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ORIGINAL RESEARCH ARTICLE

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Cholinesterase inhibition reduces arrhythmias in asymptomatic Chagas disease

Renata R. T. Castro[1] | Graciema Porphirio[2] | Sergio S. Xavier[2] | Ruy S. Moraes[3] | Elton L. Ferlin[3] | Jorge P. Ribeiro[3,†] | Antonio C. L. da Nóbrega[1]

[1]Department of Physiology and Pharmacology and Post-Graduate Program in Cardiovascular Sciences, Fluminense Federal University, Niterói, Brazil

[2]Division of Cardiology, Rio de Janeiro Federal University, Rio de Janeiro, Brazil

[3]Division of Cardiology, Rio Grande do Sul Federal University, Porto Alegre, Brazil

Correspondence
Renata R. T. Castro, Department of Physiology and Pharmacology, Fluminense Federal University, Niterói, Brazil.
Email: castrorrt@gmail.com

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Summary

Introduction: Parasympathetic dysfunction may play a role in the genesis of arrhythmias in Chagas disease.

Aim: This study evaluates the acute effects of pyridostigmine (PYR), a reversible cholinesterase inhibitor, on the occurrence of arrhythmias in patients with Chagas cardiac disease.

Method: Following a double-blind, randomized, placebo-controlled, cross-over protocol, 17 patients (age 50±2 years) with Chagas cardiac disease type B underwent 24-hour Holter recordings after oral administration of either pyridostigmine bromide (45 mg, 3 times/day) or placebo (PLA).

Results: Pyridostigmine reduced the 24-hours incidence (median [25%-75%]) of premature ventricular beats—PLA: 2998 (1920-4870), PYR: 2359 (940-3253), *P*=.044; ventricular couplets—PLA: 84 (15-159), PYR: 33 (6-94), *P*=.046. Although the total number of nonsustained ventricular tachycardia in the entire group was not different (*P*=.19) between PLA (1 [0-8]) and PYR (0 [0-4]), there were fewer episodes under PYR in 72% of the patients presenting this type of arrhythmia (*P*=.033).

Conclusion: Acute administration of pyridostigmine reduced the incidence of nonsustained ventricular arrhythmias in patients with Chagas cardiac disease. Further studies that address the use of pyridostigmine by patients with Chagas cardiac disease under a more prolonged follow-up are warranted.

KEYWORDS
Antiarrhythmia drugs, Arrhythmia, Autonomic diseases, Chagas cardiomyopathy, Cholinesterases, Parasympathetic nervous system

1 | INTRODUCTION

Chagas disease is a major health problem affecting 8 million people in Latin American countries.[1] The intensification of the migratory flow is increasing the prevalence of Chagas disease in nonendemic countries such as Japan, Australia, Canada, and United States of America.[1]

The chronic phase of Chagas disease is initially asymptomatic and half of the infected patients will never present any symptoms or signs of the chronic disease during their lives.[2] Direct neuronal parasitism during the acute phase of the infection[3] and autoimmune process involving antimuscarinic[4] or anti-beta-adrenergic[5] autoantibodies are known mechanisms of autonomic dysfunction. Autonomic nervous system impairment can be found in any presentation of the disease[6] and plays an important role in proarrhythmic mechanisms in Chagas disease.[7]

Although beta-blockers are widely used to counteract adrenergic hyperactivity in Chagas disease,[8,9] no drug is clinically used to reverse parasympathetic dysfunction in cardiovascular disease.[10,11]

[†]Deceased.

Pyridostigmine bromide is a reversible anticholinesterase agent, currently used to treat patients with Myasthenia Gravis and few other conditions.[12] The role of cholinergic stimulation in the treatment of cardiovascular diseases has not been fully investigated, but pyridostigmine has been shown to improve autonomic and hemodynamic profile of patients with coronary artery disease at rest,[13] during exercise[14] and in response to a mental stress challenge.[15]

The increase in parasympathetic tone by pyridostigmine prevented ventricular dysfunction during the onset of heart failure in rats.[16] In patients with congestive heart failure, not related to Chagas cardiac disease, short-term administration of pyridostigmine increased heart rate variability and decreased the incidence of ventricular arrhythmias.[17]

In this study, we hypothesized that pyridostigmine would reduce the incidence of cardiac arrhythmias, an independent risk factor, in Chagas chronic cardiac disease type B. Therefore, the main purpose was to determine the effects of short-term treatment with pyridostigmine on the occurrence of cardiac arrhythmias during a 24-hour dynamic electrocardiogram in patients with chronic Chagas cardiac disease.

2 | MATERIALS AND METHODS

2.1 | Patients

Patients with Chagas chronic cardiac form type B[9,18] that were clinically stable and in sinus rhythm were invited to participate in this study. This form of Chagas disease is currently diagnosed when a patient has positive Chagas disease sorologies, with electrocardiographic and/or echocardiographic evidence or cardiac structural disease, but without previous or present clinical evidence of heart failure.

The exclusion criteria were as follows: left ventricle ejection fraction <35%, implanted pacemaker, atrial fibrillation, second or third degree atrioventricular block, history of myocardial infarction, hospitalization or change of medication in the last 2 months, the presence of diabetes mellitus, alcoholism, chronic pulmonary obstructive disease, urinary retention, constipation, evidence of any other etiology of heart failure, and intolerance to pyridostigmine. Each patient has given written informed consent to participate in the study after full explanation of the procedures and their potential risks. The present investigation complied with the principles outlined in the Declaration of Helsinki and had been approved by the Institutional Research Ethics Committee.

2.2 | Protocol

This T2 translational research protocol followed a randomized, cross-over, double-blind design. Each patient was submitted to a 24-hour Holter recording (Series 8500®, Marquette Medical Systems, Milwaukee, WI, USA) on two separate days, each initiated two hours after the first oral dose of either pyridostigmine (45 mg) or placebo. Both experimental days were separated by a week period for drug washout. The tablets continued to be administered in a double-blinded manner at 8-hour intervals throughout the recording period (total of three doses of pyridostigmine or placebo). The potential effect of drug sequence was controlled using a counter-balanced design, where patients were randomly, but evenly (50%-50%), assigned to placebo-pyridostigmine or pyridostigmine-placebo. All patients continued using medication prescribed by their physicians throughout the study.

All the recordings were analyzed by the same physician (blinded to the drug administered during each recording) using a semiautomatic technique (Mars 8000 analyzer, Marquette Medical Systems, Milwaukee, WI, USA). This analyzer identifies and counts the total number of normal beats, artifacts, and ectopic beats. Ventricular premature beats were classified as isolated beats, couplets or runs of ventricular tachycardia (at least three ventricular premature beats with a mean R-R interval of 600 ms maximum).

2.3 | Statistical analysis

Statistical analysis was performed in Statistica version 7.0 (Statsoft Corporation, Tulsa, OK, USA). The normality of continuous data sets was assessed using Kolmogorov-Smirnov test. Mean heart rate and blood pressure under pyridostigmine and placebo were compared by paired *T* test. The frequency of arrhythmias under placebo and pyridostigmine was compared by the Wilcoxon matched pairs test. Correlation between the incidence of arrhythmias and left ventricle ejection fraction was assessed by pairwise linear correlation.

We have hypothetized that pyridostigmine would reduce the incidence of premature ventricular beats in 25%. Using a two sample-paired means test, with alpha=0.05 and power=0.80, the calculated sample size was 12.

Significance was set at $P<.05$. Results are presented as mean±SE or median (25%-75%) accordingly to the skewness of data.

3 | RESULTS

Seventeen patients were enrolled in the study. Their baseline characteristics and medications are shown in Table 1. Patients reported no side effects after ingestion of placebo or pyridostigmine.

TABLE 1 Demographic and clinical data of patients

Clinical data of patients	
Baseline characteristics	
Age (yrs)	50±2
Men/women (n)	12/5
Body mass index (kg/m^2)	24.4±0.8
Left ventricle ejection fraction (%)	42±3
Medication	N (%)
Beta-blockers	2 (12)
Angiotensin converting enzyme inhibitors	12 (71)
Digitalis	1 (8)
Diuretics	6 (35)
Acetylsalicylic acid	6 (35)
Amiodarone	4 (24)

TABLE 2 Density of arrhythmias (number/24 hours during Holter monitoring) in patients with Chagas cardiac disease under placebo and pyridostigmine (n=17)

Arrhythmia	Placebo	Pyridostigmine	*P**
Premature supraventricular beats	113 (47-303)	170 (47-429)	.722
Premature ventricular beats	2998 (1920-4870)	2359 (940-3253)	.044
Supraventricular bigeminism	0 (0-0)	0 (0-3)	-
Ventricular couplets	84 (15-159)	33 (6-94)	.046
Supraventricular tachycardia	0 (0-2)	1 (0-5)	-
Nonsustained ventricular tachycardia	1 (0-8)	0 (0-4)	-

**P* value in Wilcoxon matched pairs test; Data are presented as median (25%-75%).

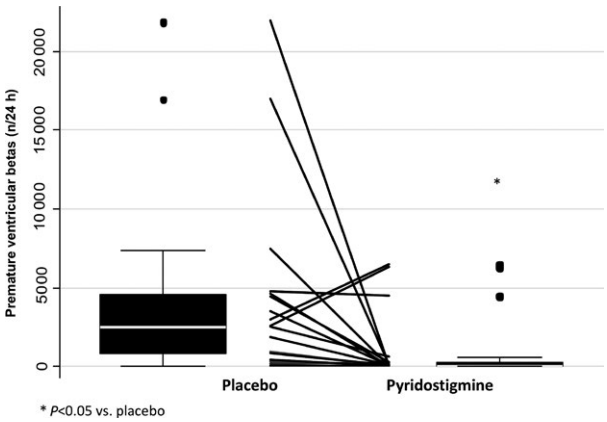

FIGURE 1 Incidence of premature ventricular beats in patients under placebo and pyridostigmine

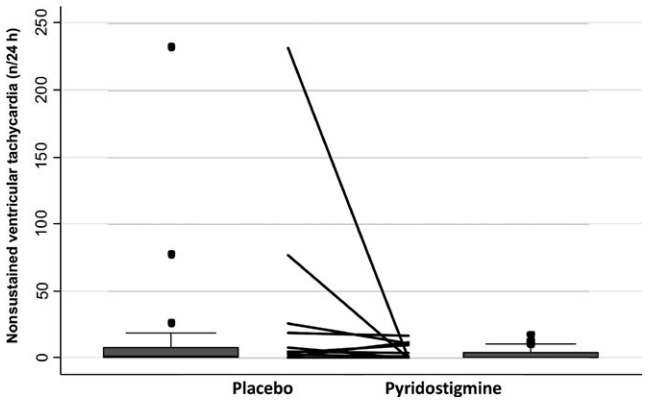

FIGURE 2 Incidence of nonsustained ventricular tachycardia in patients under placebo and pyridostigmine

Pyridostigmine reduced mean heart rate (60±2 bpm vs placebo: 65±4 bpm; *P*=.03). There was no difference between blood pressure measurements after placebo or pyridostigmine (*P*>.05).

There was no correlation between the incidence of arrhythmias and LVEF (supraventricular premature beats: r^2=.007, *P*=.979; nonsustained supraventricular tachycardia: r^2=.084, *P*=.747; ventricular premature beats: r^2=.425, *P*=.088; nonsustained ventricular tachycardia: r^2=.117; *P*=.654). The 24-hour incidence of each type of arrhythmia under placebo and pyridostigmine is shown in Table 2. No sustained arrhythmia was registered under placebo or pyridostigmine. Pyridostigmine reduced the incidence of premature ventricular beats (*P*=.04, Figure 1) and ventricular couplets (*P*=.04).

Eleven patients presented at least one episode of nonsustained ventricular tachycardia during the study. Most of them (n=8) presented less arrhythmic episodes under pyridostigmine than under placebo, while the other three presented more episodes under pyridostigmine (*P*=.03, Figure 2). Pyridostigmine markedly reduced the incidence of ventricular tachycardia in both patients who presented more than 50 episodes/24 hours after placebo (patient one: placebo=77 episodes/24 hours vs pyridostigmine=0 episodes/24 hours; patient 2: placebo=232 episodes/24 hours vs pyridostigmine=2 episodes/24 hours). These patients had left ventricle ejection fraction of 60% and 40%, respectively and were both in use of angiotensin converting enzyme inhibitors. None of them was in use of beta-blockers.

4 | DISCUSSION

Although autonomic dysfunction contributes to the development of arrhythmias in Chagas cardiac disease,[5,7,19-21] there is no established treatment to counteract parasympathetic dysfunction in these patients.[10,11] Present results showed that pyridostigmine reduced the occurrence of nonsustained ventricular arrhythmias in patients with Chagas cardiac disease.

Autonomic failure in Chagas disease is a consequence of parasympathetic neuronal depopulation[22] and impairment of membrane receptors' transduction.[4,5,7] These are not the mechanism of autonomic dysfunction in the great majority of other heart failure etiology where neurohumoral activation plays an important role.[23] Beta-blockers are widely prescribed in heart failure.[8,9] Unfortunately, the control of arrhythmias in Chagas disease is not easily accomplished with beta-blockade, and patients frequently need implanted cardiac defibrillators as a secondary prevention to sudden cardiac death.[9] Noteworthy, life-threatening ventricular arrhythmias were detected in 71% of patients with Chagas disease in use of amiodarone and beta-blockers with implantable cardiac defibrillators.[24]

The hypothesis that parasympathetic stimulation would protect from lethal arrhythmias has been investigated in different scenarios. Four independent groups[25-28] found that when scopolamine was administered in doses capable of exerting a paradoxical cholinergic

agonistic effect, it reduced heart rate and increased heart rate variability after myocardial infarction. These studies suggested that cholinergic stimulation with scopolamine would protect from complex ventricular arrhythmias by changing autonomic profile. However, the only study which tested this hypothesis failed to confirm it, as scopolamine did not prevent ventricular fibrillation during physical exertion in dogs with artificially induced coronary artery occlusion.[29]

Lerman[30] found that edrophonium, an anticholinesterasic agent, terminated nonreentrant, nonautomatic, catecholamine-mediated ventricular tachycardia. Like edrophonium, pyridostigmine increases the concentration of acetylcholine in the synaptic clefts through reversible inhibition of cholinesterase activity. Additionally, pyridostigmine can be administered orally and has a longer half-life than that of edrophonium. The dose of pyridostigmine used in the present study, although several times lower than the one usually prescribed for patients with Myasthenia Gravis, has already been shown to reduce serum cholinesterase activity.[31]

The autonomic effects of pyridostigmine were previously investigated in different groups of patients. Pyridostigmine is known to reduce the QTc interval at rest[13] and during recovery from maximal exercise[32] in patients with coronary artery disease. Pyridostigmine augments parasympathetic tone[33] and reduces the incidence of ventricular premature beats in 65% in patients with heart failure.[17] In the present study, the occurrence of ventricular premature beats was less frequent when patients were under pyridostigmine use. Most patients presented less ventricular arrhythmias during pyridostigmine than under placebo.

Ventricular arrhythmias are the main cause of death in patients with the cardiac form of Chagas disease.[34] Occurrence of nonsustained ventricular tachycardia is an independent risk factor and was the only variable in a 24-hour Holter monitoring that showed prognostic significance in patients with Chagas disease.[35]

The mechanisms of cardiac arrhythmias in Chagas disease are complex and not fully understood. A previous study showed that sera with muscarinic activity from chagasic patients can evoke ventricular arrhythmias.[36] However, our study showed that pyridostigmine, a drug that enhances muscarinic activity exerts antiarrhythmic effect in Chagas disease.

4.1 | Study limitations

There was no measurement of parasympathetic drive in the present study. Nevertheless, a previous study, using the same dose of pyridostigmine, showed a 30% reduction in cholinesterase activity in heart failure patients.[37] Unfortunately, the high incidence of cardiac arrhythmias in the studied population prevented us from analyzing heart rate variability,[38] a clinical marker of parasympathetic function. Noteworthy, the robust methodological design of the present study reduces the chances that any other mechanism different from enhancement of parasympathetic drive would have driven the results.

The presence of ventricular arrhythmias is an established risk factor for sudden death in Chagas disease.[4,5] Although the reduction in ventricular arrhythmias occurrence does not guarantee a better prognosis, 24-hours Holter monitoring is an accepted method for the evaluation of antiarrhythmic treatment.[39]

The present study evaluated 17 patients and only two of them were in use of beta-blockers. The reason for the under usage of beta-blockers was not addressed, and the study protocol prevented us to interfere in patients' prescription. It is important to note that patients included in this study were asymptomatic and this fact could explain the relative low number of prescribed medications. It is important to note that previous studies have shown that the concomitant use of pyridostigmine in patients under beta-blockade is safe.[14,32]

5 | CONCLUSIONS

Pyridostigmine was well tolerated by all patients with Chagas cardiac disease. Short-term treatment with pyridostigmine reduced the occurrence of ventricular nonsustained arrhythmias in patients with Chagas cardiac disease. More importantly, nonsustained ventricular tachycardia, a known independent risk factor in Chagas cardiac disease, was less frequent under pyridostigmine.

As the antiarrhythmic effect of pyridostigmine may improve the prognosis of patients with Chagas cardiac disease, further studies including a longer follow-up and a greater number of patients are warranted.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS

This study was approved by Institutional ethics committee, and appropriate consent was obtained from all subjects.

AUTHOR CONTRIBUTIONS

Renata Castro: Concept/design, Data analysis/interpretation, Drafting article, Critical revision of article, Approval of article, Statistics, Data collection. *Graciema Porphirio*: Concept/design, Statistics, Data collection. *Sergio Xavier*: Concept/design, Data analysis/interpretation, Data collection. *Elton Ferlin*: Concept/design, Data analysis/interpretation, Data collection. *Ruy Moraes*: Concept/design, Data analysis/interpretation, Data collection. *Antonio Nóbrega*: Concept/design, Data analysis/interpretation, Drafting article, Critical revision of article, Approval of article, Statistics.

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