



Editorial

Exercise training in chronic Chagas cardiomyopathy: Promising preliminary evidence, but long-term large clinical trials are still needed



Chagas disease (CD) is a neglected tropical disease that affects about 6 to 7 million infected people across the globe, most of them living in Latin America endemic countries [1]. As well-remembered in a recent review, the number of cases in non-endemic countries has been increasing over the last decades, as a result of migratory movements and insufficient screening strategies in these countries [2]. Approximately 30–40 % of individuals with CD will develop chronic Chagas cardiomyopathy (CCC), the most frequent and severe clinical manifestation of the chronic phase of CD, responsible for significant morbidity and mortality [1]. Thus, the need for CD intervention strategies is a global public health problem, and in the context of prevention strategies in CD, strategies to prevent morbidity and mortality of CCC fit into tertiary prevention [3]. In this setting, studies focused on tertiary prevention, evaluating intervention strategies aimed at improving the clinical and functional prognosis of individuals with CCC are urgently needed.

Exercise training (ET) has emerged as an important intervention strategy for patients with cardiovascular diseases (CVD) as it enhances clinical and functional parameters, and ultimately leads to a better quality of life (QoL) [4]. However, despite the evident benefits of ET and the strong guideline recommendations, the participation of ET programs for patients with CCC is very poor, especially in low-income and middle-income countries (as in the case of endemic areas of CD), in which ET services are usually scarce or even non-existent in many countries [5]. The investigation of ET as an intervention strategy tailored for individuals with CCC is incipient, with most large randomized clinical trials evaluating the efficacy and safety of ET in individuals with CVD not including participants with CCC. The recent updates of both the ERS/ATS Cardiovascular Rehabilitation Guidelines [6] and the Brazilian Guidelines for Cardiovascular Rehabilitation [7] did not mention any specific recommendation for CCC population.

In this issue of the International Journal of Cardiology Heart & Vasculature, Diaz-Arocutipa et al. [8] conducted a systematic review with meta-analysis that included eight studies examining the influence of ET in CCC patients. Although the evidence available was limited and heterogeneous, it was possible to conclude that ET was safe and improved functional capacity (FC) and QoL in this population. Three important aspects should be raised from the finding of this review: (1) almost all studies were conducted in Brazil (7 of 8); (2) only three studies used a standardized classification for stages of CCC; (3) only three studies were randomized clinical trials, and none of them evaluated the effect of inspiratory muscle training (IMT) or the hard outcomes such as clinical progression of CD, hospitalization, and/or mortality.

Relying on scientific evidence from studies conducted in only one country can limit the generalizability and applicability of research findings, since this approach usually does not account for regional biases, ethnic and genetic variations, healthcare system differences, or the influence of environmental factors. In Brazil, the vector-borne transmission of CD was interrupted in 2006 [9], resulting in an aging of the population with CD in Brazil compared to other countries where vector-borne transmission is still active. Moreover, studies conducted in Brazil were mostly performed in reference centers for CCC treatment, making the generalization of the results even more difficult since these patients usually received close clinical follow-up and other healthcare interventions (e.g nutritional and pharmaceutical care) as a basis of a comprehensive care program. In this setting, studies conducted in different countries/regions representing different clinical and epidemiological scenarios of CD are necessary to ensure a more comprehensive and universally applicable perspective about the safety and efficacy of CR as a treatment strategy of CCC.

In terms of classification of CCC stages, there are at least five different classifications based on major clinical signs and symptoms: the Brazilian Consensus on Chagas Disease, the Kuschnir classification, the modified Los Andes classification, the Latin American Guidelines, and the American Heart Association [2]. From eight studies included by Diaz-Arocutipa et al. [8], only three classified CCC stages (the Brazilian Consensus on Chagas Disease). Of the remaining studies, three provided information about the New York Heart Association (NYHA) functional class and one did not provide any information about classification of CCC stages or functional class. The lack of information of CCC classification in the studies precludes an appropriate comparison among studies, making difficult a more comprehensive examination about the effects of ET on patients with CCC, from changes in FC to the occurrence of adverse events, as well as the investigation of the differential responses according to specific stages of CCC. Therefore, it would be helpful that future studies use at least one of the CD classifications associated with the NYHA classification.

Robust scientific evidence demonstrates that isolated IMT improves maximal inspiratory pressure, maximum oxygen consumption, FC and QoL in patients with CVD [10]. In addition, the effects of the combination of aerobic and resistance training with IMT is being studied in patients with CVD. Compared to aerobic training, the combination with IMT leads to further improvement in this population [10,11]. Considering the CCC population, of the few studies that evaluated the effects of ET, aerobic training alone [12] or in combination with resistance

DOI of original article: <https://doi.org/10.1016/j.ijcha.2023.101256>.

<https://doi.org/10.1016/j.ijcha.2023.101272>

Received 8 September 2023; Accepted 9 September 2023

Available online 15 September 2023

2352-9067/© 2023 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

training [13,14] was used, and in both cases, the clinical benefits were clear. Nevertheless, to our knowledge, no study evaluated the effects of isolated IMT or combined aerobic/resistance/inspiratory training in patients with CCC.

Considering the worse prognosis of CCC in comparison to other CVD [15], the lack of large, long-term, randomized clinical trials evaluating hard outcomes such as clinical progression of CD, hospitalization, and/or mortality should also be acknowledged as an important limitation of the current literature that limits the ability to comprehensively understand the safety and effectiveness of ET in CCC population, decreasing the level of evidence. Therefore, the need for large, long-term, clinical trials including CCC individuals from different regions of the globe (including endemic and non-endemic areas) and analyzing the benefits of combined aerobic/resistance/inspiratory training is warranted to improve the current knowledge about this promising intervention strategy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- [1] World Health Organization, ChagasDisease (American trypanosomiasis) 2023 [https://www.who.int/news-room/fact-sheets/detail/chagas-disease-\(american-trypanosomiasis\)](https://www.who.int/news-room/fact-sheets/detail/chagas-disease-(american-trypanosomiasis)) (accessed 08 September 2023).
- [2] R.M. Saraiva, M.F.F. Mediano, F.S. Mendes, G.M. Sperandio da Silva, H.H. Veloso, L.H.C. Sangenis, et al., Chagas heart disease: An overview of diagnosis, manifestations, treatment, and care, *World, J. Cardiol.* 13 (2021) 654–675, <https://doi.org/10.4330/wjcv.v13.i12.654>.
- [3] A. Rassi, J.C. Dias, J.A. Marin-Neto, Challenges and opportunities for primary, secondary, and tertiary prevention of Chagas' disease, *Heart.* 95 (2009) 524–534, <https://doi.org/10.1136/hrt.2008.159624>.
- [4] F.L.J. Visseren, F. Mach, Y.M. Smulders, D. Carballo, K.C. Koskinas, M. Böck, et al., ESC Guidelines on cardiovascular disease prevention in clinical practice, *Eur. J. Prev. Cardiol.* 29 (2022) 5–115, <https://doi.org/10.1093/eurjpc/zwab154>.
- [5] R.S. Taylor, H.M. Dalal, S.T.J. McDonagh, The role of cardiac rehabilitation in improving cardiovascular outcomes, *Nat. Rev. Cardiol.* 19 (2022) 180–194, <https://doi.org/10.1038/s41569-021-00611-7>.
- [6] M. Ambrosetti, A. Abreu, U. Corrà, C.H. Davos, D. Hansen, I. Frederix, et al., Secondary prevention through comprehensive cardiovascular rehabilitation: From knowledge to implementation. 2020 update. A position paper from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology, *Eur. J Prev. Cardiol.* 28 (2021) 460–495, <https://doi.org/10.1177/2047487320913379>.
- [7] T. Carvalho, M. Milani, A.S. Ferraz, A.D.d. Silveira, A.H. Herdy, C.A.C. Hossri, et al., Diretriz Brasileira de Reabilitação Cardiovascular – 2020 [Brazilian Guidelines for Cardiovascular Rehabilitation - 2020], *Arq. Bras. Cardiol.* 114 (2020) 943–987. <https://doi.org/10.36660/abc.20200995>.
- [8] C. Diaz-Arocutipa, Exercise-based training programs for patients with chronic Chagas cardiomyopathy: a systematic review and meta-analysis, *IJC Heart Vasc.* (2023). Epub IJCHA-D-23-00203R3.
- [9] A. Moncayo, A.C. Silveira, Current epidemiological trends for Chagas disease in Latin America and future challenges in epidemiology, surveillance and health policy, *Mem. Inst. Oswaldo Cruz.* 104 (2009) 17–30, <https://doi.org/10.1590/s0074-02762009000900005>.
- [10] A.C.M. Azambuja, L.Z. de Oliveira, G. Sbruzzi, Inspiratory Muscle Training in Patients With Heart Failure: What Is New? Systematic Review and Meta-Analysis, *Phys. Ther.* 100 (2020) 2099–2109, <https://doi.org/10.1093/ptj/pzaa171>.
- [11] I.D. Laoutaris, S. Adamopoulos, A. Manginas, D.B. Panagiotakos, M.S. Kallistratos, C. Doulaptis, et al., Benefits of combined aerobic/resistance/inspiratory training in patients with chronic heart failure. A complete exercise model? A prospective randomised study, *Int. J. Cardiol.* 167 (2013) 1967–1972, <https://doi.org/10.1016/j.ijcard.2012.05.019>.
- [12] M.M. Lima, M.O. Rocha, M.C. Nunes, L. Sousa, H.S. Costa, M.C. Alencar, et al., A randomized trial of the effects of exercise training in Chagas cardiomyopathy, *Eur. J. Heart Fail.* 12 (2010) 866–873, <https://doi.org/10.1093/eurjhf/hfq123>.
- [13] F. de Souza Nogueira Sardinha Mendes, M.F.F. Mediano, E. de Castro, F.C. Souza, P.S. da Silva, F.M. Carneiro, M.T. de Holanda, et al. Effect of Physical Exercise Training in Patients With Chagas Heart Disease (from the PEACH STUDY), *Am. J. Cardiol.* 125 (2020) 1413–1420. <https://doi.org/10.1016/j.amjcard.2020.01.035>.
- [14] A.M.N. Viana, M.C. Vieira, F. Mazzoli-Rocha, R.S. Silva, A.X. Frota, H.S. Costa, et al., Comparative effects of a cardiovascular rehabilitation program on functional capacity in patients with chronic chagasic cardiomyopathy with or without heart failure, *Disabil. Rehabil.* 45 (2023) 51–56, <https://doi.org/10.1080/09638288.2021.2024282>.
- [15] R.M. Torres, D. Correia, M.D.C.P. Nunes, W.O. Dutra, A. Talvani, A.S. Sousa, et al., Prognosis of chronic Chagas heart disease and other pending clinical challenges, *Mem. Inst. Oswaldo Cruz.* 117 (2022) e210172.

Flavia Mazzoli-Rocha*

Evandro Chagas National Institute of Infectious Disease, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil

Mauro Felipe Felix Mediano

Evandro Chagas National Institute of Infectious Disease, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil
Department of Research and Education, National Institute of Cardiology, Rio de Janeiro, Brazil

* Corresponding author.

E-mail addresses: flamazzoli@gmail.com, flavia.mazzoli@ini.fiocruz.br

(F. Mazzoli-Rocha).