitial and perivascular spaces. A large body of evidence indicates that myocardial structure in CHD is affected by three key pathological processes: inflammation, cell death and fibrosis (Andrade 1999). The inflammatory infiltrate consists mainly of T lymphocytes, with a predominance of CD8⁺ cells. Macrophages, eosinophils, plasma cells, neutrophils and mast cells are also present to a lesser extent. The most frequently affected cells in individuals with CHD are the cardiac myocytes (myonecrosis >

myocytolysis > contraction band necrosis), the conduction system cells and the parasympathetic cardiac neurons and fibres. Cardiac damage results from the rupture of infected cells releasing trypomastigotes, the local production of some proinflammatory cytokines and other cytotoxic mechanisms involving CD8⁺ T cells and, less frequently, CD4⁺ T cells. Although intact parasites are rarely found in the hearts of chronic CHD patients using standard histologic analyses, *T. cruzi* antigen fragments and parasite DNA are frequently detected in the inflammatory lesions using highly sensitive techniques such as PCR or immunohistochemistry. Focal or diffuse areas of myocellular hypertrophy may be observed with or without adjacent inflammatory infiltrates.

Another important feature of CHD is a marked reparative and reactive fibrosis, characterised by a diffuse and dense interstitial accumulation of collagen that encloses individual fibres or groups of fibres (Rossi 1991). All areas of the heart, including the conduction system, may be involved. This explains the frequent occurrence of atrioventricular and intraventricular blocks and sinus node dysfunction in patients with CHD. The progressive destruction of cardiac fibres, the intense fibrosis replacing destroyed myocytes and the hypertrophy of the remaining myocytes all predispose the patient to heart failure and cardiac arrhythmias (Fig. 2).

Ventricular aneurysms are a common finding in CHD. Pathological and functional data suggest that the microvascular control in chagasic hearts, in comparison with non-chagasic hearts, may be severely impaired, probably due to the presence of abnormal substances induced by the inflammation and/or directly by the parasites. These microvascular disturbances might lead to the existence of regional patterns of abnormal vasodilation or vasoconstriction, especially in the watershed zones of the main epicardial coronary arteries. It has

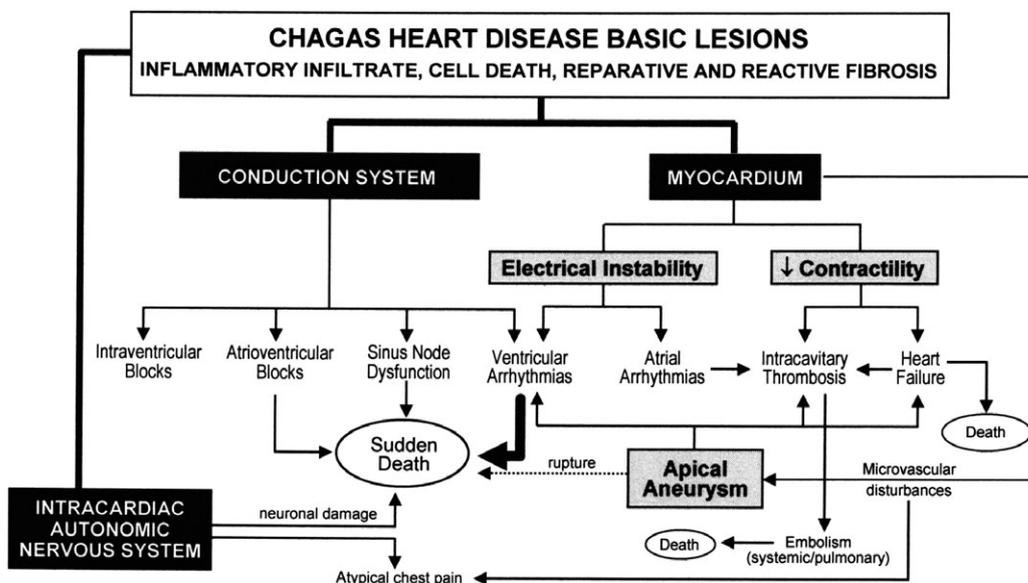


Fig. 2: diagram of the pathophysiology of CHD (adapted from Rassi Jr et al. 2000).

been postulated that the consequent low pressure perfusion and associated ischemia may occur in two border zones between the principal coronary artery branches: one involving the anterior descending and the posterior descending arteries, and resulting in the formation of the apical aneurysm, and the other between the right and the circumflex arteries, resulting in the formation of an aneurysmatic lesion at the basal posterior wall of the left ventricle (Higuchi et al. 2003).

Prognostic factors and risk stratification

CHD is a heterogeneous condition with a wide variation in clinical course and prognosis. Many patients remain asymptomatic throughout life; some have only conduction defects and mild segmental wall motion abnormalities; some develop severe symptoms of heart failure, thromboembolic phenomena and multiple disturbances of rhythm; and others die suddenly, often in the absence of previous significant symptoms (Rassi Jr et al. 2000). In general, sudden cardiac death (usually due to ventricular fibrillation) is the most common cause of death (55-65% of patients), followed by congestive heart failure (25-30% of patients) and cerebral or pulmonary embolism (10-15% patients). Although sudden death predominates in patients with less extensive myocardial involvement and in those with significant pre-existing ventricular arrhythmias, death from pump failure is

slightly more common in patients with congestive heart failure (Rassi Jr et al. 2001).

A better understanding of prognostic factors in CHD has evolved over recent decades. Knowledge of these predictors of unfavourable outcome can help to identify patients at different degrees of risk, facilitate choice among treatment alternatives and aid patient counselling.

In 2007, we published the first systematic review integrating the results of all studies on the chronic phase of Chagas disease that used multivariable regression models of prognosis and analysed a clearly defined outcome, such as all-cause mortality, sudden cardiac death or cardiovascular death (Rassi Jr et al. 2007). From 606 potentially relevant studies published between 1985-2006, 12 articles met the inclusion criteria and were thereby selected for analysis (Espinosa et al. 1991, Hagar & Rahimtoola 1991, Bestetti et al. 1994, 1996, Carrasco et al. 1994, Mady et al. 1994, Garzon et al. 1998, Rodriguez-Salas et al. 1998, Leite et al. 2003, Salles et al. 2003, Viotti et al. 2004, Rassi Jr et al. 2006). Despite differences in the sample populations between studies (e.g., some studies included only patients with CHD while others included patients with and without manifested cardiomyopathy) and in the set of prognostic variables investigated in each study, four independent markers of increased risk of death were identified: New York Heart Association (NYHA) functional class III/IV, cardiomegaly on chest radiography, impaired

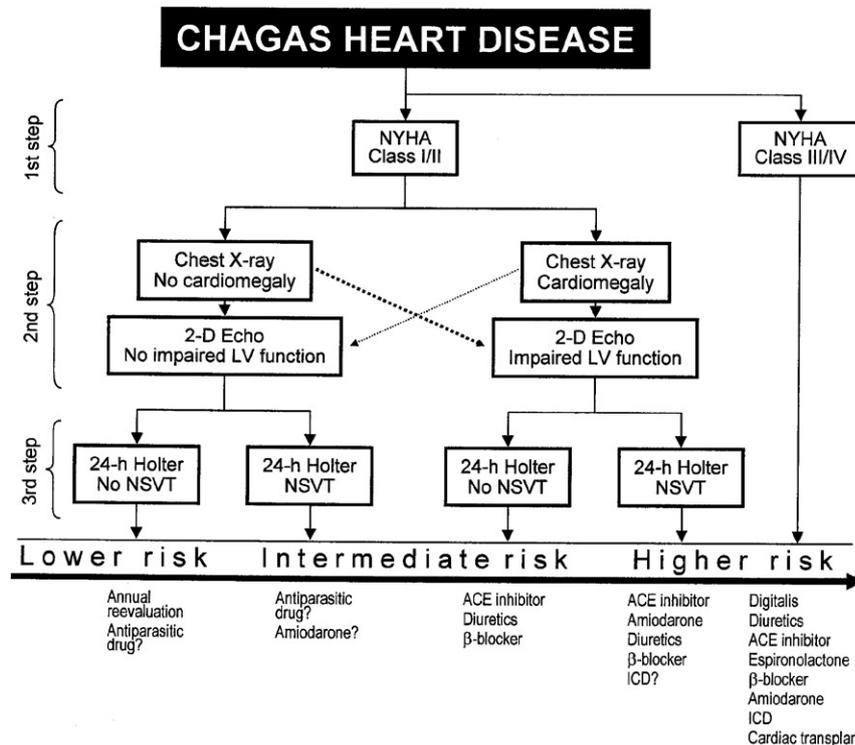


Fig. 3: proposed algorithm to guide mortality risk assessment and therapeutic decision-making in patients with Chagas heart disease (CHD). The evaluation of the functional capacity by New York Heart Association (NYHA) classification would provide the first line of risk assessment. Left ventricular (LV) function indexes obtained ideally by two techniques, chest radiography and echocardiography would represent the second step. The third method of evaluation would be the Holter monitoring for analysis of the presence of nonsustained ventricular tachycardia (NSVT) (adapted from Rassi Jr et al. 2007).

TABLE
 Characteristics of multivariable studies of prognostic factors for mortality in chronic Chagas disease

Author	Patients (n)	Chagas disease population	Follow-up (years)	All-cause mortality (%)	SCD (%)	Annual mortality rate (%)	Independent predictors of mortality (multivariable analysis; p < 0.05)
Espinosa et al. (1991)	66	CHD	Up to 10	27.3	39	NA	↓SBP; Afib; ↑CTI; ↑LVDDV
Hagar & Rahimtoola (1991)	25	CHD	4.4	32.0	75	7.3	CHF; LV aneurysm or dysfunction
Carrasco et al. (1994)	556	CHD-/CHD	Up to 15	21.4	25	NA	↑HR; NYHA IV; ↑LVDDVindex; ↑LVSS; ↓JEF
Bestetti et al. (1994)	56	CHD	2.0	28.6	69	14.3	↓JEF
Mady et al. (1994)	104	CHF (males)	2.5	48.1	64	19.2	↓JEF; ↓VO2max
Bestetti et al. (1996)	74	CHD	1.5	24.3	44	16.2	apical aneurysm; ↑LVDD
Rodriguez-Salas et al. (1998)	283	CHD	4.0	38.2	37	9.6	↑age; dyspnea; AVB; RBBB; ST ELE; ↑EPSS
Garzon et al. (1998)	987	CHD-/CHD	7.0	37.3	46	5.3	CHF; abnormal ECG; PVCs; ↑CTI; ↓JEF
Leite et al. (2003)	115	VT	4.3	39.1	NR	9.1	NYHA III/IV; SVT induction (EPS)
Salles et al. (2003)	738	CHD-/CHD	4.8	8.4	64	1.7	↑age; ↑HR; Q waves; ↑QTd; ↑CTI; ↑LVSD
Vioti et al. (2004)	849	CHD-/CHD	9.9	1.9	NR	0.2	Progression to CHF; ↑LVSD; ↓JEF
Rassi Jr. et al. (2006)	424	CHD	7.9	30.7	62	3.9	NYHA III/IV; ↑CTI; WMA; NSVT; low QRS voltage; male sex
Benchimol Barbosa (2007)	50	CHD-/CHD	7.0	18.0 ^a	NR	2.6	Apical aneurysm; ↓JEF; PVCs > 614/h (Holter)
Nunes et al. (2008)	158	CHD	2.8	27.8	36	9.8	NYHA III/IV; ↑RV Tei index; ↓EF
Ribeiro et al. (2008)	184	CHD-/CHD	6.2	7.1	NR	1.1	↓JEF; NSVT; LP (SAECC)
Theodoropoulos et al. (2008)	127	CHF	2.1	50.0	NR	23.8	No BB use; digoxin use; ↓Na ⁺ ; ↓JEF; NYHA IV
Nunes et al. (2009)	192	CHD	2.8	32.3	39	11.5	NYHA II/III/IV; ↑RV Tei index; ↓JEF; ↑LAV index; ↑E/E' ratio ^b
Gonçalves et al. (2009)	120	CHD-/CHD	18.5	35.0	17	1.9	Age ≥ 39; black colour; RBBB+LAH; LBBB; PVCs

a: cardiac mortality; b: cardiac mortality and heart transplantation; Afib: atrial fibrillation; AVB: atrioventricular block; BB: betablocker; CHD-: no Chagas heart disease; CHD: Chagas heart disease; CHF: congestive heart failure; CTI: cardiothoracic index; EF: ejection fraction; EPS: electrophysiologic study; EPSS: M-mode echocardiographic E-point septal separation; HR: heart rate; LAH: left anterior hemiblock; LAV: left atrial volume; LBBB: left bundle branch block; LP: late potential; LV: left ventricular; LVDD: left ventricular diastolic dimension; LVDDV: left ventricular diastolic volume; LVSD: left ventricular systolic dimension; LVSS: left ventricular systolic stress; NA: not available; NR: not reported; NSVT: nonsustained ventricular tachycardia; NYHA: New York Heart Association; PVCs: premature ventricular contractions; QTd: QT dispersion; RBBB: right bundle branch block; RV: right ventricular; SAECC: signal-averaged ECG; SBP: systolic blood pressure; SCD: sudden cardiac death; ST ELE: ST elevation; SVT: sustained ventricular tachycardia; VO2max: maximal oxygen consumption; WMA: wall motion abnormality (echo).

left ventricular (LV) function by echocardiogram or cineventriculography, and non-sustained ventricular tachycardia (NSVT) on 24 h Holter monitoring. Other often-mentioned prognostic factors, such as advanced age, male sex and ECG changes, showed inconsistent results. More recently, six other studies on the prognostic factors in chronic Chagas disease have been published (Benchimol Barbosa 2007, Nunes et al. 2008, 2009, Ribeiro et al. 2008, Theodoropoulos et al. 2008, Gonçalves et al. 2009). Their results were very similar to those obtained in our systematic review and corroborated our conclusions. The Table summarises the principal characteristics and global results of these 18 studies.

Based on these findings, we propose a risk stratification model for mortality in chagasic patients that combines prognostic factors related to three major clinical, pathophysiologic characteristics of the disease: symptoms of heart failure, expressed as the NYHA functional class III/IV; measures of ventricular dysfunction (i.e., cardiomegaly on chest radiography and decreased LV contractility and/or increased LV diameter on echocardiography); and a measure of ventricular electrical instability (presence of NSVT on 24 h Holter monitoring) (Fig. 3).

Patients with symptoms of heart failure, in NYHA class III/IV (because all of them invariably manifest associated cardiomegaly on chest radiography, global systolic dysfunction on echocardiogram and NSVT on Holter monitoring) and patients who are in NYHA class I/II and also have LV dysfunction on echocardiogram and NSVT on Holter monitoring are at the highest risk of death and should be regarded as candidates for aggressive therapeutic management. Conversely, patients with an abnormal ECG but who are in NYHA class I/II heart failure with neither LV dysfunction on echocardiography nor NSVT on Holter are at low risk of death. These patients should be followed up annually or biannually. Between these two extremes are patients with either LV dysfunction or NSVT. Such patients are at intermediate risk and their treatment strategies should be individualised.

REFERENCES

- Amorim DS, Marin-Neto JA 1995. Functional alterations of the autonomic nervous system in Chagas' heart disease. *São Paulo Med J* 113: 772-784.
- Andrade SG, Stocker-Guerret S, Pimentel AS, Grimaud JA 1991. Reversibility of cardiac fibrosis in mice chronically infected with *Trypanosoma cruzi*, under specific chemotherapy. *Mem Inst Oswaldo Cruz* 86: 187-200.
- Andrade ZA 1999. Immunopathology of Chagas disease. *Mem Inst Oswaldo Cruz* 94 (Suppl I): 71-80.
- Benchimol Barbosa PR 2007. Noninvasive prognostic markers for cardiac death and ventricular arrhythmia in long-term follow-up of subjects with chronic Chagas' disease. *Braz J Med Biol Res* 40: 167-178.
- Bestetti RB, Dalbo CM, Arruda CA, Correia Filho D, Freitas OC 1996. Predictors of sudden cardiac death for patients with Chagas' disease: a hospital-derived cohort study. *Cardiology* 87: 481-487.
- Bestetti RB, Dalbo CM, Freitas OC, Teno LA, Castilho OT, Oliveira JS 1994. Noninvasive predictors of mortality for patients with Chagas' heart disease: a multivariate stepwise logistic regression study. *Cardiology* 84: 261-267.
- Bonney KM, Engman DM 2008. Chagas heart disease pathogenesis: one mechanism or many? *Curr Mol Med* 8: 510-518.
- Bustamante JM, Rivarola HW, Fernández AR, Enders JE, Fretes R, Palma JA, Paglini-Oliva PA 2002. *Trypanosoma cruzi* reinfections in mice determine the severity of cardiac damage. *Int J Parasitol* 32: 889-896.
- Carrasco HA, Parada H, Guerrero L, Duque M, Duran D, Molina C 1994. Prognostic implications of clinical, electrocardiographic and hemodynamic findings in chronic Chagas' disease. *Int J Cardiol* 43: 27-38.
- Chagas C, Vilella E 1922. Cardiac form of American trypanosomiasis. *Mem Inst Oswaldo Cruz* 14: 5-61.
- Coura JR 2007. Chagas disease: what is known and what is needed - a background article. *Mem Inst Oswaldo Cruz* 102 (Suppl. I): 113-122.
- Dias JC, Prata A, Correia D 2008. Problems and perspectives for Chagas disease control: in search of a realistic analysis. *Rev Soc Bras Med Trop* 41: 193-196.
- Dutra WO, Gollob KJ 2008. Current concepts in immunoregulation and pathology of human Chagas disease. *Curr Opin Infect Dis* 21: 287-292.
- Espinosa RA, Pericchi LR, Carrasco HA, Escalante A, Martinez O, Gonzalez R 1991. Prognostic indicators of chronic chagasic cardiopathy. *Int J Cardiol* 30: 195-202.
- Fabbro DL, Streiger ML, Arias ED, Bizai ML, del Barco M, Amicone NA 2007. Trypanocide treatment among adults with chronic Chagas disease living in Santa Fe city (Argentina), over a mean follow-up of 21 years: parasitological, serological and clinical evolution. *Rev Soc Bras Med Trop* 40: 1-10.
- Garcia S, Ramos CO, Senra JF, Vilas-Boas F, Rodrigues MM, Campos-de-Carvalho AC, Ribeiro-Dos-Santos R, Soares MB 2005. Treatment with benznidazole during the chronic phase of experimental Chagas' disease decreases cardiac alterations. *Antimicrob Agents Chemother* 49: 1521-1528.
- Garzon SAC, Lorga AM, Jacob JLB, Greco OT, Vitola J, Machado NCS, Coelho WMC, Nicolau JC 1998. Predictors of mortality in chronic Chagas' heart disease: long term follow up of 987 subjects for up to 22 years. *J Am Coll Cardiol* 31 (Suppl. C): 107.
- Gonçalves JG, Dias Silva VJ, Calzada Borges MC, Prata A, Correia D 2009. Mortality indicators among chronic Chagas patients living in an endemic area. *Int J Cardiol*, in press.
- Hagar JM, Rahimtoola SH 1991. Chagas' heart disease in the United States. *N Engl J Med* 325: 763-768.
- Higuchi ML, Benvenuti LA, Reis MM, Metzger M 2003. Pathophysiology of the heart in Chagas' disease: current status and new developments. *Cardiovasc Res* 60: 96-107.
- Kierszenbaum F 2007. Mechanisms of pathogenesis in Chagas disease. *Acta Parasitol* 52: 1-12.
- Köberle F 1959. Cardiopathia parasymphaticopriva. *Munch Med Wochenschr* 101: 1308-1310.
- Leite LR, Fenelon G, Simoes A Jr, Silva GG, Friedman PA, de Paola AA 2003. Clinical usefulness of electrophysiologic testing in patients with ventricular tachycardia and chronic chagasic cardiomyopathy treated with amiodarone or sotalol. *J Cardiovasc Electrophysiol* 14: 567-573.
- Mady C, Cardoso RH, Barretto AC, da Luz PL, Bellotti G, Pileggi F 1994. Survival and predictors of survival in patients with conges-

- tive heart failure due to Chagas' cardiomyopathy. *Circulation* 90: 3098-3102.
- Marin-Neto JA, Cunha-Neto E, Maciel BC, Simoes MV 2007. Pathogenesis of chronic Chagas heart disease. *Circulation* 115: 1109-1123.
- Marin-Neto JA, Gallo L Jr, Manco JC, Rassi A, Amorim DS 1980. Mechanisms of tachycardia on standing: studies in normal individuals and in chronic Chagas' heart patients. *Cardiovasc Res* 14: 541-550.
- Marin-Neto JA, Marzullo P, Marcassa C, Gallo Júnior L, Maciel BC, Bellina CR, L'Abbate A 1992. Myocardial perfusion defects in chronic Chagas' disease as detected by thallium-201 scintigraphy. *Am J Cardiol* 69: 780-784.
- Matturri L 1996. Pathologic substrates for arrhythmogenesis in chronic chagasic cardiopathy. *Cardiovasc Pathol* 5: 221-225.
- Nunes MC, Barbosa MM, Ribeiro AL, Barbosa FB, Rocha MO 2009. Left atrial volume provides independent prognostic value in patients with Chagas cardiomyopathy. *J Am Soc Echocardiogr* 22: 82-88.
- Nunes MC, Rocha MO, Ribeiro AL, Colosimo EA, Rezende RA, Carmo GA, Barbosa MM 2008. Right ventricular dysfunction is an independent predictor of survival in patients with dilated chronic Chagas' cardiomyopathy. *Int J Cardiol* 127: 372-379.
- OPS - Organizacion Panamericana de la Salud 2006. *Estimacion Cuantitativa de la Enfermedad de Chagas en las Americas*, Montevideo, 28p.
- Rassi A, Amato Neto V, de Siqueira AF, Doles J, Leite MS, Silva OQ, Cardoso VM 1997. The influence of corticoids, in chronic Chagas disease, administered in virtue of associated disorders. *Rev Soc Bras Med Trop* 30: 93-99.
- Rassi A Jr, Rassi A, Little WC 2000. Chagas' heart disease. *Clin Cardiol* 23: 883-889.
- Rassi A Jr, Rassi A, Little WC, Xavier SS, Rassi SG, Rassi AG, Rassi GG, Hasslocher-Moreno A, Sousa AS, Scanavacca MI 2006. Development and validation of a risk score for predicting mortality in Chagas' heart disease. *N Engl J Med* 355: 799-808.
- Rassi A Jr, Rassi A, Rassi SG 2007. Predictors of mortality in chronic Chagas disease: a systematic review of observational studies. *Circulation* 115: 1101-1108.
- Rassi A Jr, Rassi SG, Rassi A 2001. Sudden death in Chagas disease. *Arq Bras Cardiol* 76: 75-96.
- Remme JHF, Feenstra P, Lever PR, Médiçi A, Morel C, Noma M, Ramaiah KD, Richards F, Seketeli A, Schmunis G, van Brakel WH, Vassal A 2006. Tropical diseases targeted for elimination: Chagas disease, lymphatic filariasis, onchocerciasis, and leprosy. In Jamison DT, Breman JG, Measham AR, Alleyne G, Claeson M, Evans DB, Jha P, Mills A, Musgrove P (eds.), *Disease control priorities in developing countries*, The World Bank and Oxford University Press, New York, p. 433-449.
- Ribeiro AL, Cavalvanti PS, Lombardi F, Nunes Mdo C, Barros MV, Rocha MO 2008. Prognostic value of signal-averaged electrocardiogram in Chagas disease. *J Cardiovasc Electrophysiol* 19: 502-509.
- Ribeiro AL, Moraes RS, Ribeiro JP, Ferlin EL, Torres RM, Oliveira E, Rocha MO 2001. Parasympathetic dysautonomia precedes left ventricular systolic dysfunction in Chagas disease. *Am Heart J* 141: 260-265.
- Rodriguez-Salas LA, Klein E, Acquatella H, Cataliotti F, Davalos VV, Gomez-Mancebo JR, Gonzalez H, Bosch F, Puigbo JJ 1998. Echocardiographic and clinical predictors of mortality in chronic Chagas' disease. *Echocardiography* 15: 271-278.
- Rossi MA 1990. Microvascular changes as a cause of chronic cardiomyopathy in Chagas' disease. *Am Heart J* 120: 233-236.
- Rossi MA 1991. The pattern of myocardial fibrosis in chronic Chagas' heart disease. *Int J Cardiol* 30: 335-340.
- Salles G, Xavier S, Sousa A, Hasslocher-Moreno A, Cardoso C 2003. Prognostic value of QT interval parameters for mortality risk stratification in Chagas' disease: results of a long-term follow-up study. *Circulation* 108: 305-312.
- Sartori AM, Ibrahim KY, Nunes Westphalen EV, Braz LM, Oliveira OC Jr, Gakiya E, Lopes MH, Shikanai-Yasuda MA 2007. Manifestations of Chagas disease (American trypanosomiasis) in patients with HIV/AIDS. *Ann Trop Med Parasitol* 101: 31-50.
- Schmunis GA 2007. Epidemiology of Chagas disease in non-endemic countries: the role of international migration. *Mem Inst Oswaldo Cruz* 102 (Suppl. I): 75-85.
- Simões MV, Pintya AO, Bromberg-Marin G, Sarabanda AV, Antloga CM, Pazin-Filho A, Maciel BC, Marin-Neto JA 2000. Relation of regional sympathetic denervation and myocardial perfusion disturbance to wall motion impairment in Chagas' cardiomyopathy. *Am J Cardiol* 86: 975-981.
- Storino R, Auger S, Caravello O, Urrutia MI, Sanmartino M, Jörg M 2002. Chagasic cardiopathy in endemic area versus sporadically infected patients. *Rev Saude Publica* 36: 755-758.
- Tarleton RL 2003a. *Trypanosoma cruzi* and Chagas disease: cause and effect. In KM Tyler, MA Miles (eds.), *World class parasites: American trypanosomiasis*, Vol. 7, Kluwer Academic Publisher, Dordrecht, p. 107-116.
- Tarleton RL 2003b. Chagas disease: a role for autoimmunity? *Trends Parasitol* 19: 447-451.
- Tarleton RL, Zhang L 1999. Chagas disease etiology: autoimmunity or parasite persistence? *Parasitol Today* 15: 94-99.
- Theodoropoulos TA, Bestetti RB, Otaviano AP, Cordeiro JA, Rodrigues VC, Silva AC 2008. Predictors of all-cause mortality in chronic Chagas' heart disease in the current era of heart failure therapy. *Int J Cardiol* 128: 22-29.
- Torres FW, Acquatella H, Condado JA, Dinsmore R, Palacios IF 1995. Coronary vascular reactivity is abnormal in patients with Chagas' heart disease. *Am Heart J* 129: 995-1001.
- Viotti RJ, Vigliano C, Laucella S, Lococo B, Petti M, Bertocchi G, Ruiz Vera B, Armenti H 2004. Value of echocardiography for diagnosis and prognosis of chronic Chagas disease cardiomyopathy without heart failure. *Heart* 90: 655-660.
- Viotti RJ, Vigliano C, Lococo B, Bertocchi G, Petti M, Alvarez MG, Postan M, Armenti A 2006. Long-term cardiac outcomes of treating chronic Chagas disease with benznidazole versus no treatment: a nonrandomized trial. *Ann Intern Med* 144: 724-734.