MEDICAL SCIENCE MONITOR

REVIEW ARTICLES

e-ISSN 1643-3750
© Med Sci Monit, 2018; 24: 4567-4571
DOI: 10.12659/MSM.907735

Received: 2017.10.25
Accepted: 2018.01.16
Published: 2018.07.02

Early Detection of Chronic Asymptomatic Chagas Infection

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

CDEF 1 Ezequiel de la Rosa
DE 2,3 Patricia Paglini-Oliva
E 4 Laura B. Prato
EF 4,5 Evangelina Benizio
EF 4,5 María Fernanda Triquell
E 2,4,5 Sonia E. Muñoz
ABCDEFG 6,7 Elmer Andrés Fernández

1 Erasmus+ Joint Master in Medical Imaging and Applications, University of Girona, University of Burgundy and University of Cassino and Southern Lazio, Girona, Spain
2 Health Science Research Institute (INICSA), National Council of Scientific and Technological Research (CONICET), Córdoba, Argentina
3 Department of Biomedical Physics, Faculty of Medical Sciences, National University of Córdoba, Córdoba, Argentina
4 Basic and Applied Sciences Institute, National University of Villa María, Villa María, Argentina
5 Institute of Cell Biology, Faculty of Medical Sciences, National University of Córdoba, Córdoba, Argentina
6 Development and Research Center in Immunology and Infection Disease (CIDIE), National Council of Scientific and Technological Research (CONICET), Córdoba, Argentina
7 Catholic University of Córdoba (UCC), Córdoba, Argentina

Corresponding Author: Elmer Andrés Fernández, e-mail: efernandez@bdmg.com.ar

Source of support: This work was supported by the Catholic University of Córdoba [grant no. BOD/2016 to E.A.F.], the Ministry of Science, Technology, and Productive Innovation (MINCyT) [grant no. PPL6/2011 to E.A.F.], the Secretary of Science and Technology of the National University of Córdoba (SECYT) [grant no. 30720150101719CB to E.A.F.], the National University of Villa María, and the National Council of Scientific and Technological Research (CONICET)

Chagas disease, also known as American trypanosomiasis, is a chronic and systemic parasitic infection which has become a serious epidemiological problem not only in endemic regions (Latin America), but also in non-endemic ones like North America, Europe, and Oceania. Subjects with the indeterminate chagasic form (ICF), a chronic asymptomatic disease stage, are the main sources of non-vectorial dissemination through blood transfusion, organ transplantation, and congenital transmission. It has been suggested that 94% of urban infections can be explained by these subjects. Under this scenario, the availability of simple and effective screening methods for ICF detection becomes crucial for both prevention of disease propagation and detection of clinical stages. Recently, a new non-invasive method has been proposed for ICF detection. It is based on surface high-resolution ECG and it could be easily adopted and included in modern ECG devices, overcoming the limitations of serological-based tests. The proposed method shows accuracy for early ICF screening, thus improving prognosis by defining the clinical stages and allowing appropriate and effective treatment.

MeSH Keywords: Chagas Disease • Electrocardiography • Mass Screening • Public Health

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/907735

2194 — — 37

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Background

Chagas disease (ChD), also known as American trypanosomiasis, is a chronic and systemic parasitic infection caused by the hemoflagellated protozoan *Trypanosoma cruzi*. Currently, around 8 million people are infected worldwide according to the World Health Organization [1], with an estimated economic global cost of more than 23 billion dollars [2]. It is endemic in 21 countries of Latin America [1], where it is principally transmitted by the feces of triatomine bugs after blood-feeding on human hosts. Although only this region has been historically affected, continuous migration from rural to urban areas as well as outside Latin America has widely spread the disease to non-endemic areas. Regions like Europe, Oceania, East Pacific Ocean countries, and North America are registering an increasing number of ChD disease patients in their populations [3]. Its impact has been compared to the burden of HIV/AIDS disease in Latin America [4] and has been recognized as a new global health problem [3–5]. In non-endemic regions, the transmission occurs by non-vectorial mechanisms, and it is known as *urban Chagas,* which mainly occurs by blood transfusion and organ transplantation, and also by congenital transmission known as the vertical route [6], primarily from undiagnosed asymptomatic carriers. Increasing numbers of patients detected by routine screenings of blood banks or organ banks in the USA led to the implementation, in early 2007, of the first diagnostic test for Chagas disease approved by the Food and Drug Administration for use in the USA [7]. It has been suggested that around 94% of new infections of urban Chagas occur from subjects with the indeterminate or chronic asymptomatic chagasic form (ICF) [8].

Transmission of *Trypanosoma cruzi* through the placenta, which leads to congenital Chagas disease, has also been well documented. The first to describe a congenital case was Dao in Venezuela in 1949. Afterwards, congenital ChD cases were reported by numerous authors reviewed in [9–12]. This type of transmission has become particularly important in non-endemic countries, which in recent years received a large influx of immigrants, including many with Chagas disease, with a large number of women of childbearing age, who would contribute in new congenital cases [13]. However, in endemic regions this form of transmission is still very important, especially where vector transmission has been interrupted; thus, in endemic areas, congenital ChD cases generate new cases. According to a 2015 World Health Organization report, it was estimated that in Argentina, for instance, there are 211 102 chagasic women of childbearing age and congenital transmission reaches 1457 cases per year, being greater than the vector transmission, which is estimated at 1078 new cases per year [14]. Moreover, early diagnosis in these congenital cases is crucial in treating infected children in the first years of life.

Chagas disease is manifested in 2 stages: acute and chronic. The first is a short-term clinical stage produced after the parasite enters the body and lasts for 4–8 weeks; its course is generally asymptomatic and in a small number of cases causes death by severe myocarditis and meningoencephalitis, especially in children [15]. The chronic stage is a long-term clinical condition that can persist for decades, having 4 different forms: indeterminate, cardiac, digestive, and cardio-digestive. From these forms, the ICF is defined as a combination of infection (which can be confirmed by either serological or parasitological tests), a normal chest radiograph and electrocardiogram (ECG), a normal barium swallow and enema, and the absence of clinical signs and symptoms of disease [16–18]. This disease stage can persist for 10–30 years or can be lifelong while the subject can remain undiagnosed. Thus, subjects with ICF can be one of the main dissemination sources of the disease by means of vertical route and/or blood or organ donation. In addition, only 30–40% of ICF cases evolve into some of the other chronic stages with clinical and detectable evidence of cardiac, digestive, or cardio-digestive symptoms.

Discussion

Current diagnosis techniques applied for *T. cruzi* detection are based on blood samples analyzed in a clinical laboratory. The applied method differs depending on the infection stage. For instance, in the acute stage, high parasitic burden leads to the direct use of microscopic-based methods for detection of the parasite in blood samples. In the chronic stage, where high levels of anti-*T. cruzi* IgG antibodies are present in serum, indirect methods are used. According to Haberland et al. [19], the most commonly used methods are ELISA test (sensitivity=94–100%, specificity=96–100%), indirect hemagglutination (HAI, sensitivity=88–99%, specificity=96–100%), and indirect immunofluorescence (IFI, sensitivity=98%, specificity=98%). Despite being highly sensitive and specific, serological tests can have some cross-reactivity, for example if the patient presents other kinetoplastid infection with intracellular parasites or bacterial diseases (e.g., malaria or toxoplasmosis) and with some autoimmune conditions such as rheumatoid arthritis and systemic lupus erythematosus [20]. Aiming to avoid false-negatives and false-positives, at least 2 different serological methods or 2 ELISA tests with different antigens are required to confirm the diagnosis. However, since ICF subjects do not manifest any sign or symptom, they are reluctant to perform a “just in case” serological test. In addition, conventional serological methods are mainly available in large urban centers, while in endemic regions, ChD infections occur in small and remote towns or in urban areas that lack laboratory infrastructure or qualified staff [21,22]. Moreover, given the fact that serological tests are commonly conducted in urban centers, blood sample transportation to a central laboratory is

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

compulsory and crucial. Serological testing of blood samples from remote areas not only requires expensive equipment and supplies, but also a cold-chain storage procedure to keep the samples in good condition prior to the test. In Latin America, ChD is mainly confined to poor and remote regions, and fulfilling these requirements is difficult. On the contrary, in non-endemic regions such as Europe and North America, chagasic subjects predominantly live in large urban areas. Moreover, serological tests are not routinely applied, thus the indeterminate asymptomatic subjects remain undetected, consequently increasing the disease dissemination potential. These scenarios require new diagnostic assays both in acute and chronic stage, as well as methods to confirm parasitic absence in cured patients [21]. They should be cheap and easy to implement to facilitate and encourage their use in routine clinical visits, in order to provide early diagnosis of ChD. It is acknowledged that early diagnosis is crucial for a successful antitrypanosomal therapy. Nevertheless, early detection of ChD is rare and, as a consequence, early treatment of asymptomatic individuals is highly underused [23]. In addition, early-diagnosed subjects have better prognosis and the proportion of patients cured after drug treatment decreases with the duration and severity of the infection [24]. For instance, according to Rassi et al. [23], anti-trypanosomal drug therapy cures the infection in 50–80% of patients in the acute stage of disease and this rate diminishes to 20–60% for the indeterminate chronic form and becomes even lower for cardiac, digestive, or cardio-digestive chronic cases. Furthermore, subjects with the ICF (ie, with normal ECG) have good prognosis, with mortality rates similar to non-chagasic cases [25]. Thus, early detection of ICF individuals could not only allow the possibility of early cardiological treatment, but also reduce parasitemia levels in the patients and avoid their evolution to more severe disease stages by proper antitrypanosomal therapy.

The parasite *Trypanosoma cruzi* has a predilection for muscles (including myocardium) and ganglion cells [26], which are often destroyed [20] and can produce alterations of the cardiovascular system leading to chronic chagasic cardiomyopathy (CCC). This cardiomyopathy is the most important clinical aspect of ChD due to its frequency and severity [17]; therefore, electrocardiography has been recognized as one of the single most effective examination techniques for patients with CCC [16]. In the last decade, useful high-resolution ECG (HRECG) methods have been developed for clinical assessment of ChD, including beat-to-beat analysis of QRS complex durations [27], 3D vectorcardiographic assessment from orthogonal HRECG channels [28], ventricular late potentials analysis using averaged HRECG [27], and prognostic value and risk stratification of ChD patients using averaged HRECG [29]. Electrocardiographic abnormalities during the course of the disease are the first clinical evidence of disease progression. However, heart involvement is mainly detected in the chronic evolved stages of the pathology, since the disease generally is asymptomatic in the early stages and the onset of ECG alterations remain undetected [30]. At present, there are no determinants of progression of the disease from the indeterminate Chagasic form to more severe stages described [18], nor is there electrocardiographic evidence in standard 12-lead ECG that could guide early detection of ICF subjects. Furthermore, it has been acknowledged that ECG techniques are powerful tools for the screening of CCC in asymptomatic patients with previously proven myocardial involvement using cardiac magnetic resonance imaging (MRI) [31]. However, the early detection of the ICF has been elusive. Hence, the availability of a portable device that can provide evidence of the disease is highly desired, since it could trigger confirmation through other more sensitive but complex methods such as serological testing.

It is important to note that the absence of ECG disturbances in the early indeterminate chagasic form do not imply an absence of functional disorders. However, a normal 12-lead ECG result indicates a favorable prognosis for a patient when compared to ECG-altered ones [30]. Although the subject could have a normal ECG, significant functional abnormalities in the chronic ICF was experimentally demonstrated [32,33]. Thus, searching for disease conduction disorders on ECG, several researchers used HRECG for asymptomatic chagasic identification of subjects. Early attempts using QRS slopes found potential disturbances in myocardial conduction in a chronic asymptomatic ICF cohort [34]. Mainly, alterations exposed in the downward slope of the QRS complex were reported. Similarly, in a report using the high-frequency components of the QRS (an index also reflecting conduction propagation through the myocardium), a weak relationship between healthy and ICF subjects was reported [35]. However, these methods fail in early disease detection and lack appropriate validation.

Recently, a novel high-resolution ECG-derived index called VLFCI (very low-frequency correlation index) was proposed and evaluated in a database of chagasic patients, suggesting a differential behavior between healthy and ICF individuals [36]. The index was assessed and validated [37], from which a simple and easy VLFCI-based algorithm for early detection of subjects with asymptomatic ICF was presented. The method is simple enough to be implemented in commercial ECG devices (such as Holters or clinical electrocardiographs) as a routine screening test. Moreover, it could introduce a point-of-care solution for the early identification of ChD, overcoming the strong limitations of serological tests for diagnosis in difficult-to-access rural areas (a common problem in endemic regions). The method is fast and takes just 7 minutes of ECG record acquisition. Its implementation in portable devices could result in a low-cost solution to ChD screening, since no reactives or supply chain is required for its use.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Subjects with ICF could benefit most, since early detection implies a better therapy outcome. By means of the proposed algorithm, indeterminate-form ChD patients could be screened quickly, easy, and *in situ*. The method is based on the evaluation of the correlation between very low-frequency spectral bands from HRECG time series using the orthogonal lead system, allowing identification of 68.4% of subjects with ICF, with ~84% confidence (positive predictability). In this context, the proposed method is able to detect a population prone to potential disease dissemination and at the same time a population that could benefit from adequate therapy leading to higher chances of cure.

It is worth pointing out that the method is not able to replace conventional blood-sample tests. However, it leads to massive and fast *in situ* screening for the disease, requiring post-confirmation by conventional serological techniques. Although this latter analysis can be determinate in detecting a *Trypanosoma cruzi* infection, they are difficult to implement in endemic regions and are not routinely conducted in many non-endemic countries. Hence, massive ChD screening could be crucial in terms of early disease identification in both endemic or non-endemic regions. The availability of an automatic screening method for ICF could positively impact early treatment of ICF subjects by providing better prognosis and potentially preventing irreversible organ damage. Such a screening technology could also improve public health management by help control ChD propagation.

Conclusions

To the best of our knowledge, this is the first report on the use of the VLFCI and ECG to diagnose individuals with ICF. More importantly, it can be used as a simple screening/classification tool to help physicians detect the disease in the early stage. By appropriate statistical modeling and covariance structure definition, we have validated the VLFCI findings. Results obtained from 2 separate datasets coming from different populations and different recording devices suggest the reliability, appropriateness, and reproducibility of the test, since VLFCI estimated values from both datasets shared similar distribution ranges. Nonetheless, the proposed methodology requires validation in larger-scale datasets and further experiments to better define VLFCI parameters, thus allowing improvements in screening performance. Due to the lack of proper high-resolution ECG databases, future validation will demand the development of new databases with careful attention to the recording protocols and characteristics of the recording device. For proper assessment of the VLFCI, we strongly recommend the use of high-quality ECG devices to acquire noiseless records.

References:

1. World Health Organization: Research priorities for Chagas disease, Human African Trypanosomiasis and Leishmaniasis: Technical report of the TDR Disease Reference Group on Chagas disease, Human African Trypanosomiasis and Leishmaniasis. Technical Report Series no. 975. Geneva: World Health Organization, 2012
2. Lee BY, Bacon KM, Bottazzi ME, Hotez PJ: Global economic burden of Chagas disease: A computational simulation model. Lancet Infect Dis, 2013;13: 342–48
3. Klein N, Hurwitz I, Durvasula R: Globalization of Chagas disease: A growing concern in nonendemic countries. Epidemiol Res Int, 2012; 2012: 136793
4. Hotez PJ, Dumonteil E, Woc-Colburn L et al: Chagas disease: The new HIV/AIDS of the Americas. PLoS Negl Trop Dis, 2012; 6: e1498
5. Coura JR, Vias PA: Chagas disease: A new worldwide challenge. Nature, 2010; 465: S6–S7
6. Prata A: Clinical and epidemiological aspects of Chagas disease. Lancet Infect Dis, 2001; 1: 92–100
7. U.S. Food and Drug Administration, 2006. FDA approves first test to screen blood donors for Chagas disease. FDA News. Available at: *http://www.fda.gov/bbs/topics/NEWS/2006/NEW01524.html*
8. Fabrizio MC, Schweigmann NJ, Bartolini NJ: Modelling inter-human transmission dynamics of Chagas disease: Analysis and application. Parasitology, 2014; 141: 837–48
9. Freilij H, Altcheh J: Congenital Chagas' disease: Diagnostic and clinical aspects. Clin Infect Dis, 2015; 21(3): 551–55
10. Schijman AG: Congenital Chagas disease. In Zuckerman A, Mushahwar I (eds.), Congenital and other related infectious disease of the newborn. 2015; 223–58
11. Carlier Y, Truyens C, Deloron P, Peyron F: Congenital parasitic infections: A review. Acta Tropica, 2012; 121(2), 55–70
12. Carlier Y, Sosa-Estani S, Luquetti AO, Buekens P: Congenital Chagas disease: An update. Mem Inst Oswaldo Cruz, 2015; 110: 363–68
13. Soriano-Arandes A, Angheben A, Serre-Delcor N et al: Control and management of congenital Chagas disease in Europe and other nonendemic countries: Current policies and practices. Trop Med Int Health, 2016; 21(5): 590–96
14. World Health Organization: Chagas disease in Latin America: An epidemiological update based on 2010 estimates. Wkly Epidemiol Rec, 2015; (6): 33–44
15. Henao-Martínez AF, Schwart DA, Yang IV: Chagasic cardiomyopathy, from acute to chronic: Is this mediated by host susceptibility factors?. Trans R Soc Trop Med Hyg, 2012; 106: 521–27
16. Ribeiro AL, Nunes MP, Teixeira MM, Rocha MO: Diagnosis and management of Chagas disease and cardiomyopathy. Nat Rev Cardiol, 2012; 9: 576–89
17. Nunes MC, Dones W, Morillo CA et al: Chagas disease: An overview of clinical and epidemiological aspects. J Am Coll Cardiol, 2013; 62: 767–76
18. Lescure FX, Le Loup G, Freilij H et al: Chagas disease: Changes in knowledge and management. Lancet Infect Dis, 2010; 10: 556–70
19. Haberland A, Saravia SG, Wallukat G et al: Chronic Chagas disease: From basics to laboratory medicine. Clin Chem Lab Med, 2013; 51: 271–94
20. Teixeira ARL, Nitz N, Guimaro MC et al: Chagas disease. Postgrad Med J, 2006; 82: 788–79
21. Médecins Sans Frontières. Campaign for Access to Essential Medicines: International meeting: New diagnostic tests are urgently needed to treat patients with Chagas disease. Rev Soc Bras Med Trop, 2008; 41: 315–19
22. Lirio M, Maia ZPG, Nakatani M et al: The significance of electrocardiographic abnormalities and serology for *T. cruzi* infection. J Trop Dis, 2013; 1: 121
23. Rassi A Jr., Rassi A, Marin-Neto JA: Chagas disease. Lancet, 2010; 375: 1388–402
24. Gascon J, Bern C, Pinazo MJ: Chagas disease in Spain, the United States and other non-endemic countries. Acta Trop, 2010; 115: 22–27
25. de Alencar MC, Rocha MO, Lima MM et al: Heart rate recovery in asymptomatic patients with Chagas disease. PLoS One, 2014; 9: e100753

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

26. Rassi A Jr., Rassi A, Marcondes de Rezende J: American trypanosomiasis (Chagas disease). Infect Dis Clin North Am, 2012; 26: 275–91
27. Laciar E, Jané R, Brooks DH: Evaluation of myocardial damage in chagasic patients from the signal-averaged and beat-to beat analysis of the high resolution electrocardiogram. Comput Cardiol, 2006; 33: 25–28
28. Correa R, Laciar P, Arini P, Jané R: Analysis of QRS loop in the vectorcardiogram of patients with Chagas' disease. Conf Proc IEEE Eng Med Biol Soc, 2010; 2010: 2561–64
29. Ribeiro AL, Cavalvanti PS, Lombardi F et al: Prognostic value of signal-averaged electrocardiogram in Chagas disease. J Cardiovasc Electrophysiol, 2008; 19: 502–9
30. Paglini-Oliva P, Lo Presti MS, Rivarola HW: Electrocardiography as a diagnostic method for Chagas disease in patients and experimental models. In: Immunology and Microbiology "Parasitology", Manjur Shah M (ed.), 2012; Chapter 5: 77–92
31. Bochard-Villanueva B, Estornell-Erill J, Fabregat-Andrés Ó et al: Diagnostic performance of surface electrocardiogram in early detection of chagasic cardiomyopathy. Med Clin (Barc), 2015; 144(6): 254–56 [in Spanish]
32. Presti MSL, Rivarola HW, Bustamante JM etal: Some components of the cardiac b-adrenergic system are altered in the chronic indeterminate form of experimental trypanosoma cruzi infection. Int J Parasitol, 2008; 38(13): 1481–92
33. Baez AL, Presti MSL, Fretes R et al: Chronic indeterminate phase of Chagas disease: Mitochondrial involvement in infection with two strains. Parasitology, 2013; 140(03): 414–21
34. Pueyo E, Laciar E, Anzuola E et al: Assessment of myocardial damage in chronic chagasic patients using QRS slopes. Comp Cardiol, 2007; 34: 725–28
35. de la Rosa E, Paglini-Oliva P, Fernández EA: High frequency QRS components: A comparative analysis to assess myocardial damage in chronic chagasic patients. Biennial Congress of Argentina (ARGENCON), 2016; 1–5
36. de la Rosa E, Fernández EA: Spectral bands analysis of ECG derived signals in Chagasic patients. IFMBE Proceedings CLAIB 2014, 2015; 49: 760–63
37. de la Rosa E, Paglini-Oliva P, Prato L et al: Non-invasive chronic asymptomatic Chagas disease screening through high-resolution electrocardiography (ECG). Med Sci Tech, 2017; 7(58): 77–86

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]