

Nonpharmacological strategies against hypertension: Effect of resistance training and acclimation on cardioprotection

Estratégias não farmacológicas contra a hipertensão arterial: efeito do treinamento resistido e aclimação na cardioproteção

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ABSTRACT

Introduction: Hypertension (HT) is the main risk factor for myocardial infarction. Together, these events are the main causes of death worldwide. The conventional treatment is pharmacological. Non-pharmacological strategies, such as resistance training (RT) and heat acclimation (HA), may affect reducing cardiovascular risk. **Objective:** The present study aimed to evaluate the effects of RT and HA on ventricular function, systolic blood pressure (SBP), and cardioprotection of spontaneously hypertensive rats (SHR). **Methods:** The experimental procedures were authorized under registration number 14/2022 (CEUA/ICBS/UFRJ). SHR were divided into a control group (CTR, $n = 7$), a group trained 3x/week/10 weeks (TG, $n = 8$), and a group acclimated in a heated bath for 11 consecutive days (HWI, $n = 9$). SBP was assessed by tail plethysmography. Left ventricular function (LVF) was evaluated by the isolated heart method. Cardioprotection assessment was based on LVF in the 60 min after global ischemia (IQ = 30 min) and on the analysis of the infarct area. **Results:** After the trials, only CTR showed higher SBP ($p < 0.01$). Left ventricular developed pressure (LVDP) was better during reperfusion in the HWI groups compared to CTR ($p < 0.05$) and TG ($p < 0.05$). The infarct area after IQ was smaller only in HWI ($p < 0.05$). **Conclusion:** TG and HWI demonstrated an effect on maintaining and reducing SBP in the experimental groups, but only HWI was effective in promoting cardioprotection.

Keywords: hypertension; resistance training; heat acclimation; cardioprotection; health

RESUMO

Introdução: A hipertensão arterial (HA) é o principal fator de risco para o infarto do miocárdio. Juntos, estes eventos são as principais causas de morte no mundo. O tratamento convencional é o farmacológico. Estratégias não farmacológicas, como o treinamento resistido (TR) e a aclimação ao calor (ACC), podem ter efeito na redução do risco cardiovascular. **Objetivo:** O presente estudo teve como objetivo avaliar os efeitos do TR e da ACC sobre a função ventricular, pressão arterial sistólica e cardioproteção de ratos espontaneamente hipertensos (SHR). **Métodos:** Os procedimentos experimentais foram autorizados sob registro nº 14/2022 (CEUA/ICBS/UFRJ). SHR foram divididos em grupo controle (CTR, $n = 7$), grupo treinado 3x/semana/10 semanas (TR, $n = 8$) e grupo aclimatado em banho aquecido por 11 dias consecutivos (HWI, $n = 9$). A pressão arterial sistólica (PAS) foi avaliada por pletismografia de cauda. A função ventricular esquerda (FVE) foi avaliada pelo método de coração isolado. A avaliação de cardioproteção baseou-se na FVE nos 60min após isquemia global (IQ = 30 min) e na análise da área de infarto. **Resultados:** Após os ensaios, apenas CTR apresentou maior PAS ($p < 0,01$). A pressão desenvolvida pelo ventrículo esquerdo (PDVE) foi melhor durante a reperfusão nos grupos HWI comparados a CTR ($p < 0,05$) e TR ($p < 0,05$). A área de infarto após IQ foi menor apenas em HWI ($p < 0,05$). **Conclusão:** TR e HWI demonstraram efeito na manutenção e redução da PAS nos grupos experimentais, mas apenas HWI foi efetivo na promoção da cardioproteção.

Palavras-chave: hipertensão; treinamento resistido; aclimação ao calor; cardioproteção; saúde

Introduction

Cardiovascular diseases lead the ranking of causes of death in the world [1]. Hypertension (HT) is one of the main cardiovascular risk factors and can result in serious consequences in different organs (heart and blood vessels) [2–5]. HT is characterized by a SBP greater than or equal to 140 mmHg and a diastolic pressure above 90 mmHg [5]. These elevated blood pressure (BP) values have traditionally been associated with the risk of ischemic heart disease [5].

The conventional treatment for hypertension is pharmacological. This works through different mechanisms of action (diuretics, angiotensin-converting enzyme inhibitors, angiotensin II AT1 receptor blockers, among others). However, the use of these drugs generates negative effects on the health and life quality [6,7] of patients. This type of treatment also has a significant socioeconomic impact due to the high medical costs resulting from comorbidities, mainly in the kidneys and brain, organs adjacent to the cardiovascular system that are subject to fatal or non-fatal events [5,8,9].

Seeking to minimize these side effects, new therapies have been proposed to control and reduce SBP exclusively or as adjuvant therapies [7,10]. RT has shown effectiveness in reducing BP [11–13], in addition to improving myocardial function [14]. Heat acclimatization or heat therapy is also an alternative to mitigate hypertensive effects [15].

Individually, these strategies have not yet demonstrated their effect on the heart after ischemia and reperfusion injury (IRI), as well as on the extent of the infarct area and cardioprotection. The impossibility of performing invasive procedures in humans led us to use an experimental model to carry out these evaluations. Therefore, in this study, we used spontaneously hypertensive rats (SHR), animals that present a hypertensive phenotype analogous to that of human hypertension. This phenotype is due to their genetic predisposition [16] and the increase in total peripheral resistance without volume expansion [17].

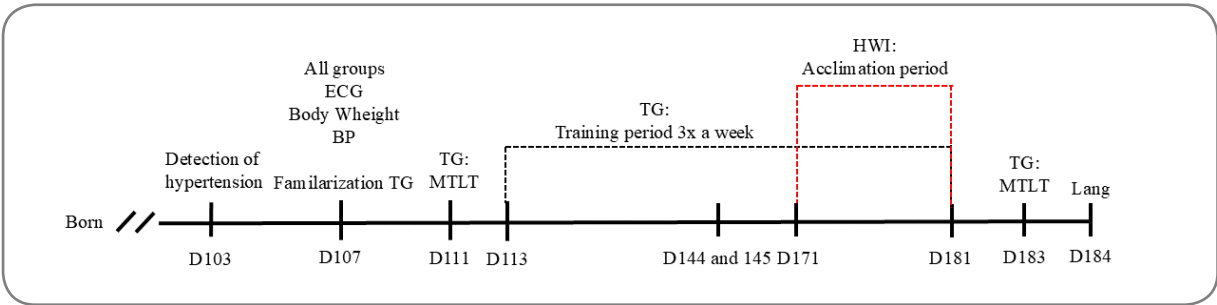
The hypothesis that the trained group (TG) and the group acclimated to heat in a heated bath (HWI) would be able to improve cardioprotection and better recovery of ventricular function after IRI was tested. The aim of the study was to verify the effect of TG and HWI on SBP and infarct area after 30 min of ischemia in SHR hearts.

Methods

Animals

SHR, males, were randomly divided into control (CTR, $n = 9$), heat-acclimated (HWI, $n = 9$), and resistance trained (TG, $n = 9$) groups. Experimental procedures were approved by the Ethics Committee for Animal Use of the Institute of Biomedical and Health Sciences of UFRRJ (CEUA 14/2022/ICBS/UFRRJ).

Experimental design



ECG = electrocardiogram; MTLT = maximum transported load test; TG = trained group; HWI = heat acclimated group; Lang = Langendorff isolated heart protocol

Figura 1 - Experimental design. D, day. RT, resistance training. BP, blood pressure

Familiarization with the training apparatus

The rats in the TG group were familiarized with the resistance training apparatus to minimize failures in the execution of the training. The familiarization routine is described in Table I.

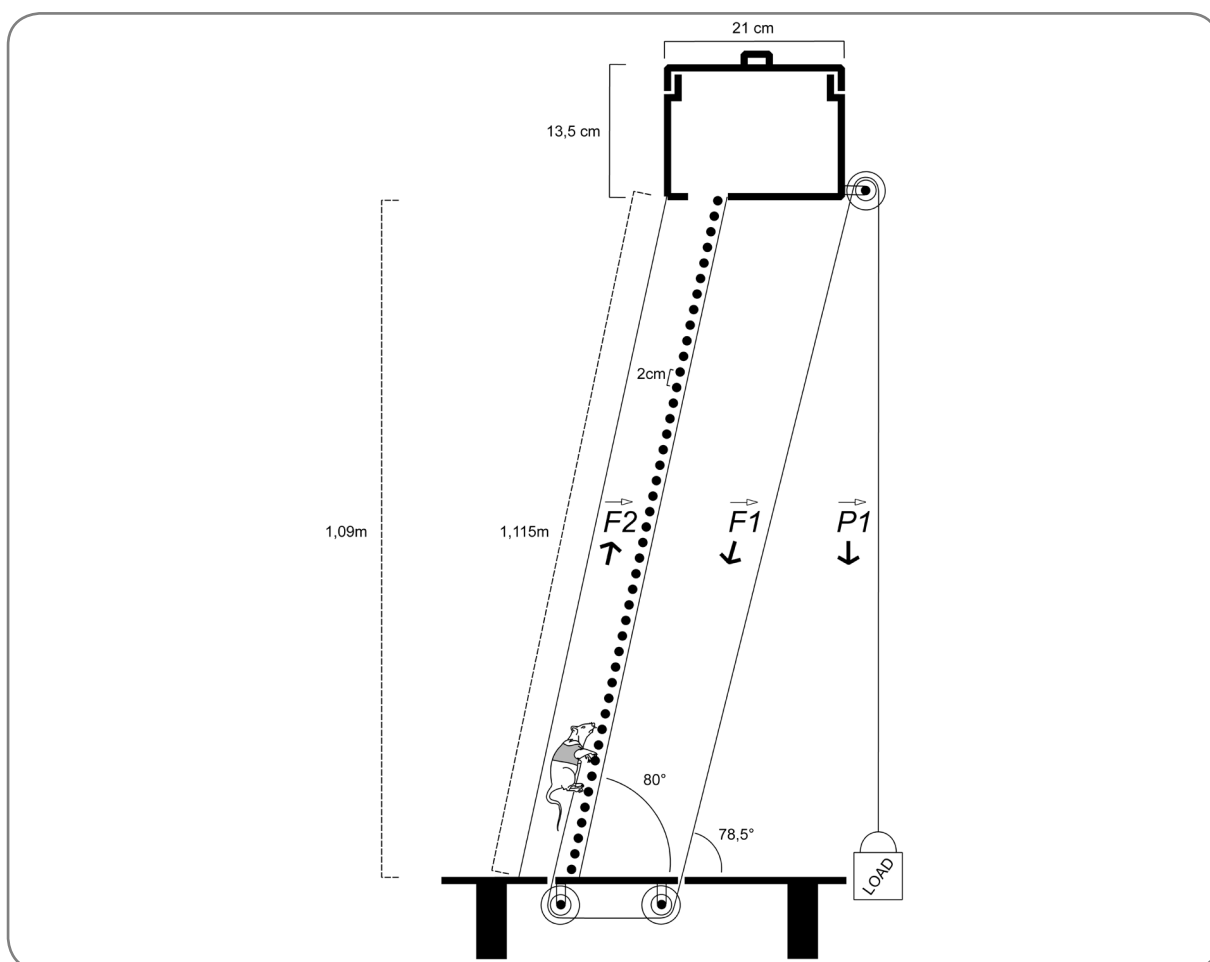
Table I - Adaptation protocol for resistance training apparatus

Day	Description of the adaptation
1	10 min on the box positioned at the top of the stairs 10 consecutive climbs without load and without a vest. Free interval between climbs
2	10 min on the box positioned at the top of the stairs 10 consecutive climbs without load and without a vest. Free interval between climbs
3	10 consecutive climbs without load and with vest. Free interval between climbs At the end, leave the animal for 10 minutes in the box positioned at the top of the stairs
4	10 consecutive climbs, 3 climbs without load and with vest followed by 7 climbs with load (10 g) and with vest. Free interval between climbs
5	10 consecutive climbs, 3 climbs without load and with vest followed by 7 climbs with load (10 g) and with vest. Free interval between climbs
6	10 consecutive climbs, 3 climbs without load and with vest followed by 7 climbs with load (20 g) and with vest. Free interval between climbs
7	10 consecutive climbs, 3 climbs without load and with vest followed by 7 climbs with load (10 g) and with vest. Free interval between climbs

Resistance training (RT) was performed on a ladder with a height of 110 cm and an 80° inclination [18] with a vest fixed to the chest, developed by our laboratory. The rats were positioned at the base of the ladder and were adapted to climb to the top, where there was a box for accommodating the animals in the 120 s interval between series.

Maximum transported load test (MTLT)

The test was performed on up to two consecutive days. On the first day, the animals were forced to climb the ladder carrying an initial load of 50% of their body mass (BM). The load was attached to the end of a cable fixed to the chest vest. If the climb was successful, the load was increased by 10% of the BM on the subsequent climbing attempt for a second attempt. If the climb was successful again, the load was increased by another 5% of the BM. If the climb was still successful on this last attempt of the day, the test was restarted on the following day, adding 5% to the last load carried. This was repeated up to a maximum of the third attempt on the second day. All animals reached their maximum load by the second day. Failure was determined when the animal was unable to climb the ladder after three consecutive stimuli on the tail (with a tweezer), with a rest interval of 120 s between each climb.



The load pulled by the animal corresponds to the initial load (LOAD) at the opposite end of the pulley as they are fixed pulleys

Figure 2 - Training apparatus using a vest

Training protocol

The training load was calculated based on the individual maximum load (load of the last complete climb) for each rat. The exercise load was adjusted in the fifth week according to the new maximum test load. RT was performed 3 days/week, for

10 weeks with a load of 30-70% of the maximum load. The rats performed 6 to 8 climbs, depending on the training week. A 1-minute interval between climbs was used [11,19]. A new load test was performed every 15 training sessions to readjust the load.

Table II - Resistance training protocol on the stairs with pulley and vest

Training week	Climbing on stairs	% of maximum load
1	1-3	30
	4-6	50
2-3	1-2	30
	3-6	50
	7	60
4-10	1-2	30
	3-4	50
	5-6	60
	7-8	70

Acclimation protocol

Rats in the HWI group were subjected to a hot bath for eleven days, starting on the first day with a 20-minute stay and adding 5 minutes each day, until reaching 60 minutes on the ninth day. From the ninth to the eleventh day, the session was 60 minutes long. The hot bath was performed in a pool for rats with a water temperature of 40 °C.

SBP measurement

A noninvasive tail cuff measurement system was used to acquire systolic blood pressure (SBP) (Digital Tail Plethysmograph with Dual-Channel Heater, Bonther, Ribeirão Preto, SP, Brazil), previously validated by Feng *et al.* [20]. This system detects SBP based on volume changes in the tail [20]. Although it is associated with less stress caused by restraint, the tail cuff technique is more acceptable to meet the “refinement” requirement in the 3Rs principle, since it is performed without the need for anesthesia or surgery. The blood pressure measurement experiments were conducted in a controlled, quiet, temperature-regulated environment (22 ± 1 °C), where the rats warmed up for a period of 30 to 40 min before the start of the experiments. The rats were then subjected to experimental protocols adapted from those described previously [21] and briefly reported below. The occlusion cuff was placed at the base of the tail, and the sensor cuff was placed adjacent to the occlusion cuff. The base of the apparatus consists of a heating platform that preheats the animal to 37 °C. To measure BP, the occlusion cuff was inflated to 210–280 mmHg and deflated for 20 s. Each recording session consisted of 2 inflation and deflation cycles per set according to the manufacturer’s standard recommendation, of which the first 2 cycles were “adaptation” cycles, while the subsequent cycles were used for analysis. Rats were adapted for 5 consecutive days before baseline blood pressure measurements.

Electrocardiogram (ECG)

ECGs were performed before and after the experimental protocol 3 days before the start of the protocol. The animals remained for 10-15 min with the electrodes so that they could adapt to the equipment and, in this way, any noise during the ECG at the beginning and end of the experiment would be reduced. An analog-digital interface (Power Lab 400, ADInstruments, United States of America - USA) was used for data collection and the data were stored on a computer for later analysis. Data analysis was performed using Lab Chart 8 Pro software (ADInstruments, United States of America). The complementary modules ECG Analysis 2.4 (ADInstruments, USA) and Heart Rate Variability 2.0 (HRV 2.0, ADInstruments, USA) were used for ECG analysis.

Isolated heart protocol

The hearts were removed and connected to the Langendorff apparatus by inserting a cannula with a continuous flow of 10 ml.min⁻¹ into the aorta, characterizing retrograde flow of this technique. The artificial perfusion solution used was the modified Krebs-Henseleit (KHS) containing 118 mM NaCl, 4.7 mM KCl, 1.2 mM MgSO₄, 1.2 mM KH₂PO₄, 25 mM NaHCO₃, 10 mM C₆H₁₂O₆, 1.8 mM CaCl₂, saturated with a carbogenic mixture (95% O₂ + 5% CO₂). The solution was adjusted to pH 7.4 and kept warm at 37 °C, being pumped with a continuous flow through the circuit through the perfusion pump. A latex balloon connected to a pressure transducer was inserted through the left atrium. The balloon was filled with distilled water and a pressure of 10 mmHg was adjusted. Through an amplifier (ML110, ADInstruments, United States of America), it was possible to record the intraventricular pressure developed by the left ventricle through an analog-digital interface (PowerLab 400, ADInstruments, United States of America) and stored with the aid of software for analysis of biological signals (Lab Chart 8 Pro, ADInstruments, United States of America).

The isolated heart protocol consisted of removing the heart and mounting it in the apparatus, followed by 20 min of accommodation. The first recording was 10 min of basal performance. The next step was 30 min of ischemia and 60 min of reperfusion.

Morphometry

Rats were weighed (Toledo Prix 3, Toledo, Brazil) pre- and post-training in this study. After euthanasia and heart extraction, the right tibia was collected for measurement and normalization of body mass and heart mass. Samples were also collected from the soleus and flexor hallucis longus muscles, as they are more involved during this resistance exercise. The samples were weighed on a microbalance (AD 500, Marte, Brazil) and then frozen in liquid nitrogen to be stored in a freezer at -80 °C for future analyses. Immediately after the isolated heart protocol, all hearts were weighed on an analytical balance (AD 500, Marte, Brazil), the apex removed, and placed for 10 minutes at -20 °C to better prepare the slices for staining.

Measurement of the infarct area

The apices were discarded, and slices were prepared in sections of approximately 1 mm in thickness from the apex to the base for mounting on slides. To improve the contrast between viable and necrotic tissues, the slices were incubated in 1% triphenyltetrazolium chloride in phosphate buffer (pH 7.4) for 5 min at 37 °C and then incubated in 10% formaldehyde solution for 24 h. The sections were placed between two glass slides, and their images were digitally acquired using a scanner (Lide 300 USB, Cannon, Brazil). The infarct size was determined using ImageJ software (public domain, version 1.54k).

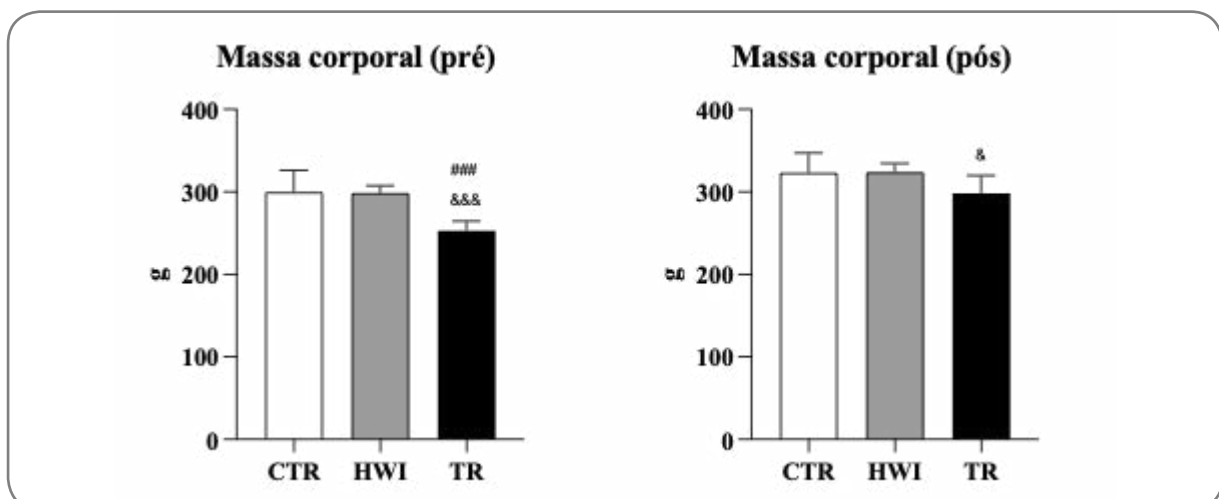
Statistics

Data were presented as mean $\pm$ standard error of the mean (SEM). The Shapiro-Wilk test was used to verify the normality of measurements. One-way analysis of variance (ANOVA) was used to analyze continuous response variables and categorical explanatory variables. Two-way ANOVA with Sidak's post-test was used for temporal analysis of ex-vivo data. When normality in the distribution was not verified, the Wilcoxon paired rank test was used. GraphPad Prism 10.1.1 software (GraphPad Software, USA) was used for the analyses. Statistical differences were considered significant when the significance value was less than 5% ($p < 0.05$).

Results

Pre-experimental morphometry (in vivo)

The analysis of body mass before the tests showed lower mass in the TG: 252.7 $\pm$ 4.8 g (95% CI = 240.2 to 265.1) compared to CTR (CTR: 299.8 $\pm$ 9.3 g (95% CI = 277.7 to 321.8 g)), $p < 0.001$) and HWI (HWI: 298.4 $\pm$ 3.0 g (95% CI = 291.5 to 305.4 g, $p < 0.001$)). At the end of the experiment, with access to the tibia length, TG equaled CTR and decreased the difference in HWI ($F(2, 24) = 3.863$; $p = 0.0373$), demonstrating a significant gain in BM resulting from the training performed.

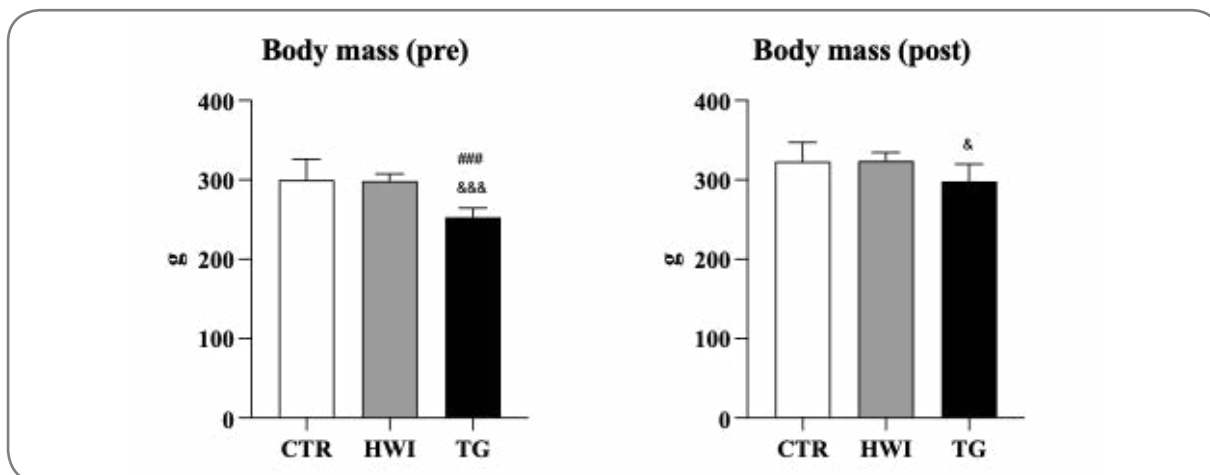


Data are expressed as mean $\pm$ SEM. & TG vs HWI ($p = 0.0373$); &&& TG vs HWI ($p = 0.0002$); ### TR vs CTR ($p = 0.0002$). CTR = Control; HWI = Acclimatizing; TG = Trained group

Figure 3 - Pre- and post-experimental morphometry between groups

Systolic blood pressure (SBP)

At the end of the experimental protocol, SBP in HWI (200.2 ± 5.4 mmHg, 95% CI = 187.7 to 212.7 mmHg) and TG (206.4 ± 8.9 mmHg, 95% CI = 185.9 to 226.9 mmHg) remained constant, while CTR (235.4 ± 8.8 mmHg, 95% CI = 213.9 to 257) showed an increase in SBP, as expected for this particular strain ($F(2, 24) = 5.253$; $p = 0.0128$).

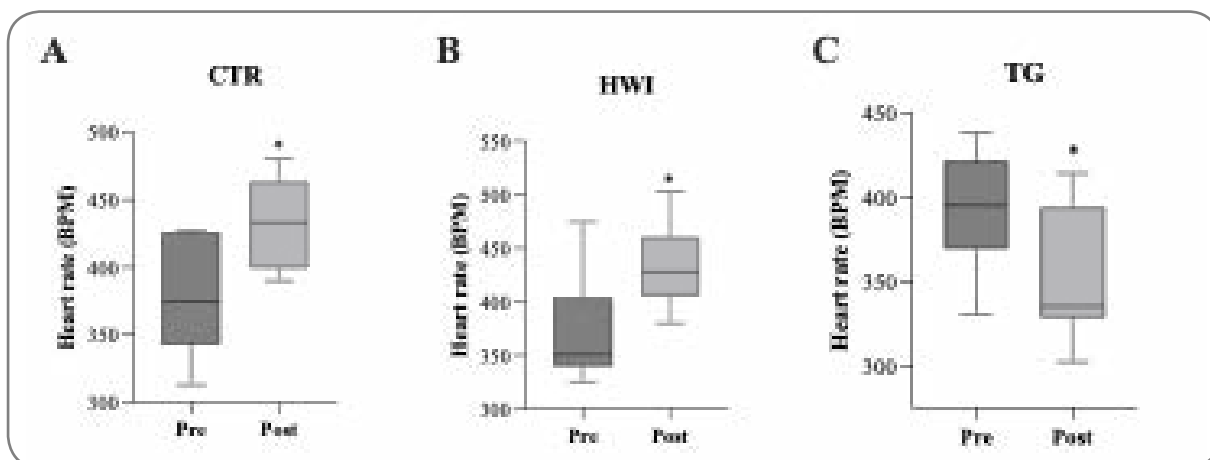


HWI reduced SBP from week 8 compared to CTR and from week 10 compared to TG. *HWI vs CTR ($p = 0.0065$); &TG vs CTR ($p = 0.0364$). CTR = Control; HWI = Acclimating; TG = Trained Group

Figure 4 - Systolic blood pressure

ECG

The ECG was used to assess heart rate (HR) before and after the experimental intervention. It was observed that both CTR (pre: 378.0 ± 18.4 bpm, post: 434.2 ± 11.8 bpm, $p = 0.0196$) and HWI (pre: 370.8 ± 15.9 bpm, post: 432.1 ± 12.5 bpm, $p = 0.0149$) had an increase in HR comparing their pre vs post moments. TG showed a reduction in HR after the experimental protocol (pre: 393.3 ± 11.4 bpm, post: 354.7 ± 12.4 bpm, $p = 0.0281$).



Data are expressed as mean $\pm$ SEM. *(CTR: $p = 0.0196$; HWI: $p = 0.0149$; TG: $p = 0.0281$). CTR = Control; HWI = Acclimating; TG = Trained Group; Pre = pre-experimental; Post = post-experimental

Figure 5 - Intragroup heart rate

Hemodynamics

Left ventricular performance was not different between groups at baseline ($p = 0.4601$). During the ischemic period (20–50 min), HWI and TG had an attenuated reduction in contractility in the first 5 min (HWI vs CTR: $p = 0.0451$; TG vs CTR: $p = 0.0324$), which suggests cellular energy savings. During reperfusion, only HWI had better recovery of ventricular function (LVDP) compared to CTR and TG ($F(2, 24) = 4.631$; $p = 0.0216$).

Table III – Ventricular performance

	PDVE _{basal} (mmHg)	PDVE _{5minIG} (mmHg)	PDVE _{reperusão} (mmHg)
CTR	78.13 ± 1.6	11.27	5.17 ± 0.08
HWI	71.19 ± 1.7	17.0	14.34 ± 0.3 *
TG	62.24 ± 1.35	22.11	7.19 ± 0.2

Left ventricular pressure developed at baseline, LVDP_{basal}; Left ventricular pressure developed at 5 minutes of GA, LVDP_{5minIG}; Left ventricular pressure developed during reperfusion, LVDP_{reperusão}; Data are expressed as mean ± SEM. CTR = Control group; HWI = Heat acclimated group; TG = Trained group. * $p = 0.0216$

Ex-vivo morphometry

At the end of the 10 weeks of training, TR had a higher heart mass normalized by body mass than CTR and HWI ($F(2, 24) = 21.90$; $p < 0.0001$).

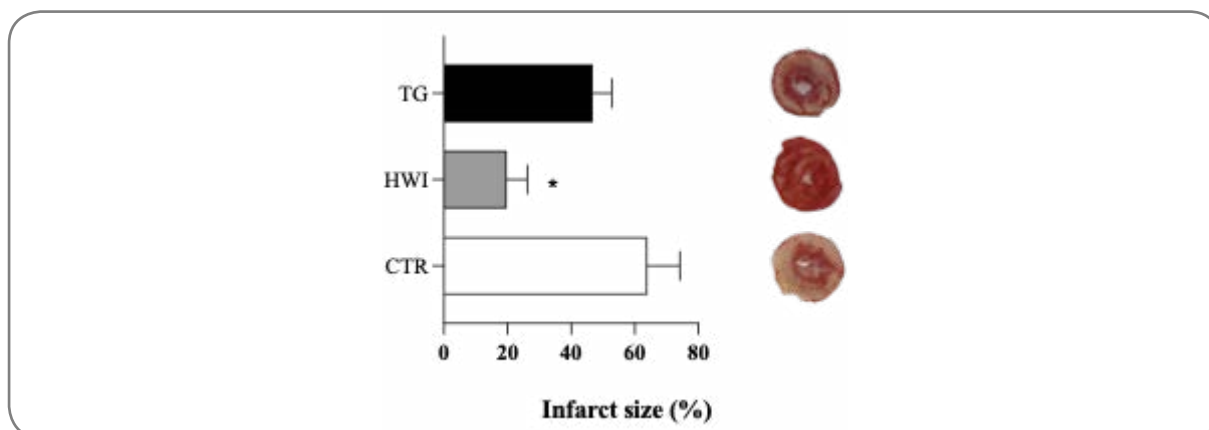
Table IV – Ex-vivo cardiac morphometry

	Massa cardíaca / Massa corporal
CTR	0.005477 ± 0.0001116
TR	0.006388 ± 0.0001968 *#
HWI	0.005206 ± 3.647e-005

*CTR vs HWI; #CTR vs TR; $P < 0.0001$

Analysis of the infarct area

No differences were observed in the contractility index between the groups ($p = 0.2392$). The infarct area was smaller in HWI compared to CTR ($p = 0.0129$) and TG ($p = 0.0446$).



A = Infarct area; B = Representative images. Data are expressed as mean $\pm$ SEM. * $p = 0.0110$. CTR = Control; HWI = Acclimating; TG = Trained Group

Figure 6 - HWI reduced the infarct area, represented as a percentage of the total area

Discussion

Among the groups, TG had the lowest body mass before the interventions. After the trials, the body mass of TG did not differ from CTR and HWI ($p > 0.05$). This increase demonstrated the effect of training and suggests the hypertrophic effect, even though it was not the main objective of this study.

SHR rats have the characteristic of gradually increasing their SBP throughout their lives [22]. Resistance training was able to stabilize the SBP of the TG group, corroborating the findings of studies [19,23]. We also noted the decrease in heart rate, observed previously [19,23], which can be explained by a decrease in sympathetic tone [24]. Increased cardiac output during exercise increases shear stress on the blood vessel wall, stimulating the endothelium to release nitric oxide (NO) [25]. NO, when diffusing into endothelial smooth muscle cells, promotes vasodilation [26,27] which decreases peripheral vascular resistance. Especially in the early phase of hypertension, resistance training has been shown to decrease peripheral resistance [27], which facilitates venous return, increasing preload and greater LVDP resulting from increased preload and in line with the Frank-Starling mechanism [28]. Furthermore, TG generates cardiac hypertrophy [29] and lower demand per contractile unit, according to La Place's Law [30]. Taken together, these factors contributed to the increase in stroke volume and the decrease in HR in maintaining cardiac output.

Post-exercise hypotension in humans has already been explained by the withdrawal of sympathetic tone and central vasodilation through NO [31]. Sustained post-exercise hypotension, regardless of the increase in NO [32], appears to involve other mechanisms and be multifactorial, including the action of histamine, formed and released within active skeletal muscle tissue [31], activation of the kallikrein-kinin system, dopaminergic system and natriuretic system, as well as inhibition of the sympathetic nervous system [33]. All these physiological adaptations can generate cumulative effects resulting in lower SBP and a reduction in HR, not only immediately after exercise, but also in a sustained manner.

Heat acclimation through sauna bathing has already been described as an acute hypotensive therapy [34–36]. Recently, unique heat adaptation strategies have been described as potential thermal therapies [37–38]. This therapeutic approach mainly favors hypotension, but its effects on cytoprotection have not yet been described. The cardioprotective effects of resistance training and heat acclimatization have not yet been described in hypertensive rats. Analogous to human physiology, potential cardioprotective effects observed reflect the action of mechanisms that preserve cardiac function, especially after the occurrence of an eventual ischemic episode, the main cause of cardiovascular death, with HT as the greatest risk factor.

The effects of the training protocol and heat acclimation on hemodynamics were evident in the first 5 min of the IQ period, when TG and HWI presented higher LVDP values. This fact demonstrates that the myocytes of both groups sustained some degree of contractility for longer, without nutrition. There was no significant difference in the contractility index between the groups, therefore the ischemic contracture was not attenuated by acclimation or resistance training. In the reperfusion period, HWI demonstrated better recovery.

The increased cardiac mass in TG reflects the effect of training. This expected adaptation did not result in better cardiac performance or even better recovery after IQ. Thus, no evidence of cardioprotection was observed in this group. Analysis of the infarct area demonstrated a smaller area of infarcted tissue after 60 min of reperfusion in HWI hearts. This observation, together with the better recovery of left ventricular function in the HWI group, demonstrates the cardioprotection conferred by the acclimatization protocol to which the animals were subjected. The mechanism related to this cardioprotection involves the action of the response to thermal stress mediated by heat shock proteins [39]. These act as chaperones and act mainly in the maintenance and repair of cellular function.

Limitations

Although SBP is measured using the inflatable cuff method, which is non-invasive and less stressful for the animal, this technique does not yet provide a reliable measurement for diastolic blood pressure, in addition to depending on a period of pre-experimental familiarization of the animals with the apparatus, in order to avoid or at least reduce the stress of contraction during the measurement. We chose this technique to meet the demand of the 3Rs principle and to reduce the number of animal lives in the experiment performed.

We used only male animals, but the use of females would be of great value to expand the conclusions and clarify any questions dependent on sex.

Another factor that we observed throughout the experiments in our laboratory and that was more evident in this study was the use of 30 minutes of IQ. We believe that this period can be reduced so that we can better assess the recovery of the hearts during the reperfusion period and prevent viable hearts from being lost due to excessive IQ time.

Conclusion

According to the data obtained in this study, we observed that the resistance training protocol decreased heart rate and stabilized SBP in SHR rats, while heat acclimatization conferred cardioprotection in SHR rats, which had not yet been demonstrated in the literature. Taken together, these data demonstrate the potential effect of training and acclimatization, which, if performed in a planned manner, can promote health by reducing cardiovascular risk. Further studies are needed to verify the exact mechanisms of cardioprotection observed.

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Conflicts of interest

The authors declare no conflicts of interest.

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Authors' contributions

Conception and design of the research: Santos JS, Almeida RACS; **Data collection:** Santos JS, Almeida RACS, Amorim LS; **Acquisition of data:** Santos JS, Amorim LS; **Analysis and interpretation of the data:** Santos JS, Almeida RACS; **Statistical analysis:** Almeida RACS; **Obtaining financing:** Olivares EL; **Writing of the manuscript:** Santos JS, Almeida RACS; **Critical revision of the manuscript for important intellectual content:** Silveira ALB, Olivares EL.

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