

Heart Rate Variability and Chagas Heart Disease

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We believe that the present study is relevant, which investigated the effect of exercise training on heart rate variability (HRV) in patients with Chagas heart disease¹. However, there are some issues in this study, which should be further discussed.

The use of amiodarone in approximately 80% of patients may have decreased their autonomic response², affecting the validity of HRV parameters.

Furthermore, low-ejection fraction (mean, 37%) may have acted as a confounding factor, and this finding may need to be investigated by inclusion of a control group without Chagas heart disease but with similar ejection fraction; inclusion of a control group with Chagas heart disease but

with ejection fraction close to normal; or better yet, the inclusion of both groups.

A small sample size (37 subjects divided into two groups) masks potential differences; for a power of 80% and a two-tailed alpha of 0.05, we estimate that the effect size ("d") of a large magnitude ($d = 0.95$) would be required to be detectable.

In fact, even when calculating the sample size, underpowering has been one of the major obstacles in clinical studies³. Although we did not consider a very high standard deviation (which would lead to greater difficulties), the effective post hoc power to detect intergroup differences considering a SDNN value of 0.15 would be only 7.3%, according to our calculations.

Moreover, we believe that, instead of the separate use of paired tests and tests for independent samples to answer the original question, other models (e.g., panel data or mixed models) are better adjusted to the experimental design and to the proposed objectives.

Keywords

Heart Rate; Chagas Cardiomyopathy, Amiodarone/Therapeutic Use; Ventricular Dysfunction.

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Manuscript received October 09, 2014; revised manuscript November 13, 2014; accepted November 13, 2014.

DOI: 10.5935/abc.20150003

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Reply

Thank you for your comments on the article titled “Effects of exercise training on heart rate variability in Chagas heart disease”¹. Herein, we would like to address some concerns raised by the reviewers.

Our study mainly aimed to evaluate changes in heart rate variability (HRV) in response to a physical training program in patients with Chagas cardiomyopathy in comparison with a control group that was physically inactive. In this context, the effects of amiodarone on HRV are known^{2,3}, particularly in patients with ectopic foci of arrhythmia, which is an underlying complication commonly observed in patients with Chagas heart disease, and we acknowledge that these effects could be a confounding factor. However, the percentage of patients taking the medication was high and statistically similar between the groups (77.8% and 84.2%, $p = 0.62$), suggesting that these effects were probably balanced and decreased the possibility of interferences in the differences in the delta values of HRV indices at the end of the study. In addition, drug withdrawal during the study would be unethical, and consequently, we would not be able to otherwise obtain the required data. However, the bias introduced by the use of drugs acting on the cardiac rhythm—widely used for the treatment of left ventricular dysfunction—should always be considered in HRV studies.

With regard to the non-inclusion of patients with ventricular dysfunction caused by other etiologies and the noninclusion of patients with Chagas heart disease with preserved ejection fraction, the presence of autonomic dysfunction has been reported in a large number of patients with Chagas heart disease, even in the absence of heart disease⁴. Similarly, decreased HRV in patients with ventricular dysfunction caused by other etiologies (with diagnostic and prognostic validation)⁵ as well as their positive response to exercise have been reported⁶. The inclusion of the above-mentioned groups would undoubtedly provide valuable information to our findings, including the results of HRV among patients with the indeterminate form of the disease. However, we believe that this result is not essential to answer the central question of this study, which is whether the prognostic benefit

of physical training in patients with Chagas heart disease—largely demonstrated in previous studies—evaluated with HRV indices would be mediated by changes in the autonomic system. For this reason, we only recruited patients with a similar underlying condition and those who were physically inactive during the study period as controls.

With respect to the power of the study to detect differences between groups, the example used would apply when comparing the SDNN parameter between the groups, or within the same group, in different periods. However, the variable of interest used to calculate the sample size was the variation in the SDNN parameter (Δ SDNN), which was compared between the groups. In the absence of a study with similar design to compare individuals with Chagas heart disease, we considered previous data on heart disease due to other etiologies⁷. Therefore, to detect Δ SDNN differences of 10–15 ms between the groups with β error of 20%, samples sizes of <40 patients would be sufficient even when considering the large dispersion values observed. Therefore, we believe that underpowering in relation to this reference index did not occur.

Finally, we evaluated longitudinal data in two different periods in this study. The aforementioned analytical methods (panel data and mixed models) would be more appropriate in longitudinal studies with multiple observations. However, the use of paired tests (Student’s *t* test and Wilcoxon test) and the comparison of changes (delta values) between the groups with two measures are methodologically appropriate for the present experimental design⁸.

We appreciate the comments and criticism of the authors and hope we have adequately addressed the issues raised.

Sincerely Yours,

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Marcia Maria Oliveira Lima
Manoel Otávio da Costa Rocha
Antonio Luiz Pinho Ribeiro.

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