SHORT COMMUNICATION

A cardiac rehabilitation exercise program potentially inhibits progressive inflammation in patients with severe Chagas cardiomyopathy: A pilot single-arm clinical trial

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Background: Cardiac rehabilitation exerts anti-inflammatory effect on several cardiovascular diseases; however, these effects were not described for Chagas cardiomyopathy, which is associated with pro-inflammatory imbalance. **Materials and Methods:** Ten patients with severe Chagas cardiomyopathy performed 8 months of exercise training in a cardiac rehabilitation program. Interleukin-1 beta (IL-1β), IL-8, IL-10, interferon gamma (IF-γ), tumor necrosis factor alpha (TNF-α), and monocyte chemoattractant protein-1 (MCP-1) serum levels were measured using enzyme-linked immunosorbent assay at baseline, 4, and 8 months. The influence of exercise on cytokine levels was evaluated using the one-way analysis of variance for repeated measurements, with Bonferroni posttest for multiple comparisons. **Results:** Levels of pro-inflammatory (TNF-α, IL-1β, IL-8, IF-γ, and (MCP-1) and anti-inflammatory (IL-10) cytokines did not vary significantly during the observation period. **Conclusion:** Exercise may benefit patients with severe Chagas cardiomyopathy by curbing the production of pro-inflammatory cytokines in this disease characterized by a continuous state of inflammation.

Key words: Cardiac rehabilitation, Chagas cardiomyopathy, cytokines, heart failure

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INTRODUCTION

Chagas disease is a life-threatening illness caused by *Trypanosoma cruzi*, a protozoan parasite. The symptoms occurring during the chronic phase of this disease are thought to result from dysregulation of the immune system. The progression from the chronic indeterminate form of Chagas disease to chronic chagas cardiomyopathy (CCC) has been associated with the overproduction of several pro-inflammatory cytokines such as interferon gamma, tumor necrosis factor alpha (TNF-α), and interleukin-1 beta (IL-1β), and the underproduction of the anti-inflammatory cytokine IL-10.[1,2]

Cardiac rehabilitation programs (CRPs) include regular physical exercise, which apparently lowers morbidity and mortality rates in patients with cardiovascular diseases by reducing inflammation.[3] Specifically, exercise decreases the serum levels of pro-inflammatory cytokines such as TNF-α, IL-6, and monocyte chemoattractant protein-1 (MCP-1) and increases the serum levels of anti-inflammatory proteins such as IL-10

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and IL-1 receptor antagonist.[4] However, whether it also ameliorates inflammation in patients with severe CCC is unknown. Thus, this study aimed to determine the effects of a CRP on the levels of inflammation markers in patients with severe CCC.

MATERIALS AND METHODS

In the present pilot study, patients were included from March 2013 to December 2014 at the Evandro Chagas National Institute of Infectious Disease (INI/FIOCRUZ, Rio de Janeiro, Brazil). Details of the pilot study, along with the clinical characteristics of the patients were presented elsewhere.[5] In brief, the selected patients were >18 years of age and were clinically stable during the 3 months before the study. They tested positive for *T. cruzi* in two serological tests (an enzyme-linked immunosorbent assay [ELISA] and indirect immunofluorescence, administered concurrently). Patients with Stages C or D Chagas cardiomyopathy were included if they presented with typical electrocardiographic alterations, left ventricular ejection fraction (LVEF) <45% and HF symptoms.[6] Patients were excluded if they regularly exercised at the admission period, were unable to attend thrice-weekly exercise training sessions, had any systemic condition that limited physical activity (e.g., a neuromuscular disorder or chronic obstructive pulmonary disease), or if their cardiopathy was unrelated to Chagas disease. The presence of nonchagasic cardiomyopathy was determined based on medical history and a detailed clinical screening including electrocardiogram, echocardiogram, and cardiopulmonary exercise tests.

The present study was approved by the Ini/Fiocruz Research Ethics Committee in accordance with resolution 466/2012 of the Brazilian National Council of Health. All patients signed an informed consent form before beginning the CRP (ClinicalTrials.gov identifier NCT02516293).

The CRP comprised exercise training, nutritional orientation, and pharmaceutical guidance. Exercise training was performed three times a week, 60 min/session, for 8 months. Each session consisted of aerobic exercise (30 min on a treadmill or cycle ergometer, including an initial 5-min warm-up and a final 5-min cooldown), strength exercises for the major muscle groups (20 min), and stretching (10 min). The exercise training intensity was based on the patient's heart rate during cardiopulmonary exercise testing, corresponding to the anaerobic threshold minus 10% in the first month of exercise training and the anaerobic threshold plus 10% in the following months.

Blood samples were collected at baseline, 4, and 8 months after starting the CRP. Aliquots of plasma and serum were isolated from the blood samples and frozen at −70°C within 2 h of being drawn. Levels of serum cytokines (IL-1β, IL-8, IL-10, IF-γ, TNF-α, and MCP-1) were measured, through ELISAs according to the manufacturer's instructions (EBioscience, San Diego, CA, USA), and presented as mean ± standard error of the mean. The influence of exercise on cytokine levels was evaluated using the one-way analysis of variance for repeated measurements, with Bonferroni posttest for multiple comparisons. The significance level was set at 0.05.

RESULTS

Ten patients with severe CCC were included in the present analysis. The mean age was 54.2 ± 14.4 years old. Weight and body mass index had a mean of 58.5 ± 12.5 kg and 24.4 ± 3.6 kg/m^2, respectively. Overall, most of patients were female (n = 7; 70%), self-reported their race as mulatto (n = 7; 70%), and were classified on stage C of Chagas heart disease (n = 9; 90%). The mean of Simpson LVEF was 30.5 ± 7.8%, and VO_2 peak was 16.9 ± 4.8 mL/kg/min. All participants were receiving medications for neurohumoral blockade for heart failure (HF) management (beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, and aldosterone antagonist).

Table 1 shows the mean serum cytokines levels, and Figure 1 exhibits the individual changes for all cytokines assessed at baseline and during the follow-up. Levels of TNF-α, IL-10, IL-1β, IL-8, IF-γ, and MCP-1 did not vary significantly during the study period. No significant changes were observed for medication usage (drug classes and dosages) during the follow-up (4 and 8 months).

Table 1: Inflammatory cytokine levels during the follow-up

	Mean±SEM			ANOVA (*P*)
	Baseline (*n*=10)	4 months (*n*=8)	8 months (*n*=5)	
IL-1β (pg/mL)	54.9±3.5	51.1±3.4	58.4±4.9	0.95
IL-8 (pg/mL)	52.5±1.5	56.6±1.4	52.2±1.7	0.64
IL-10 (pg/mL)	7.7±0.7	6.3±0.7	4.7±1.1	0.08
IF-γ (pg/mL)	380.7±20.4	375.0±21.2	321.2±27.1	0.75
TNF-α (pg/mL)	39.5±1.2	36.8±1.4	40.2±1.6	0.51
MCP-1 (pg/mL)	265.2±12.3	282.9±10.9	242.4±16.1	0.29

Data expressed as mean±SEM. Statistical analysis=One-way ANOVA, with Bonferroni posttest for multiple comparisons. TNF-α=Tumor necrosis factor alpha; MCP-1=Monocytes chemoattractant protein-1; SEM=Standard error of the mean; ANOVA=Analysis of variance; IL-1β=Interleukin-1 beta; IL-8=Interleukin-8; IL-10=Interleukin-10; IF-γ=Interferon gamma

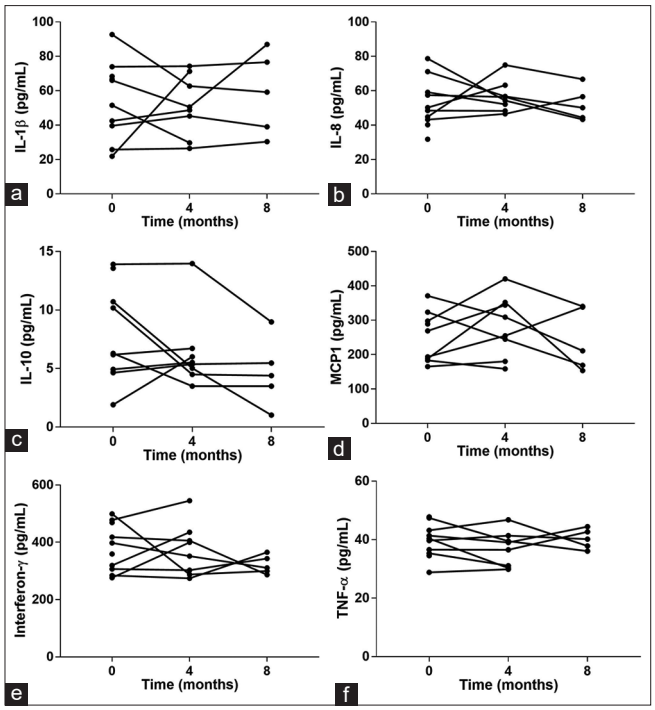

Figure 1: Individual cytokine changes during the follow-up. The levels of (a) interleukin 1β, (b) interleukin-8, (c) interleukin-10, (d) monocyte chemoattractant protein-1, (e) interferon-γ, and (f) tumor necrosis factor-α of each volunteer are presented for baseline, 4 and 8 months of follow-up. IL1-β = Interleukin 1β; IL-8 = Interleukin 8; IL-10 = Interleukin 10; MCP-1 = Monocytes chemoattractant protein-1; TNF-α = Tumor necrosis factor α

DISCUSSION

CCC is characterized by sustained low-grade inflammation, which has been linked to its physiopathology, severity, and progression.[3] This study describes first evidence regarding the influence of an 8-month exercise program on the serum levels of inflammation-related cytokines in patients with severe CCC that are commonly neglected from major clinical trials. Levels of the pro-inflammatory cytokines did not increase during the training period. Hence, exercise may have a benefit in patients with CCC by curbing the expected progression of the pro-inflammatory state. Furthermore, levels of the anti-inflammatory cytokine IL-10 did not fall at the end compared with the beginning of the training period. Collectively, these findings suggest that the benefits of exercise are derived from modulation of pro- and anti-inflammatory cytokines. In this setting, Silva *et al*. suggested that decreases in IL-10 levels are part of the natural course of CCC since IL-10 levels were reduced after 2 months of follow-up in CCC patients.[7]

Previous studies found that the levels of the pro-inflammatory cytokines IL-1β, IF-γ, TNF-α, and MCP-1 were higher in patients with CCC than in those without CCC.[1,2,8] TNF-α[9] and MCP-1 are overproduced in CCC patients with low ventricular ejection fractions and hence may contribute to disease severity and progression in these patients.[2] Increases in TNF-α levels worsen the prognosis of patients with HF, whereas decreases improve cardiac function.[10]

Moreover, IL-10 levels are lower in CCC patients than in those with the CI form of Chagas disease.[8] This is evidence of the overall pro-inflammatory status of patients with CCC.[1] In several chronic diseases, including HF, exercise increases IL-10 serum concentrations by transiently stimulating the production of IL-6 in the muscle.[11] IL-10 may, in turn, reduce TNF-α and IL-β levels, as suggested by previous studies of chronic exercise.[12,13]

It has been demonstrated that CRP may reduce inflammation in patients with nonchagasic HF, mainly from ischemic etiology;[14,15] however, whether they do so in patients with CCC remains unclear. Although our study was limited by its small sample size and the lack of a control group, that prevents us from determining the exact role of exercise attenuating the decline of anti-inflammatory or limiting the increase of pro-inflammatory cytokines in patients with CCC, it provides initial insights about the effects of exercise on the inflammatory profile among patients with severe CCC that are usually excluded from major studies. Therefore, randomized clinical trials with larger sample sizes are urgently needed to fully understand the association between exercise and inflammation in these patients.

CONCLUSION

The serum levels of both anti- and pro-inflammatory cytokines were stable during an 8-month exercise training period in this disease characterized by a continuous state of inflammation. Our findings suggest that exercise may benefit patients with Chagas HF by modulating the production of pro-inflammatory cytokines.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Sousa GR, Gomes JA, Fares RC, Damásio MP, Chaves AT, Ferreira KS, *et al*. Plasma cytokine expression is associated with cardiac morbidity in Chagas disease. PLoS One 2014;9:e87082.
2. Talvani A, Rocha MO, Barcelos LS, Gomes YM, Ribeiro AL, Teixeira MM. Elevated concentrations of CCL2 and tumor

necrosis factor-alpha in chagasic cardiomyopathy. Clin Infect Dis 2004;38:943-50.
3. Brandt C, Pedersen BK. The role of exercise-induced myokines in muscle homeostasis and the defense against chronic diseases. J Biomed Biotechnol. 2010;2010:520258. doi: 10.1155/2010/520258. Epub 2010 Mar 9.
4. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: Mechanisms and implications for the prevention and treatment of disease. Nat Rev Immunol 2011;11:607-15.
5. Mediano MF, Mendes Fde S, Pinto VL, Silva GM, Silva PS, Carneiro FM, *et al*. Cardiac rehabilitation program in patients with Chagas heart failure: A single-arm pilot study. Rev Soc Bras Med Trop 2016;49:319-28.
6. Dias JC, Ramos AN Jr., Gontijo ED, Luquetti A, Shikanai-Yasuda MA, Coura JR, *et al*. Brazilian consensus on Chagas disease, 2015. Epidemiol Serv Saude 2016;25:7-86.
7. Silva PS, Mediano MF, Silva GM, Brito PD, Cardoso CS, Almeida CF, *et al*. Omega-3 supplementation on inflammatory markers in patients with chronic Chagas cardiomyopathy: A randomized clinical study. Nutr J 2017;16:36.
8. Keating SM, Deng X, Fernandes F, Cunha-Neto E, Ribeiro AL, Adesina B, *et al*. Inflammatory and cardiac biomarkers are differentially expressed in clinical stages of Chagas disease. Int J Cardiol 2015;199:451-9.
9. Ferreira RC, Ianni BM, Abel LC, Buck P, Mady C, Kalil J, *et al*. Increased plasma levels of tumor necrosis factor-alpha in asymptomatic/"indeterminate" and Chagas disease cardiomyopathy patients. Mem Inst Oswaldo Cruz 2003;98:407-11.
10. Pedersen BK. Anti-inflammatory effects of exercise: Role in diabetes and cardiovascular disease. Eur J Clin Invest 2017;47:600-11.
11. Ertek S, Cicero A. Impact of physical activity on inflammation: Effects on cardiovascular disease risk and other inflammatory conditions. Arch Med Sci 2012;8:794-804.
12. Pedersen BK. The anti-inflammatory effect of exercise: Its role in diabetes and cardiovascular disease control. Essays Biochem 2006;42:105-17.
13. Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. J Appl Physiol (1985) 2005;98:1154-62.
14. Batista Júnior ML, Lopes RD, Seelaender MC, Lopes AC. Anti-inflammatory effect of physical training in heart failure: Role of TNF-α and IL-10. Arq Bras Cardiol 2009;93:643-51.
15. Smart NA, Steele M. The effect of physical training on systemic proinflammatory cytokine expression in heart failure patients: A systematic review. Congest Heart Fail 2011;17:110-4.