Carvedilol Enhances the Antioxidant Effect of Vitamins E and C in Chronic Chagas Heart Disease

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Abstract

Background: Chagas disease is still an important endemic disease in Brazil, and the cardiac involvement is its more severe manifestation.

Objective: To verify whether the concomitant use of carvedilol will enhance the antioxidant effect of vitamins E and C in reducing the systemic oxidative stress in chronic Chagas heart disease.

Methods: A total of 42 patients with Chagas heart disease were studied. They were divided into four groups according to the modified Los Andes classification: 10 patients in group IA (normal electrocardiogram and echocardiogram; no cardiac involvement); 20 patients in group IB (normal electrocardiogram and abnormal echocardiogram; mild cardiac involvement); eight patients in group II (abnormal electrocardiogram and echocardiogram; no heart failure; moderate cardiac involvement); and four patients in group III (abnormal electrocardiogram and echocardiogram with heart failure; severe cardiac involvement). Blood levels of markers of oxidative stress were determined before and after a six-month period of treatment with carvedilol, and six months after combined therapy of carvedilol with vitamins E and C. The markers analyzed were as follows: activities of superoxide dismutase, catalase, glutathione peroxidase, glutathione S-transferase and reductase, myeloperoxidade and adenosine deaminase; and the levels of reduced glutathione, thiobarbituric-acid reactive substances, protein carbonyls, vitamin E, and nitric oxide.

Results: After treatment with carvedilol, all groups showed significant decrease in protein carbonyls and reduced glutathione levels, whereas nitric oxide levels and adenosine activity increased significantly only in the less severely affected group (IA). In addition, the activity of most of the antioxidant enzymes was decreased in the less severely affected groups (IA and IB). By combining the vitamins with carvedilol, a reduction in protein damage, in glutathione levels, and in the activity of most of the antioxidant enzymes were observed.

Conclusions: The decrease in oxidative stress levels observed by means of the markers tested was more significant when carvedilol was used in combination with the antioxidant vitamins. The findings suggest that both carvedilol alone and in combination with the vitamins were effective in attenuating the systemic oxidative stress in patients with Chagas heart disease, especially those less severely affected, thus suggesting the possibility of synergism between these compounds. (Arq Bras Cardiol. 2013;101(4):304-310)

Keywords: Chagas, Cardiomyopathy / therapy; Adrenergic Beta-Antagonists; Antioxidants; Vitamin E; Vitamin C.

Introduction

Cardiac involvement is the most severe and common manifestation in the chronic phase of Chagas disease in endemic areas, and is the main death cause in patients aged between 30-50 years[1].

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The pathogenesis of chronic Chagas heart disease (CCHD) is not yet fully understood, partly because the disease progression depends on a complex parasite-host interaction. Some mechanisms have been proposed to explain the pathogenesis of CCHD, one of which is the hypothesis of an amplified immune-inflammatory response, among other processes, resulting from the generation of oxygen-reactive species (ORS) in the presence of the parasite or its antigen[2,3].

Conventional treatment strategies for heart failure, such as betablockers, have shown a significant improvement in survival and progression of heart failure (HF). However, strategies focusing specifically on CCHD are still scarce[4,5].

Carvedilol is a combination of beta-1 with alpha-1 adrenergic blockers approved for the treatment of heart failure and left ventricular dysfunction. Many experimental and clinical evidences suggest that, in addition to its adrenergic blockade, the drug also has a potent antioxidant activity[6].

We have recently shown that increased oxidative stress is associated with the progression of Chagas disease[7], and that the use of antioxidants was effective in reducing it, thus potentially being able to influence the course of the disease[8,9]. Our group has also recently shown that the administration of carvedilol was effective in attenuating oxidative stress in the different stages of the disease, an effect that may be particularly important in CCHD[10].

The main objective of this study was to investigate whether carvedilol would enhance the antioxidant effect of vitamins E and C, previously demonstrated in studies conducted in our laboratory, by means of biomarkers of inflammatory and oxidative stress in the blood of patients with CCHD.

Methods

Study design

This is a prospective therapeutic intervention study (RBR-95, JNQP) of a sample from an open cohort comprised of patients followed up in the Service of Cardiology of Clementino Fraga Filho University Hospital (HUCFF-UFRJ).

Patient selection

The study sample was comprised of patients who had spontaneously followed the treatment flowchart of the HUCFF-UFRJ Chagas disease outpatient clinic. Only patients with chronic Chagas disease aged between 21-70 years, who had maintained their nutritional habits, had no associated diseases, and had been away from endemic zones for more than 20 years were included in the study. Patients with arterial hypertension, chronic obstructive pulmonary disease, cardiomyopathy of an etiology other than Chagas disease, heart valve disease, thyroid dysfunction, excessive tobacco/alcohol intake, known immune diseases, abnormal serum electrolyte levels (potassium and calcium), or systemic disease were excluded from the study. The study project was approved by the HUCFF-UFRJ Research Ethics Committee (CEP resolution no. 053/07). All patients received information about the study and gave written informed consent.

The patients were followed up by the same team of physicians. Medical visits were scheduled regularly on an outpatient basis at mean intervals of four months and, when necessary, the patients underwent laboratory tests. All patients had been clinically stable for at least three months when their blood sample was collected for the present study. The patients' diet was poor in major nutritional antioxidants and, therefore, the intake of vitamins C and E was considered negligible. Medications that interfered with the fluid and electrolyte balance were discontinued for 48 hours prior to the laboratory and clinical tests, and no clinical events were recorded during this period.

The patients were divided into four groups according to the modified Los Andes classification[11]: 10 patients in group IA (normal electrocardiogram and echocardiogram; no cardiac involvement); 20 patients in group IB (normal electrocardiogram and abnormal echocardiogram; mild cardiac involvement); eight patients in group II (abnormal electrocardiogram and echocardiogram; no heart failure; moderate cardiac involvement); and four patients in group III (abnormal electrocardiogram and echocardiogram with heart failure; severe cardiac involvement).

The levels of biomarkers of oxidative stress were determined prior to and six months after treatment with carvedilol alone (at a dose of 12.5mg TID, in a total daily dose of 37.5 mg) and prior to and after six months of the combination of carvedilol with vitamins E (800IU) and C (500mg) in a single daily dose. Between the phases of carvedilol used alone and in combination with the vitamins, there was an interval of six months with no medication.

Serological diagnosis of Chagas disease

The serological diagnosis of Chagas disease was made in all patients by means of anti-*T. cruzi* antibody detection using two methods. The dilution considered as a positive serological reaction was that established by the laboratory of the Manguinhos-Fiocruz/RJ reference center.

Patients were considered as testing positive when they showed two positive serological tests in two samples collected separately. In case of doubtful results of the two methods, the serum samples were retested using the immunofluorescence method; if discrepancy persisted, the result of immunofluorescence prevailed. Blood samples were always collected by the same person, on the same day of the week, in the morning, and with the patients fasted.

Medications and reagents

Carvedilol, (RS)-1-(9H-carbazol-4-yloxy)-3-[2-(2-ethoxyphenoxyl) ethylamine] propan-2-ol, and vitamins E (E-Tabs) and E (Energil C) were kindly supplied by a pharmaceutical industry from the State of São Paulo (Brazil), of the EMS Sigma Farma group.

The reagents used for the analyses of oxidative stress biomarkers were obtained from Sigma Chemical Co. (St. Louis, USA).

Statistical analysis

Statistical comparisons of inflammatory and oxidative stress markers within the different groups were made using the one-factor analysis of variance (ANOVA) complemented by the Tukey-Kramer test. Data were analyzed using the generalized linear models for repeated measures. The SPSS version 11.5.0 acquired under license by Federal University of Santa Catarina in 9/6/2002 was used for all analyses. The level of significance was set at 5%.

Results

The radiological assessment showed that the cardiothoracic index increased with the degree of cardiac involvement (p = 0.0001) and was considered as cardiomegaly when values were greater than 0.50. Echocardiography showed ejection fraction values significantly lower in group III patients than in patients of the other groups (p = 0.0001). The left ventricular end-diastolic diameter was corrected for body surface, and values above 32 mm/m^2 were considered abnormal. Based on this criterion, 12 patients showed left ventricular dilatation. Right myocardial impairment, as expressed by pulmonary hypertension, was observed in groups II and III patients (Table 1).

The analysis of the profile of the different groups showed that group IA patients had significantly decreased GSH levels, both after treatment with carvedilol (0.18 ± 0.12 μmol ml^{-1}) and after treatment with carvedilol combined with the antioxidant vitamins (0.14 ± 0.10 μmol ml^{-1}), in comparison with untreated individuals (0.31 ± 0.17 μmol ml^{-1}).

TBARS and vitamin E levels remained unchanged when compared to the treatment with carvedilol alone. However, after combination with vitamins, plasma TBARS levels significantly decreased in comparison to those of untreated patients (13.11 ± 9.98 nmol ml^{-1} – 6.10 ± 3.02 nmol ml^{-1}), whereas plasma vitamin E levels increased in relation to the treatment with carvedilol alone (12.44 ± 2.85 μmol L^{-1} – 16.18 ± 3.45 μmol L^{-1}) (Table 2). However, the protein carbonyls (PC) level was significantly decreased in patients treated with carvedilol (0.04 ± 0.01 nmol mg^{-1}) and vitamins (0.09 ± 0.03 nmol mg^{-1}), in comparison to that of untreated patients (0.15 ± 0.07 nmol mg^{-1}). When we compared the activity of the antioxidant enzymes SOD, GST and GPx within group IA, we observed a significant reduction in relation to untreated patients in both treatment regimens, whereas CAT activity was initially higher with carvedilol and then remained unchanged with the combination with vitamins. GR activity remained unchanged with treatment with carvedilol (5.02 ± 0.71 μmol min^{-1} ml^{-1} – 4.78 ± 1.26 μmol min^{-1} ml^{-1}, respectively) and decreased significantly with the combination with vitamins (3.89 ± 0.71 μmol min^{-1} ml^{-1}) (Table 3). As for the inflammatory markers, after treatment with carvedilol there was a significant increase in nitric oxide (NO) levels in comparison to those of untreated patients (10.93 ± 3.19 μM and 17.96 ± 3.24 μM, respectively) followed by a decrease after the combination with vitamins (9.09 ± 1.00 μM). A significant increase in ADA activity was observed after both interventions (10.03 ± 1.28 Ul^{-1}, 17.17 ± 2.49 Ul^{-1} and 17.58 ± 2.21 Ul^{-1}), whereas MPO activity remained unchanged (Table 2).

Group IB patients treated with carvedilol plus vitamins showed a very similar response to that of group IA patients. GSH levels (0.16 ± 0.13 μmol ml^{-1} – 0.11 ± 0.09 μmol ml^{-1}, respectively) were also significantly lower when compared to those of untreated patients (0.22 ± 0.17 μmol ml^{-1}) in both interventions, whereas TBARS and vitamin E levels remained unchanged when compared to those of patients receiving treatment with carvedilol alone. However, in the combination with vitamins, TBARS levels decreased significantly in comparison to those of untreated patients (10.02 ± 6.18 nmol ml^{-1} – 6.52 ± 2.92 nmol ml^{-1}, respectively), whereas vitamin E levels increased in relation to those of carvedilol (15.70 ± 4.68 μmol L^{-1} – 22.02 ± 11.0 μmol L^{1}, respectively; Table 2). In addition, like in group IA patients, CP levels significantly decreased in patients treated with carvedilol alone (0.05 ± 0.02 nmol mg^{-1}) and with carvedilol plus the combination of vitamins (0.09 ± 0.08 nmol mg^{-1}) when compared to those of untreated patients (0.6 ± 0.19 nmol mg^{-1}). The profile of the antioxidant enzymes activity in this group was also very similar to that of group IA, whereas the inflammatory markers remained unchanged, except for the MPO activity, which increased significantly in relation to patients treated with carvedilol combined with antioxidant vitamins (420.70 ± 27.88 μM – 531.54 ± 25.84 μM, respectively) (Table 2).

Table 1 - Radiologic, electrocardiographic and echocardiographic data of the chagasic patients

Variable	IA (n = 10)	IB (n = 20)	II (n = 8)	III (n = 4)	ANOVA p
Chest radiography					
Cardiothoracic index (m ± sd)	0.45 ± 0.02	0.45 ± 0.02	0.48 ± 0.04	0.52 ± 0.02	0.0001*
consistent with CHF (%)	0	0	20	100	0.001†
Electrocardiography					
RBBB (%)	0	55.7	62.3	97.8	0.001‡
RBBB + LAHB (%)	0	68.9	72.1	99.1	0.003‡
Inactive area (%)	0	2	55	89.3	0.001‡
Echocardiography					
LVEF (%)	65.2	61.6	42.4	37.6	0.0001§
LVEDDI (mm/m^2)	28.3 ± 1.8	29.2 ± 1.2	32.3 ± 4.8	35.9 ± 1.9	0.001§
Pulmonary hypertension (%)	0	0	25	44	0.001§

RBBB: complete right bundle branch block; LVEF: left ventricular ejection fraction; LAHB: left anterior hemiblock; LVEDDI: left ventricular end-diastolic diameter index; Tukey (IA ¹ III); (IA ¹ III) †; (IB ¹ III) ‡; (IA ¹ III) §*

Table 2 - Comparison, within the same group, of GSH, TBARS, PC, vitamin E and •NO levels and MPO and ADA activities, in the blood of chagasic patients at three different treatment times

	Group IA (n = 10)			Group IB (n = 20)			Group II (n = 8)			Group III (n = 4)		
	Untreated	After 6 months of treatmen with Carvedilol	After 6 months of combined treatment	Untreated	After 6 months of treatmen with Carvedilol	After 6 months of combined treatment	Untreated	After 6 months of treatmen with Carvedilol	After 6 months of combined treatment	Untreated	After 6 months of treatmen with Carvedilol	After 6 months of combined treatment
TBARS	13.11 ± 9.98	9.5 ± 4.28	6.10 ± 3.02β*	10.02 ± 6.18	7.71 ± 1.17	6.52 ± 2.92β*	11.34 ± 4.60	8.33 ± 1.55	7.13 ± 3.40	15.19 ± 5.04	9.50 ± 2.22	7.25 ± 4.06
PC	0.15 ± 0.07	0.04 ± 0.01α**	0.09 ± 0.03β**γ**	0.16 ± 0.19	0.05 ± 0.02α*	0.09 ± 0.1β**γ***	0.17 ± 0.07	0.05 ± 0.01α***	0.10 ± 0.03β*γ***	0.15 ± 0.10	0.05 ± 0.01α*	0.09 ± 0.12β*γ*
GSH	0.31 ± 0.17	0.18 ± 0.12α*	0.14 ± 0.10β**	0.22 ± 0.17	0.16 ± 0.13α**	0.11 ± 0.09β**	0.29 ± 0.10	0.18 ± 0.11α*	0.16 ± 0.06β*	0.38 ± 0.15	0.16 ± 0.09*α	0.18 ± 0.10β*
Vit. E	17.36 ± 8.11	12.44 ± 2.85	16.18 ± 3.45γ*	17.12 ± 8.93	15.70 ± 4.68	22.02 ± 11.0γ*	19.64 ± 9.25	12.24 ± 2.18	29.40 ± 15.08γ*	11.72 ± 3.40	11.18 ± 3.83	20.76 ± 3.38β*γ*
ADA	10.03 ± 1.28	17.17 ± 2.5α*	17.58 ± 2.21β*	10.67 ± 1.08	15.36 ± 2.29	16.01 ± 0.92	14.02 ± 2.27	12.90 ± 2.14	14.94 ± 1.41	10.63 ± 3.52	9.05 ± 4.06	16.01 ± 0.59
•NO	10.93 ± 3.19	17.96 ± 3.2 α*	9.09 ± 1.00γ*	11.18 ± 1.38	16.07 ± 1.50	13.70 ± 1.53	15.49 ± 3.42	18.86 ± 2.60	17.17 ± 1.89	13.17 ± 4.62	12.10 ± 1.00	10.92 ± 1.98
MPO	417.3 ± 40.1	544.18 ± 70.05	553.96 ± 39.21	430.97 ± 31.53	420.70 ± 27.9	531.54 ± 25.84γ*	409.54 ± 80.95	352.13 ± 50.36	707.42 ± 104.83β**γ***	440.92 ± 68.15	395.08 ± 60.10	559.04 ± 66.62

ADA: adenosine deaminase (UI-1); GSH: reduced glutathione (μmol ml^{-1}); PC: protein carbonyl (nmol mg^{-1}); •NO: nitric oxide (μM); MPO: myeloperoxidase (mU ml^{-1}); TBARS: thiobarbituric-acid reactive substances (nmol ml^{-1}); vitamin E (μmol ml^{-1}).
*Values are expressed as mean ± standard deviation *p < 0.05, **p < 0.01,***p < 0.001 represent significant differences within the same chagasic group.*

Table 3 – Comparison, within the same group, of antioxidant enzymes in the blood of chagasic patients at three different treatment times

	Group IA (n = 10)			Group IB (n = 20)			Group II (n = 8)			Group III (n = 4)		
	Untreated	After 6 months of treatmen with Carvedilol	After 6 months of combined treatment	Untreated	After 6 months of treatmen with Carvedilol	After 6 months of combined treatment	Untreated	After 6 months of treatmen with Carvedilol	After 6 months of combined treatment	Untreated	After 6 months of treatmen with Carvedilol	After 6 months of combined treatment
SOD	144.99 ± 29.0	64.04 ± 6.05α***γ*	59.44 ± 3.76β***	171.52 ± 41.16	66.37 ± 8.56α***	59.89 ± 4.36β*** γ**	141.26 ± 46.6	70.9 ± 11.2 α**	68.05 ± 4.75 β**	145.4 ± 44.1	69.20 ± 6.54α*	68.91 ± 5.01β**
GPx	2.35 ± 0.22	1.48 ± 0.54α***	1.19 ± 0.60β***	2.32 ± 0.35	1.49 ± 0.39α***	1.05 ± 0.47β***γ***	2.75 ± 0.73	2.36 ± 0.35	2.27 ± 0.41	2.48 ± 0.17	2.14 ± 0.40	2.13 ± 0.33
CAT	8.87 ± 2.55	13.27 ± 3.88α*	10.25 ± 5.06	9.21 ± 2.01	11.62 ± 4.10α*	10.67 ± 2.07	8.43 ± 3.14	9.50 ± 4.06	9.46 ± 3.65	7.54 ± 3.93	12.51 ± 6.43	12.56 ± 3.89
GST	30.61 ± 2.58	24.0717 ± 3.68*	17.68 ± 3.52β**γ**	35.41 ± 9.42	24.58 ± 9.64α***	17.63 ± 4.70β***γ***	34.10 ± 5.64	20.81 ± 2.9α***	19.08 ± 1.52β***	26.66 ± 7.51	23.28 ± 5.33	21.93 ± 2.58
GR	5.02 ± 0.71	4.78 ± 1.26	3.89 ± .71β*	4.94 ± 1.43	4.86 ± 1.70	4.11 ± 0.79β*	4.76 ± 1.16	4.00 ± 1.09	4.20 ± 0.65	4.69 ± 0.81	4.73 ± 1.52	4.67 ± 0.27

CAT: catalase (mmol min^{-1} ml^{-1}); GPx: glutathione peroxidase (μmol min^{-1} ml^{-1}); GR: glutathione reductase (μmol min^{-1} ml^{-1}); GST: glutathione S-transferase (μmol min^{-1} ml^{-1}); SOD: superoxide dismutase (U SOD ml^{-1}).
*Values are expressed as mean ± standard-deviation. *p < 0.05, **p < 0.01,***p < 0.001 represent significant differences within the same chagasic group.*

In group II patients, the behavior of the parameters analyzed was also very similar to that found in the less severely affected patients (groups IA and IB) (Table 2). GSH levels were significantly lower when patients treated with carvedilol and with carvedilol plus vitamins were compared to those of untreated individuals (0.18 ± 0.11 – 0.16 ± 0.06 and 0.29 ± 0.10 μmol ml^{-1}, respectively), whereas no significant difference in TBARS levels and a significant increase in vitamin E levels were found when compared to those of patients receiving the combined treatment with vitamins (29.40 ± 15.08 μmol L^{-1}) and those of untreated patients (19.64 ± 9.25 μmol L^{-1}). Again, PC values were significantly lower after treatment with carvedilol alone (0.05 ± 0.01 nmol mg^{-1}) as well as after the combination with vitamins (0.10 ± 0.03 nmol mg^{-1}), in comparison to those of untreated individuals (0.17 0.07 nmol mg^{-1}). After treatment with carvedilol combined with vitamins, the levels of inflammatory markers remained unchanged, except for MPO, which significantly increased (707.42 ± 104.83 μM) in comparison to values of untreated patients (409.54 ± 80.95 μM) and of those treated with carvedilol alone (352.13 ± 50.3 μM) (Table 2). SOD and GST activities decreased significantly with both treatments, whereas CAT, CR and GPx activities were not significantly different in comparison to those of untreated patients (Table 3).

Similar to what was found in the other groups, GSH levels of patients classified as group III decreased significantly when compared to those of patients treated with carvedilol alone (0.16 ± 0.09 μmol ml^{-1}), with the combination carvedilol plus vitamins (0.18 0.10 μmol ml^{-1}) and untreated patients (0.38 ± 0.15 μmol ml^{-1}) (Table 2). Also, same as for the values found in groups IA, IB and II, no significant differences were observed in TBARS levels of patients treated with carvedilol alone and after combination with vitamins. Vitamin E levels increased in patients treated with vitamins when compared to those of untreated patients (11.72 ± 3.40 μmol ml^{-1} – 20.76 3.38 μmol ml^{-1}), whereas CP values were decreased, both in patients treated with carvedilol alone (0.05 ± 0.01 nmol mg^{-1}) and in those treated with the combination of carvedilol plus vitamins (0.09 ± 0.12 nmol mg^{-1}), when compared to those of untreated patients (0.15 ± 0.06 nmol mg^{-1}) (Table 2). CAT, GR, GST and GPx activities were not significantly different in relation to the therapy used. However, SOD activity was decreased in individuals treated with carvedilol alone (69.20 ± 6.54 ml^{-1}) and with the combination carvedilol plus vitamins (68.91 ± 5.01 ml^{-1}) when compared to that of untreated individuals (145.44 44.12 USOD ml^{-1}). Same as for the results obtained in other groups, the levels of inflammatory markers remained unchanged after treatment with carvedilol alone and in combination with the vitamins (Table 2).

Discussion

In the present study, the patients showed increased oxidative damage in lipids and proteins prior to the antioxidant therapy in comparison to that in the post-treatment period. A generalized increase in the activity of most of the antioxidant enzymes was also observed prior to treatment.

In an animal model of infection by *Trypanosoma cruzi*, increased oxidative modification of cell proteins[12,13] was detected, as well as increased levels of malondialdehyde (MDA, a major product of lipid peroxidation), findings that corroborate those of the present study. The first studies with carvedilol showed that this drug is much more potent in inhibiting the production of hydroxyl radicals (OH) in comparison to other betablockers, and that it is able to inhibit lipid peroxidation[14]. We observed a significant decrease in levels of the marker of protein damage in all groups with CCHD as well as a decrease in TBARS levels, which could be attributed to the potent antioxidant properties of carvedilol[11]. In another similar study, carvedilol also prevented lipid peroxidation in the myocardial cell membranes, initiated by oxygen radicals generated by chemical, enzymatic or cell systems, both in vitro and in vivo[15].

The inflammatory process that characterizes Chagas disease is more pronounced in the acute phase and seems to be correlated with the severity of the heart disease[16]. In this study, we observed that the levels of most of the inflammatory markers (NO, ADA and MPO) remained unchanged with the treatment with carvedilol, thus suggesting an additional effect of this drug on the inflammatory process. The anti-inflammatory activity of carvedilol has been demonstrated in studies by means of the reduction of C-reactive protein, amyloid protein, and monocyte chemotactic protein[17]. This effect could be related to its antioxidant ability to decrease ROS generation and impair inflammatory cells infiltration in the myocardium[18,19]. Increased ADA and NO levels were observed only in group IA patients, classified as the group less severely affected by CCHD. Histopathological findings in individuals with heart disease have shown an increase in mononuclear cells with TNF-α production by activated macrophages and T lymphocytes[20]. This finding could justify the increase in ADA, which is an enzyme released by mononuclear cells. Increased NO levels in this group of patients could indicate a response against infection by *T. cruzi*, since these patients are less severely affected in comparison to those of the other groups. By combining the antioxidant vitamins with the treatment with carvedilol, it is possible to suggest a synergistic association of this combination of the three non-enzymatic antioxidants. This synergy could be reflected in the significant reduction in the levels of most of both the lipid and protein markers of damage, in comparison to those of untreated patients.

A significant increase in vitamin E plasma levels was observed in all groups, thus indicating that vitamin E was properly absorbed by the patients. These results corroborate those of Bhogade et al[21] in which, after supplementation with vitamin E, there was elevation of its plasma levels, with a concomitant decrease in MDA levels.

The activity of most of the antioxidant enzymes decreased significantly or remained unchanged, and this could be explained by synergy between the three antioxidants used in the prevention of the oxidative damage.

The levels of the inflammatory marker NO decreased only in group IA after combination of carvedilol with the vitamins, an effect that could be attributed to the ability of vitamin E to prevent NO toxicity via peroxynitrite formation[22].

The increased MPO activity observed in group II after combination of vitamins with carvedilol could be justified by the relationship that this enzyme has with the progression and severity of the heart disease. Lobbes et al[23] showed that increased serum MPO levels were significantly associated with coronary artery disease in patients with acute myocardial infarction in comparison with those of healthy controls. Bellotti et al[24] sought to investigate the presence of parasites in the hearts of chronic Chagas disease patients, and frequently found them. The authors correlated this finding with the severity of the myocardial inflammatory process, thus supporting the perception of the important role of the parasites in the pathophysiology of the chronic phase[25].

Conclusion

Based on the findings of this study, we can conclude that both the treatment with carvedilol alone and in combination with antioxidant vitamins were effective in attenuating the systemic oxidative stress in the blood of patients with chronic Chagas heart disease (CCHD), as evidenced by the reduction in TBARS and PC levels, and the reduction in the activity of most of the antioxidant enzymes. The combination of carvedilol with vitamins E and C indicates the possibility of synergism between these three nonenzymatic antioxidants in reducing the oxidative damage associated with CCHD. It is clear that the reduction in the oxidative stress levels, as verified by means of the markers tested, was more significant when carvedilol was combined with the antioxidant vitamins. On the other hand, the use of both carvedilol alone and in combination with the antioxidant vitamins were apparently unable to halt the progression of the inflammatory process, as indicated by the increase in ADA and MPO levels in the two intervention moments.

Author contributions

Conception and design of the research: Budni P, Pedrosa RC, Wilhelm Filho D; Acquisition of data, Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Budni P, Pedrosa RC, Dalmarco EM, Dalmarco JB, Frode TS, Wilhelm Filho D; Statistical analysis and Writing of the manuscript: Budni P, Wilhelm Filho D.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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