

Cardiac resynchronization therapy for patients with chronic systolic heart failure secondary to Chagas cardiomyopathy in the 21st century

Terapia de ressincronização cardíaca em pacientes com insuficiência cardíaca crônica sistólica secundária à cardiomiopatia da doença de Chagas no século 21

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In the 21st century, Chagas disease continues to be a major health problem in South America because it affects 10 million people, and other 20 million are at risk of acquiring the disease [1]. It must be emphasized, however, that the disease is no longer confined to South America due to international immigration. In fact, Chagas disease has persistently been identified in non-endemic countries such United States, Spain, Canada, and Australia [1]. As a result, the global economic burden of the disease is impressive, reaching the figure of US 8 billion annually [2].

Chagas disease is caused by the protozoan *Trypanosoma cruzi*, which is transmitted to humans when the feces of a sucking bug contaminate a skin lesion or eye mucosae [1]. However, chronic Chagas disease appears many years after initial infection (in general, up two decades). Chagas cardiomyopathy is the protean clinical manifestation of the chronic disease, manifesting by ventricular dysrhythmias [3], sudden cardiac death [4], thromboembolism [5], and chronic heart failure (CHF) [6].

In Chagas disease patients, CHF is associated with reduced systolic function, as no case of CHF with preserved left ventricular function has been described in patients with this condition. The disease can affect up to 5% of patients of a population-based and about 50% of a referral center-based cohort [6]. Chagas disease heart failure has a higher annual mortality [7], and its prognosis is worse than that observed in non-Chagas disease heart failure [8]. Irreversible left ventricular systolic dysfunction is the most frequent mode of death in patients with this condition in the contemporary era [9].

The pathogenesis of Chagas disease heart failure is similar to that seen in non-Chagas disease heart failure, with the neurohormonal activation playing a pivotal role. In addition,

an intracardiac autonomic imbalance [10] can expose the myocardium to the toxic effects of catecholamine [11]. Some studies suggest a benefit effect for angiotensin converting enzyme inhibitor as well as for beta-blocker therapy both experimentally [12] and in patients with this condition [8,13,14]. Obviously, other types of treatment modality are necessary, mainly in patients in the advanced stages of CHF.

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Cardiac resynchronization therapy (CRT) is an established therapeutic modality for patients with non-Chagas heart disease heart failure to improve mortality in those with advanced heart failure and left bundle branch block [15,16]. In a Brazilian scenario, this therapy is also cost-effective [17]. By contrast, little is known about the effects of CRT in patients with CHF secondary to Chagas cardiomyopathy in view of the few studies carried out in patients with this condition. Silva Menezes [18] has clearly shown that CRT with bifocal right ventricular pacing has no effect on left ventricular reverse remodeling in the mid-term follow up, besides increasing the number of arrhythmic episodes. Silva et al. [19] studied 29 patients with CHF, 52% of them with CHF secondary to Chagas cardiomyopathy with permanent right ventricular pacing. They showed in this small sample that CRT improves clinical status and left ventricular ejection fraction in the mid-term follow up in patients with Chagas disease heart failure, although a definite conclusion could not be established because such a study was neither randomized nor double-blinded. Therefore, further studies on the effect of CRT on patients with CHF sec-

Abbreviations, acronyms & symbols

CHF	Chronic heart failure
CRT	Cardiac resynchronization therapy

ondary to Chagas cardiomyopathy are sorely needed if we are planning to improve morbidity and mortality in such patients.

In this issue of the journal, Araújo et al. [20] presents a paper dealing with CRT in patients with CHF secondary to Chagas cardiomyopathy. The authors enrolled 72 patients in class III/IV, 100% on beta-blocker therapy (mean carvedilol daily dose=20 mg), 70% on angiotensin converting enzyme inhibitor/angiotensin receptor block, 47% with left bundle branch block, mean QRS duration 148.1 ± 17.5 msec, 15% on permanent right ventricular pacing, mean left ventricular systolic diameter 66.2 ± 7.6 mm, and mean left ventricular ejection fraction $27.3 \pm 7.7\%$. After a mean follow-up of 47 months, only 13% were in class III/IV, there was an 81% increase in the left ventricular ejection fraction, and a 12% decrease in the left ventricular systolic diameter. Importantly, this is the largest cohort of patients with CHF secondary to Chagas cardiomyopathy receiving CRT thus far reported. Araújo et al [20], therefore, did observe left ventricular reverse remodeling in such patients. However, it must be emphasized that such a study was neither randomized nor double-blinded.

In the absence of evidence-based medicine support, it could be difficult to recommend CRT to treat patients with Chagas cardiomyopathy with CHF. Of course, a randomized, double-blinded controlled trial would be paramount to recommend or not to recommend CRT to Chagas disease patients. However, it should be borne out that Chagas disease is neglected, and therefore such a study will probably never be carried out in patients with this disease. Therefore, in a scenario like that, it seems to me to be reasonable to indicate CRT to patients with CHF secondary to Chagas cardiomyopathy with a clinical picture similar to that found in non-Chagas disease heart failure patients. This is an important question because even patients with non-Chagas disease heart failure have different types of heart disease, but have been treated similarly. This is the case, for example, for patients with CHF secondary to either idiopathic dilated cardiomyopathy or ischemic cardiomyopathy, which are distinct entities.

With the limitations discussed earlier, the paper by Araújo et al. [20] may be seen as another block in the construction of the treatment of patients with CHF secondary to Chagas cardiomyopathy in the contemporary era. Furthermore, Araújo et al. paper lends support to the notion that such patients, treated with guideline drugs (at target doses) [21], with increased QRS complex duration (ideally with left bundle branch block), and advanced left ventricular remodeling (as detected by left ventricular ejection fraction $< 30\%$ and left ventricular systolic dimension > 50 mm), will benefit of CRT.

REFERENCES

1. Chagas disease (American trypanosomiasis): fact sheet (revised in August 2012). *Wkly Epidemiol Rec.* 2012;87(51/52):519-22.
2. Lee BY, Bacon KM, Bottazzi ME, Hotez PJ. Global economic burden of Chagas disease: a computational simulation model. *Lancet Infect Dis.* 2013;13(4):342-8.
3. Bestetti RB, Santos CR, Machado-Júnior OB, Ariolli MT, Carmo JL, Costa NK, et al. Clinical profile of patients with Chagas' disease before and during sustained ventricular tachycardia. *Int J Cardiol.* 1990;29(1):39-46.
4. Bestetti RB, Cardinalli-Neto A. Sudden cardiac death in Chagas' heart disease in the contemporary era. *Int J Cardiol.* 2008;131(1):9-17.
5. Ribeiro AL, Nunes MP, Teixeira MM, Rocha MO. Diagnosis and management of Chagas disease and cardiomyopathy. *Nat Rev Cardiol.* 2012;9(10):576-89.
6. Bestetti RB, Theodoropoulos TA, Cardinalli-Neto A, Cury PM. Treatment of chronic systolic heart failure secondary to Chagas heart disease in the current era of heart failure therapy. *Am Heart J.* 2008;156(3):422-30.
7. Bertolino ND, Villafanha DF, Cardinalli-Neto A, Cordeiro JA, Arcanjo MJ, Theodoropoulos TA, et al. Prognostic impact of Chagas' disease in patients awaiting heart transplantation. *J Heart Lung Transplant.* 2010;29(4):449-53.
8. Issa VS, Amaral AF, Cruz FD, Ferreira SM, Guimarães GV, Chizzola PR, et al. Beta-blocker therapy and mortality of patients with Chagas cardiomyopathy: a subanalysis of the REMADHE prospective trial. *Circ Heart Fail.* 2010;3(1):82-8.
9. Ayub-Ferreira SM, Mangini S, Issa VS, Cruz FD, Bacal F, Guimarães GV, et al. Mode of death on Chagas heart disease: comparison with other etiologies. a subanalysis of the REMADHE prospective trial. *PLoS Negl Trop Dis.* 2013;7(4):e2176.
10. Bestetti RB, Coutinho-Netto J, Staibano L, Pinto LZ, Muccillo G, Oliveira JS. Peripheral and coronary sinus catecholamine levels in patients with severe congestive heart failure due to Chagas' disease. *Cardiology.* 1995;86(3):202-6.
11. Bestetti RB, Ramos CP, Figuerêdo-Silva J, Sales-Neto VN, Oliveira JS. Ability of the electrocardiogram to detect myocardial lesions in isoproterenol induced rat cardiomyopathy. *Cardiovasc Res.* 1987;21(12):916-21.
12. Bestetti RB, Sales-Neto VN, Pinto LZ, Soares EG, Muccillo G, Oliveira JS. Effects of long-term metoprolol administration on the electrocardiogram of rats infected with *T. cruzi*. *Cardiovasc Res.* 1990;24(7):521-7.
13. Botoni FA, Poole-Wilson PA, Ribeiro AL, Okonko DO, Oliveira BM, Pinto AS, et al. A randomized trial of carvedilol after renin-

- angiotensin system inhibition in chronic Chagas cardiomyopathy. *Am Heart J.* 2007;153(4):544.e1-8.
14. Bestetti RB, Otaviano AP, Cardinalli-Neto A, Rocha BF, Theodoropoulos TA, Cordeiro JA. Effects of beta-blockers on outcome of patients with Chagas' cardiomyopathy with chronic heart failure. *Int J Cardiol.* 2011;151(2):205-8.
 15. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, et al; Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med.* 2004;350(21):2140-50.
 16. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al; Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med.* 2005;352(15):1539-49.
 17. Bertoldi EG, Rohde LE, Zimmerman LI, Pimentel M, Polanczyk CA. Cost-effectiveness of cardiac resynchronization therapy in patients with heart failure: the perspective of a middle-income country's public health system. *Int J Cardiol.* 2013;163(3):309-15.
 18. Silva Menezes A. Outcome of right ventricular bifocal pacing in patients with permanent atrial fibrillation and severe dilated cardiomyopathy due to Chagas disease: three years of follow-up. *J Interv Card Electrophysiol.* 2004;11(3):193-8.
 19. Silva RT, Martinelli Filho M, Lima CE, Martins DG, Nishioka SA, Pedrosa AA, et al. Functional behavior of patients with conventional pacemakers undergoing cardiac resynchronization. *Arq Bras Cardiol.* 2008;90(2):138-43.
 20. Araújo EF, Chamlian EG, Peroni AP, Pereira WL, Gandra SMA, Rivetti LA. Cardiac resynchronization therapy in patients with chronic Chagas cardiomyopathy: long-term follow up. *Rev Bras Cir Cardiovasc.* 2014;29(1):31-6.
 21. Bocchi EA, Marcondes-Braga FG, Bacal F, Ferraz AS, Albuquerque D, Rodrigues Dde A, et al. Updating of the Brazilian guideline for chronic heart failure – 2012. *Arq Bras Cardiol.* 2012;98(1 Suppl 1):1-33.