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ORIGINAL ARTICLE

Effect of cardiac rehabilitation on the nociceptive threshold increased of hypertensive subjects

Efeito da reabilitação cardíaca sobre o limiar nociceptivo aumentado de indivíduos hipertensos

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Abstract

Objectives: Hypertensive subjects have an increased nociceptive threshold, which may contribute to the pain perception reduction. Thus, the aim of this study was to evaluate the effect of a cardiac rehabilitation program (CRP) on the increased nociceptive threshold of hypertensive subjects. **Methods:** Forty-one participants were divided into two groups: a normotensive group and hypertensive group. In both groups, the body mass index, abdominal circumference, systolic and diastolic blood pressure, heart rate, nociceptive threshold and functional capacity by six-minute walking test (6MWT) were evaluated. The CRP was composed of aerobic exercises on a treadmill for 30 min, 3

times a week for 7 weeks. *Results:* After the CRP, there was a reduction ($p < 0.001$) in the mechanical nociceptive threshold and an increase in the distance walked during the 6MWT ($p < 0.001$) in the hypertensive group. No differences were found in the body mass index between the groups. *Conclusion:* The results of the present study suggested that aerobic exercise is an important modality to normalize the nociceptive threshold and improved the functional capacity of the hypertensive subjects.

Keywords: cardiac rehabilitation; hypertension; analgesia.

Resumo

Objetivos: Indivíduos hipertensos apresentam um limiar nociceptivo aumentado, o que pode contribuir para uma redução da percepção da dor. Assim, o objetivo deste estudo foi avaliar o efeito de um programa de reabilitação cardíaca (PRC) sobre limiar nociceptivo aumentados de indivíduos hipertensos. *Métodos:* Quarenta e um participantes foram divididos em dois grupos: grupo normotenso e grupo hipertenso. Nos dois grupos, foram avaliados a massa corporal, índice de massa corporal (IMC), circunferência abdominal, pressão arterial sistólica e diastólica, frequência cardíaca, limiar nociceptivo e a capacidade funcional pelo teste de caminhada de seis minutos (TC6). O PRC foi composto de exercícios aeróbicos em esteira com duração de 30 minutos, 3 vezes por semana, durante 7 semanas. *Resultados:* Após o PRC, houve uma significativa redução ($p < 0,001$) no limiar mecânico nociceptivo e um aumento na distância percorrida durante o TC6 ($p < 0,001$) no grupo composto por indivíduos hipertensos. *Conclusão:* Os resultados do presente estudo sugeriram que o exercício aeróbico é uma modalidade importante para normalizar o limiar nociceptivo e melhorar a capacidade funcional de indivíduos hipertensos.

Palavras-chave: reabilitação cardíaca; hipertensão; analgesia.

Introduction

According to the World Health Organization, 330 million people worldwide have hypertension, and this number could increase to approximately 1.56 billion by the year 2025 [1]. Hypertension is considered to be a major risk factor for the development of coronary artery disease (CAD), and therefore, sudden cardiac death [2]. With regard to CAD, recent studies have shown that a silent ischemic infarction was a common manifestation in 50% of the subjects [3].

In addition to the risk of developing CAD, studies have found that hypertensive individuals have a lowered pain sensitivity [4], which correlates with an increased incidence of silent ischemic infarctions and heart attacks [5]. Glazier *et al.* [6] found a

higher pain tolerance in patients who had silent ischemic infarction episodes when compared to those who had painful ischemic episodes.

Because pain is a one of the body's protective mechanisms, it is of paramount importance that its physiology always functions under normal conditions [7]. Many studies have investigated the mechanisms responsible for the high pain threshold that occurs at the onset of hypertension, and several have indicated the role of the baroreflex system in pain modulation. A reduction or interruption in the afferent activity of the sinoaortic baroreceptors attenuated the increased nociceptive threshold in several experimental models of hypertension [8,9]. In addition to the baroreflex system, some endogenous systems may also be involved in the high nociceptive threshold found in hypertension. Zamir *et al.* [10] demonstrated that chronic treatment with naloxone, an antagonist to opioid receptor, reduced the nociceptive threshold, which was increased in spontaneously hypertensive rats, suggesting that these peptides participate in this effect. The renin-angiotensin system has also been suggested, in which nociceptive threshold normalization was found in spontaneously hypertensive rats after 3 consecutive days of treatment with captopril, an angiotensin AT1 receptor antagonist [11].

With regard to treatment, regular physical activity has been used as a nonpharmacological therapeutic strategy for controlling hypertension [12]. In addition, Galdino *et al.* [13] found a reduction in the nociceptive threshold, which was increased in spontaneously hypertensive rats, after 4 weeks of aerobic exercise. However, this effect has not been investigated in humans.

Based on the abovementioned information, the present study aimed to investigate the effects of a cardiac rehabilitation program (CRP) on the nociceptive threshold and arterial blood pressure (BP) levels in hypertensive subjects.

Methods

Participants

This study was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) and approved by the research ethics committee of the university (protocol number: 478.427). All participants signed the informed consent form and this clinical trial study and was registered at www.ensaiosclinicos.gov.br (number: RBR-67hvhy, principal investigator: Ana Clara Desiderio Maldonado, date of registration: august 04, 2018). In addition, this study complied with the Transparent Reporting of Evaluations with Nonrandomized Designs statement [14].

From September 2018 to December 2018, 63 participants were assessed and divided into two groups: a hypertensive group (HG, $n = 30$) composed of subjects with clinical diagnoses of hypertension and a normotensive group (NG, $n = 11$) composed of normotensive subjects. The use of this group was important for demonstrating how the nociceptive threshold of normotensive subjects and the effect of exercise on this threshold, besides comparing hypertensive subjects. Due to the lack of individuals, it was not possible to have a control group constituted by hypertensives. Thus, the data obtained before the intervention were used as data referring to the hypertensive group not exercised.

The hypertension diagnoses were made by a certified cardiologist according to the criteria established by the European Society of Hypertension and the European Society of Cardiology [15]. Hypertensive subjects were recruited from cardiology clinics of our University and the normotensive subjects were recruited through posters and word of mouth. The enrolled hypertensive subjects had no histories of the following: unstable angina, thrombophlebitis, recent embolism, acute systemic infection, third-degree atrioventricular block (without the use of a pacemaker), acute myocarditis or pericarditis, uncontrolled arrhythmia, mitral stenosis without adequate treatment, decompensated heart failure, uncontrolled hypertension (SBP ≥ 200 mmHg or DBP ≥ 110 mmHg), ST segment depression > 2 mm, uncontrolled diabetes mellitus, acute systemic sickness or fever of unknown origin, and other uncompensated metabolic problems. In addition, for inclusion in the study, normotensive subjects were required to have BP lower than 140/90 mmHg, whereas hypertensive subjects were required to have BP between 140/90 and 159/99 mmHg. The participants smokers, engaged in regular physical activity, using pain medication, antidepressants, tranquilizers, or any medicine that could interfere with the nociceptive threshold, or drugs or alcohol users were excluded from the study. Moreover, the participants had to present an assiduity to the CRP $> 80\%$.

Procedures

Before starting the CRP, each of the patients had an interview with a physiotherapist. The interview questions concentrated on the hypertension onset time, symptoms, life quality, pharmacotherapy, physical activity, and work. In addition, anthropometric measurements of the subjects' physical characteristics were performed, including the weight (kg), height (m), and mass by height based on the body mass index (BMI, kg/m^2).

The BP, heart rate (HR), and nociceptive threshold were also measured, and the functional capacity was obtained by using the six-minute walk test (6MWT), as described below.

Nociceptive threshold measurement

The mechanical nociceptive threshold was measured using a pressure algometer (EMG System of Brazil, São José dos Campos, SP, Brazil). The force was displayed digitally in increments of 1 kgf, and the cut-off pressure was set at 10 kgf to avoid tissue damage. Pressure was applied to the skin (right hand extensor region), and when the participant vocally reported pain, the stimulus was stopped. The value scored on the apparatus was described as the latency of the nociceptive threshold. The nociceptive threshold was measured initially and after the CRP in each group of participants. The threshold measurements were performed in triplicate, and the results were presented as the mean \pm the standard error of the mean (S.E.M).

Evaluation of functional capacity

To evaluate the cardiovascular and physical conditioning gains, the 6MWT was used. The participants walked along an enclosed level corridor for 30 meters. They were encouraged and instructed to walk at their own pace, but to cover as much ground as possible in 6 minutes. They tolerated the 6MWT without any adverse effects. The HR, arterial BP, rating of perceived exertion (RPE), and arterial oxygen saturation were measured at rest, continuously every 2 minutes while walking, and after the test [16].

Cardiac rehabilitation program

The CRP was performed in accordance with the Guidelines for Rehabilitation in Patients with Cardiovascular Disease [17]. The participants underwent 20 CRP sessions performed at the physical therapy clinic of our University. The CRP used in this study was composed of aerobic exercises on a treadmill (RT250; Movement, Manaus, AM, Brazil). Each patient started with a 10-minute warm-up at a low velocity, followed by 30 minutes at a velocity that maintained the target HR, and ended with an appropriate cooling-off period of 10 minutes of slow walking and stretching. The CRP exercises were conducted 3 times a week for 7 weeks. The patients exercised at 60% to 70% of their HR calculated according to the Karvonen formula: $[(\text{maximal HR} - \text{resting HR}) \times \% \text{ exercise intensity}] + \text{resting HR}$. The HR was measured continuously with a portable

HR monitor (RS200; Polar Electro Inc., Woodbury, NY, USA). The monitor was set to maintain a target HR and to signal (by a beep) when the HR fell outside of the chosen exercise's target range. The BP was monitored periodically during each workout to ensure that it was within safe limits (SBP \leq 210 mmHg for the males and \leq 190 mmHg for the females and DBP \leq 110 mmHg for both the males and females) [18]. The workload was adjusted to maintain the target HR and BP within the prescribed limits throughout the exercise session. The patients were also subjectively rated using a modified Borg RPE scale [19]. For those participants who did not reach the target HR, the intensity was determined by a score of 5-7 on the modified RPE scale. The arterial BP, HR, and RPE were measured before, during (every 10 minutes), and after the exercise program. The patients were advised to consume water, according to their medical status, before checkout.

The CRP was carried out in the morning (8 am to 12 pm) in order to minimize the impact of the circadian rhythm on the cardiovascular variables. The room temperature was maintained at 23°C, and the relative air humidity was between 40% and 60%. The participants were acquainted with the experimental protocol, and they were instructed to abstain from stimulants (coffee, tea, and soft drinks) and alcoholic beverages for 24 hours preceding the CRP. They were advised to have a light meal at least two hours before the procedure. Additionally, the subjects were asked to avoid physical activity one day before the procedure.

Statistical analysis

The descriptive data were expressed as means and standard deviations. The data normality was tested using the Kolmogorov-Smirnov and Shapiro-Wilk tests, followed by the paired t test for the intragroup analyses and the independent t test for the intergroup analyses. The parametric variables were expressed as means and standard deviations, and the frequencies were expressed by absolute numbers and percentages. For the sample calculation, we used the results of a previous study [20], considering a confidence level of 95% and a margin of error of 5%. All statistical analysis was performed using SPSS v.20.0 (IBM Corp., Armonk, NY, USA).

Results

From a list of approximately 63 individuals, 22 were excluded due to low assiduity (< 80%), resulting in a total of 41 participants (Fig. 1).

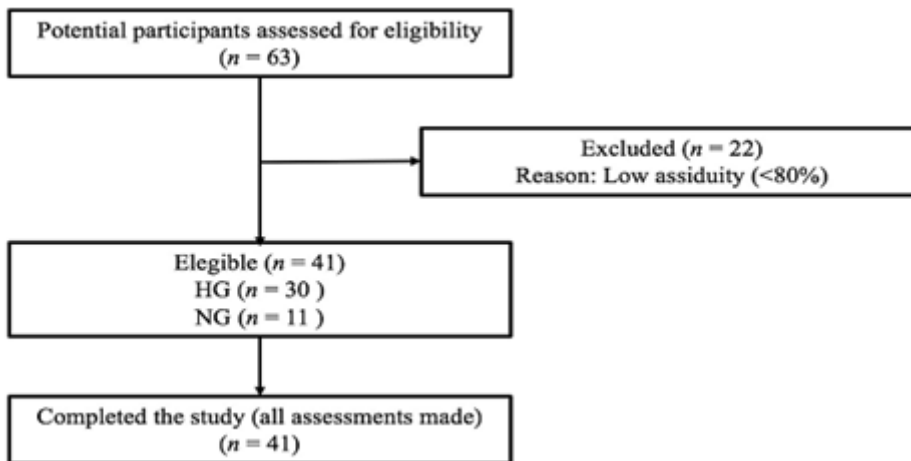


Figure 1 - Flow-chart

Sixty-three participants were assessed and divided into two groups: a hypertensive group (HG, $n = 30$) composed of subjects with clinical diagnoses of hypertension and a normotensive group (NG, $n = 11$) composed of normotensive subjects. 22 individuals were excluded due to low assiduity, resulting in a total of 41 participants.

Regarding baseline clinical characteristics of the subjects that participated in this study, approximately 53% of the HG was composed of males, with 47% females. In the NG, the male population was 27% and the female population was 73%. Furthermore, with regard to age, there were no significant differences between the groups, being the average age of 61.9 ± 10.4 . When evaluating the associated diseases, the HG had a higher percentage of individuals with associated diseases (8 diabetes mellitus, 12 sleep disturbances and 12 lung diseases) when compared to the NG (5 diabetes mellitus, 4 sleep disturbances and 3 lung diseases). In addition, in the HG, 6 subjects had acute myocardial infarction and 7 were submitted to cardiac surgery and none of the subjects in the NG had heart disease.

We also evaluated the anthropometric variables of the groups before and after the CRP. Table I shows that the baseline values of the body mass (BM) and abdominal circumference (AC) were higher ($p < 0.05$ and $p < 0.001$, respectively) in the HG when compared to the baseline values of the NG. In addition, the BM and AC values at the end of the CRP were also higher ($p < 0.05$ and $p < 0.01$, respectively) in the HG.

For the intragroup comparisons of the anthropometric variables, we did not find differences between the baseline and final values in either group (Table II).

Table I - Anthropometric variables of groups before and after CRP

	HG Initial	NG Initial	p value	HG Final	NG Final	p value
BM (kg)	87.1 ± 19.5	72.9 ± 18.8	0.04	86.8 ± 19.9	71.9 ± 18.2	0.03
BMI (kg/m ²)	32.2 ± 7.2	28.4 ± 6.4	0.12	32.3 ± 6.9	27.7 ± 6.3	0.06
AC (cm)	106.8 ± 13	94.1 ± 11.7	0.00	106.1 ± 14.6	93.1 ± 10.4	0.01

Source: Research data; CRP = cardiac rehabilitation program; AC = abdominal circumference; BM = body mass; BMI = body mass index; HG = hypertensive group; NG = normotensive group. Values are expressed as mean ± standard error (mean ± SEM)

Table II - Intra-group anthropometric variables of groups before and after CRP

	HG Initial	HG Final	p value	NG Initial	NG Final	p value
BM (kg)	87.1 ± 19.5	86.8 ± 19.9	0.65	72.93 ± 18.8	71.9 ± 18.2	0.13
BMI (kg/m ²)	32.2 ± 7.2	32.3 ± 6.9	0.90	28.4 ± 6.4	27.7 ± 6.3	0.14
AC (cm)	106.8 ± 13	106.1 ± 14.6	0.56	94.1 ± 11.7	93.1 ± 10.4	0.26

Source: Research data; CRP = cardiac rehabilitation program; AC = abdominal circumference; BM = body mass; BMI = body mass index; HG = hypertensive group; NG = normotensive group. Values are expressed as mean ± standard error (mean ± SEM)

We also analyzed some of the clinical variables before and after the CRP. In the between-group evaluations, we verified that the HG presented higher baseline values for the SBP ($p < 0.001$), DBP ($p < 0.05$), and mechanical nociceptive threshold ($p < 0.01$) when compared to the NG (Table III). Table IV shows also that the 6MWT baseline values were higher ($p < 0.01$) in the NG.

After the CRP, the SBP and DBP values remained higher ($p < 0.01$ and $p < 0.05$, respectively) in the HG when compared to the NG (Table III). For the mechanical nociceptive threshold and 6MWT values, there were no differences between the groups after the CRP (Table III).

Table III - Clinical variables, nociceptive threshold and physical performance of groups before and after CRP

	HG Initial	NG Initial	p value	HG Final	NG Final	p value
HR (bpm)	76.1 ± 12.5	79.1 ± 12.7	0.501	73.8 ± 12.1	79.9 ± 12.2	0.165
SBP (mmHg)	135.6 ± 12.5	114.5 ± 8.2	0.000	129.3 ± 19.2	110 ± 16.1	0.005
DBP (mmHg)	82.6 ± 12	74.5 ± 8.2	0.046	79.3 ± 9	71.8 ± 9.8	0.027
MNT (kgf)	6.3 ± 1.2	5.07 ± .79	0.002	5.2 ± 1.1	4.9 ± 1	0.456
6MWT (m)	399.8 ± 117.9	509.7 ± 82.3	0.007	468.2 ± 104	527 ± 90.8	0.106

Source: Research data; CRP = cardiac rehabilitation program; 6MWT = six minutes walking test; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; HG = hypertensive group; NG = normotensive group; MNT = mechanical nociceptive threshold; SBP = systolic blood pressure. Values are expressed as mean ± standard error (mean ± SEM)

The intragroup analysis of the clinical variables showed that after the CRP there was a reduction ($p < 0.001$) in the mechanical nociceptive threshold and an increase in the distance walked in the 6MWT ($p < 0.001$) in the HG when compared to the baseline

values (Table IV). In the NG, there were no statistical differences between the clinical variables before and after the CRP (Table IV).

Table IV - Intra-group clinical variables, nociceptive threshold and physical performance of groups before and after CRP

	HG Initial	HG Final	p value	NG Initial	NG Final	p value
HR (bpm)	76.1 ± 12.5	73.8 ± 12.1	0.259	79.1 ± 12.7	79.9 ± 12.2	0.721
SBP (mmHg)	135.6 ± 12.5	129.3 ± 19.2	0.100	114.5 ± 8.2	110 ± 16.1	0.271
DBP (mmHg)	82.6 ± 12	79.3 ± 9	0.161	74.5 ± 8.2	71.8 ± 9.8	0.192
MNT (kgf)	6.3 ± 1.2	5.2 ± 1.1	0.000	5.07 ± .79	4.9 ± 1	0.673
6MWT (m)	399.8 ± 117.9	468.2 ± 104.1	0.000	509.7 ± 82.3	527 ± 90.8	0.129

Source: Research data; CRP = cardiac rehabilitation program; 6MWT = six minutes walking test; DBP = diastolic blood pressure; HR = heart rate; HG = hypertensive group; NG = normotensive group; MN = mechanical nociceptive threshold; SBP = systolic blood pressure. Values are expressed as mean ± standard error (mean ± SEM)

Discussion

The present study determined that the CRP increased the physical conditioning and normalized the mechanical nociceptive threshold that was increased in the hypertensive subjects.

In the analysis of the BMI, the HG presented class 1 obesity and a high CAD risk, whereas the NG was classified as overweight with a lower cardiovascular risk [21]. The BM, AC, and BMI are not only indicators of obesity, they are among the factors associated with hypertension. Moreover, these variables are increased in hypertensive subjects, and they are risk factors for CAD [22,23]. Thus, corroborated by the evidence previously cited, we suggest that the HG in the present study had a greater cardiovascular disease (CVD) risk than the NG.

The BP level evaluation showed that the SBP and DBP levels were higher in the HG when compared to the NG before and after the CRP. In accordance with the new high BP clinical guidelines [24], we suggest that the participants in the HG had stage 1 hypertension. Previous studies have demonstrated graded associations between higher SBP and DBP levels and an increased CVD risk [25,26]. Thus, nonpharmacological therapies, such as exercise, have been used to treat and control this condition.

However, when we investigated the effects of the CRP on these values, we did not find any statistical differences in either of the groups. Several factors may have contributed to these results. First, we believe that the reduced sample size may have interfered with the results, because there was a tendency toward a reduction in these levels, but no statistical significance. Another factor could be the aerobic training duration. In our study, the CRP lasted 7 weeks, but in most of the other studies, the

training lasted 10 weeks [27]. However, our results in the 6MWT demonstrated that the physical conditioning of the HG improved after the CRP.

Although there was no statistically significant difference in the BP values after the CRP, there was a reduction in the SBP (from 135.67 ± 12.51 to 129.33 ± 19.29 in the HG and from 114.54 ± 8.20 to 110.0 ± 16.12 in the NG) and the DBP (from 82.67 ± 12.01 to 79.33 ± 9.07 in the HG and from 74.54 ± 8.20 to 71.82 ± 9.82 in the NG). Randomized clinical trials have documented that lowering the BP is associated with reductions in the CVD and all-cause mortality risks [28,29]. In addition, studies have also shown a strong, independent, and log-linear association between the normal SBP and DBP levels and mortality from CVD and all causes with no evidence of a threshold down to at least 115 mmHg and 75 mmHg, respectively [30]. Moreover, when following the new high BP clinical guidelines, the BP category in the HG changed from stage 1 hypertension (SBP from 130–139 mmHg or DPB from 80-89 mmHg) to elevated (less than 120/80 mmHg) [24]. Thus, despite the fact that the reductions in the BP values after the CRP were not statistically significant, the program may have helped reduce the BP in the hypertensive subjects, which reinforces the importance of physical of exercise in this population.

After evaluating the physical conditioning of the participants in the present study by using the 6MWT, the results only demonstrated an increase in the distance walked after the CRP in the HG. However, the baseline values demonstrated that the NG already had good physical conditioning. The 6MWT is commonly used to assess the fitness level of healthy adults and older adults with disabilities and pathologies, such as strokes, chronic obstructive pulmonary disease, pulmonary arterial hypertension, and heart failure [31-33].

The results of the present study also showed that the hypertensive subjects presented an increase in the baseline nociceptive threshold in relation to the normotensive subjects. This finding was first reported by Zamir and Shuber [34] who measured the pain perception by using electrical stimulation applied to the tooth pulp of 21 hypertensive and 34 normotensive subjects.

An early explanation for the increased nociceptive threshold of the hypertensive subjects could be that BP elevations may activate the baroreceptor pathways and induce a general inhibition of central nervous system processes and the pain via the activation of the descending control of pain [35]. One study found that bilateral sinoaortic denervation in spontaneously hypertensive rats partially reversed the attenuated response of the dorsal horn neurons, which is consistent with the view of a descending inhibitory baroreflex influence on the spinal nociceptive transmission in this form of experimental hypertension [36].

The involvement of endogenous analgesic substances that may be released by the descending control of the pain pathway are also associated with the increase in the nociceptive threshold found in hypertensive rats. A study showed an association between an increased nociceptive threshold and an increase in the β endorphin levels in 20 hypertensive subjects [37]. In addition to the opioid system, one study demonstrated the participation of angiotensin II in the increased nociceptive threshold in hypertensive patients [11]. Thus, one possible mechanism to explain the normalization of the nociceptive threshold in the hypertensive subjects after chronic physical training could be the reduction of the elevated levels of the endogenous analgesic substances.

With regard to the occurrence of silent myocardial ischemia (SMI), which may be associated with the increase in the nociceptive threshold found in hypertensive individuals, Glazier *et al.* [6] found a greater tolerance to pain in those patients with SMI episodes when compared to those with episodes of painful ischemia. In parallel, Nalbantgil *et al.* [38] reported that the SMI prevalence was significantly higher in hypertensive individuals. This occurred in 26.2% of the hypertensive subjects, 18.8% of the individuals with white coat hypertension, and 6.4% of the normotensive subjects in their study.

Study limitations

One of the study limitations was the small sample size of normotensive patients to the cardiac rehabilitation program due to low adherence, as well as the low assiduity. Although studies have demonstrated that hypertensive subjects presented hypalgesia and this finding is associated with SMI, the present study did not have access to the angina threshold of each individual, evaluated by an ergometric test and compared this threshold after aerobic training. However, we have shown that aerobic training reduced the nociceptive threshold increased in hypertensive individuals and this effect may be related to a reduction of the angina threshold.

Conclusion

The results of the present study showed a reduction in the nociceptive threshold of the hypertensive subjects after aerobic training, suggesting that aerobic exercise can be a strategy of prevention of SMI. In addition, CRP was efficient in control the arterial BP and improve the physical conditioning in hypertensive subjects. Further investigations are needed to elucidate the specific mechanisms that contribute increased

nociceptive threshold in hypertensive subjects and the control of this alteration by exercise.

Conflicts of interest

The authors report no conflicts of interest.

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Author' contributions

Conception and research design: Maldonado ACD, Galdino G; Data collection: Maldonado ACD; Prado JP; Data analysis and interpretation: Maldonado ACD, Aquino TN, Galdino G; Statistical analysis: Aquino TN, Vidigal FC; Writing of the manuscript: Maldonado ACD; Galdino G; Borges JBC; Critical revision of the manuscript for important intellectual content: Galdino G, Borges JBC, Prado JP

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