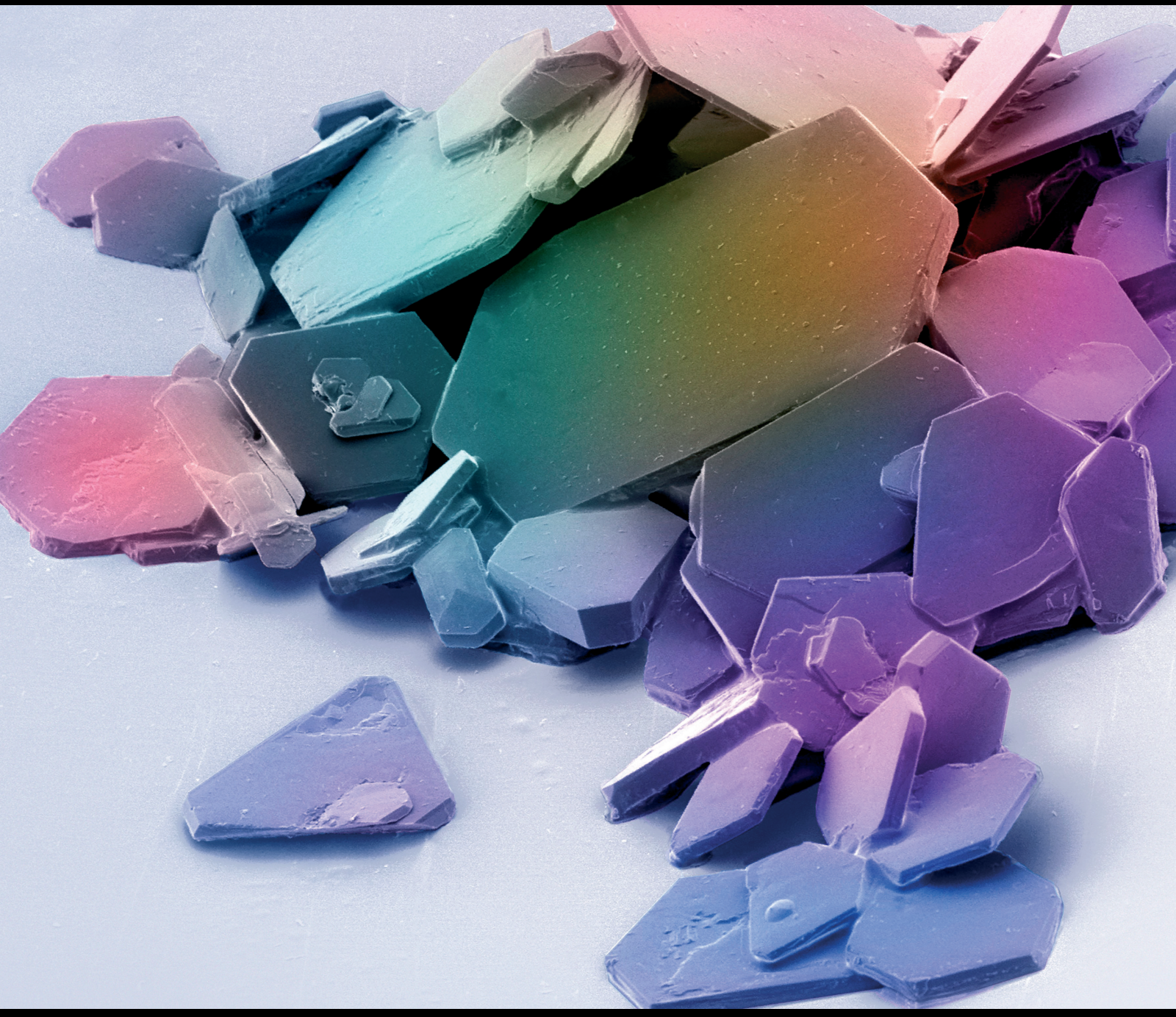
Cardiovascular Therapeutics

From Pathological Basis to Therapy of Resistance Hypertension

Lead Guest Editor: Bruno Rodrigues
Guest Editors: Heitor Moreno and Hélio José Coelho Júnior



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Research Article

Extended Renal Artery Denervation Is Associated with Artery Wall Lesions and Acute Systemic and Pulmonary Hemodynamic Changes: A Sham-Controlled Experimental Study

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Objectives. We sought to assess acute changes in systemic and pulmonary hemodynamics and microscopic artery lesions following extended renal artery denervation (RDN). *Background.* RDN has been proposed to reduce sympathetic nervous system hyperactivation. Although the effects of RDN on systemic circulation and overall sympathetic activity have been studied, data on the impact of RDN on pulmonary hemodynamics is lacking. *Methods.* The study comprised 13 normotensive Landrace pigs. After randomization, 7 animals were allocated to the group of bilateral RDN and 6 animals to the group of a sham procedure (SHAM). Hemodynamic measures, cannulation, and balloon-based occlusion of the renal arteries were performed in both groups. In the RDN group, radiofrequency ablation was performed in all available arteries and their segments. An autopsy study of the renal arteries was carried out in both groups. *Results.* The analysis was performed on 12 pigs (6 in either group) since pulmonary thromboembolism occurred in one case. A statistically significant drop in the mean diastolic pulmonary artery pressure (PAP) was detected in the RDN group when compared with the SHAM group (change by 13.0 ± 4.4 and 10.0 ± 3.0 mmHg, correspondingly; $P = 0.04$). In 5 out of 6 pigs in the RDN group, a significant decrease in systemic systolic blood pressure was found, when compared with baseline (98.8 ± 17.8 vs. 90.2 ± 12.6 mmHg, $P = 0.04$), and a lower mean pulmonary vascular resistance (PVR) (291.0 ± 77.4 vs. 228.5 ± 63.8 dyn $*$ sec $*$ cm^{-5}, $P = 0.03$) after ablation was found. Artery dissections were found in both groups, with prevalence in animals after RDN. *Conclusions.* Extensive RDN leads to a rapid and significant decrease in PAP. In the majority of cases, RDN is associated with an acute lowering of systolic blood pressure and PVR. Extended RDN is associated with artery wall lesions and thrombus formation underdiagnosed by angiography.

1. Introduction

The autonomic nervous system is involved in the pathogenesis of cardiovascular diseases, including hypertension. In conditions such as hypertension, pulmonary arterial hypertension (PAH), coronary artery disease, chronic heart failure, excessive activation of sympathetic impulsation, and a decrease in parasympathetic activity have been noted. There is evidence that sympathetic hyperactivation makes a significant contribution to the development of both systemic hypertension and pulmonary hypertension [1].

Renal artery denervation (RDN) has been proposed to reduce sympathetic hyperactivation. Although the results of the Symplicity HTN-3 trial were neutral [2], this method has been shown effective in several newer studies [3–5].

The impact of RDN on systemic circulation and on overall sympathetic activity has been extensively studied. However, data on the effects of RDN on pulmonary hemodynamics is lacking. Thus, a few preclinical studies in small animals have evaluated right ventricle (RV) remodeling and pulmonary vascular effects of RDN [6, 7]. Importantly, these experimental studies have implemented no specialized instrumentation for RDN and may not be reproducible in larger animals or humans. Currently, there are technologies allowing radiofrequency (RF) ablation not only in the renal artery (RA) trunk but also in distal branches (extended RDN). There have been several studies analyzing acute and chronic effects of extended RDN on systemic hemodynamics [4, 8]; the acute effects of extended denervation of the RA on pulmonary hemodynamics have not been reported.

The aim of our study was to assess acute changes in systemic and pulmonary hemodynamics following extended RDN and possible associations of the ablation extent with hemodynamic changes and histologically verified artery wall damage.

2. Methods

The experiment was conducted on thirteen normotensive breed Landrace pigs (the mean weight 33.4 ± 2.46 kg, age 3-4 months). All procedures and protocols were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) (protocol 19-12PZ#V1). After randomization, seven animals were allocated to the group of bilateral RDN, and six animals were allocated to the group of a sham procedure (SHAM). All procedures were performed in an experimental operating room equipped with a fluoroscopic C-arm (BV Endura, Philips, Netherlands).

The animals were sedated by intramuscular injection of 1.5 ml Zoletil 100 (Virbac, Carros, France); then, the outer ear vein was cannulated, and the animals were intubated for mechanical ventilation. Ventilation was performed using the anesthetic respiratory apparatus WATO EX-35 (Shenzhen Mindray Bio-Medical Electronics Co., Ltd, China) with the following parameters: FiO_2 0.3, tidal volume 10 ml/kg, peak end-expiratory pressure (PEEP) 6 cm H_2O. Anesthesia was maintained by ventilation with 1% isoflurane (Baxter Healthcare Corp., Puerto Rico). Circulating blood volume support was carried out by continuous saline and Gelofusine (B. Braun, Germany) infusion at a rate of 10 ml/kg/h each.

A longitudinal 5 cm incision was performed in the right paratracheal region; after which the right jugular vein, right common carotid artery, and the right n. vagus were isolated. A 7 F vascular hemostatic sheath (Avanti, Cordis, USA) was inserted into the right jugular vein; the 8 F 62 cm length multipurpose Preface sheath (Biosense Webster, USA) was introduced through the external carotid artery and placed in the abdominal aorta under fluoroscopic guidance. After vascular access, a solution of heparin sodium at a dose of 300 IU/kg/h was administered intravenously.

Continuous registration of invasive blood pressure (BP) was performed. The core body temperature was kept at 37°C with a thermostatically controlled blanket (Warm-Touch™, Medtronic, MN, USA).

2.1. Renal Artery Cannulation, Stimulation, and Denervation Procedure. A 6F pigtail catheter (Cordis, Johnson and Johnson, USA) was placed in the abdominal aorta, and RA angiography was performed using 15 ml contrast media (Optiray 300, Guerbet, France).

According to previous reports, electrical high-frequency stimulation through the RA wall was suggested to identify sites with sympathetic response before RF ablation [9, 10]. The absence of stimulation-elicited BP response was considered as a potential endpoint for denervation procedures. In order to assess the possible BP reactions to RA electrical stimulation, the angiographic catheter was replaced with a 4 mm tip steerable electrophysiological catheter (Celsius, Biosense Webster, USA), which was introduced into the RA. The catheter was connected to the electrophysiological system Elcart (Electropulse, Tomsk, Russia). Electrical high-frequency 30 Hz (1 ms, 15 mA output) stimulation inside the RA was performed from at least 20 points (10 points per side). Stimulation trains were of 20 s length. Before, during, and after RA stimulation BP tracings were registered and stored.

After electrical stimulation, the catheter was exchanged with the 4 or 5 mm Vessix balloon ablation catheter, depending on the angiographic artery diameter. The balloon catheter was introduced over the PT2 guidewire 0.014in × 185 cm (Boston Scientific, USA). A solution of isosorbide dinitrate 0.1% (Isoket, EVER Pharma, Germany) was injected into the RA at a dose of 50 μg. Balloon inflation was performed with diluted contrast media at 1-2 atm pressure until complete RA occlusion, as confirmed by contrast injection into the Preface sheath.

In the RDN group, ablation was performed bilaterally in all available RA branches and segments. Each RF application was 30 s in duration, temperature 65-68°C, and automatically adjusted power 0.5-1 Watt. After RDN, electrical stimulation of RAs was repeated according to the method described above.

In the SHAM group, the procedure was performed using the same protocol, including angiography, RA stimulation, nitrate injection, and the number and duration of balloon inflations. However, no RF energy was delivered.

In both groups, selective RA angiography was performed at the end of the procedure in order to visualize potential changes of arterial lumen; all alterations were recorded (Figure 1).

2.2. Hemodynamic Measures. The baseline hemodynamic parameters were considered after the placement of all vascular sheaths and just before RA cannulation, and initially stable hemodynamic was noted in all animals. A Swan Ganz catheter, 6 F (B. Braun, Germany), was inserted into the distal part of the pulmonary artery (PA) through the right jugular vein under fluoroscopic control, and the pulmonary artery wedge pressure (PWP) was measured. Pressures in the PA,

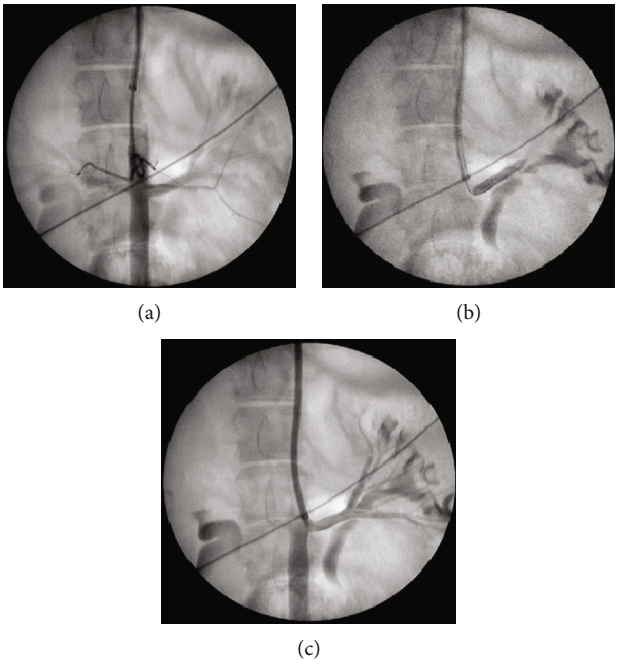

Figure 1: Ablation of the left RA: pig no. 3. (a) RA angiography using a pigtail catheter. (b) Inflation of a RF balloon with complete obstruction of the left main RA. (c) Repeat angiography of the RA after ablation. A slight RA lumen narrowing can be seen. RA: renal artery; RF: radiofrequency.

RV, and right atrium were measured. Arterial blood samples were taken from the abdominal aorta; venous blood samples were taken from the PA for evaluation of SatO2. Blood tests were carried out using the i-STAT portable analyzer (Abbott Laboratories, USA). Cardiac output (CO) was calculated using the Fick equation. Pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR) were calculated with an established formula. Following renal artery denervation in the RDN group and balloon inflations in the SHAM group, repeated measurements were performed after a 15-minute interval.

2.3. Autopsy Study. At the end of the experiment, the animals were euthanized by intravenous injection of a potassium chloride solution (OZON, Russian Federation) at a dose of 800 mg. After the onset of biological death, the kidneys and abdominal aorta with the RA were excised and fixed in a solution of 10% buffered formalin as a single unit for further macroscopic and histological examinations. Immunohistochemical methods were applied to the RA specimens in both animal groups: in the RDN group, immunolabeling was performed on the specimens containing ablation sites, and in the control group on the random specimens. Immunolabeling was performed with antibodies to tyrosine hydroxylase (TH; antigen of adrenergic receptors of the sympathetic nervous system; Abcam, UK). Morphometric analysis was carried out using the image analyzer Leica Application Suite V 4.5.0 and Leica Scope (Germany). TH expression was scored as follows: 1 point—weak expression, 2—moderate expression, 3—mild expression, and 4—extensive expression.

2.4. Statistical Analysis. Continuous variables were presented as mean ± SD and median with interquartile ranges (IQR), where appropriate; categorical variables were presented as percentages. Group comparisons were performed using the Mann–Whitney U test. Comparisons within the groups were performed using Wilcoxon's test for dependent samples. Correlations were analyzed with Pearson's test. Graphical representations were made using box and whisker plots showing a mean, mean ± standard error, and mean ± 1.96 ∗ SE. A two-sided $P < 0.05$ was considered statistically significant. The analysis was performed using the Statistica 12.0 (StatSoft Inc., Tulsa, Oklahoma, USA).

3. Results

The mean weight of the animals was slightly higher in the RDN group than in the controls (31.8 ± 2.8 vs. 34.8 ± 0.6 kg , correspondingly; $P = 0.07$). The total number of RF ablation points in the RDN group was 124 (20.3 ± 2.9 per animal); the range of ablation temperature was 66.7-68.3°C. Angiographic characteristics of RA and the number of RF ablation points in each artery are presented in Table 1.

3.1. Hemodynamic Parameters before and after Renal Denervation. Hemodynamic data obtained from one animal in the RDN group was withdrawn from the analysis, since massive left PA embolism with hemodynamic instability was diagnosed during repeat catheterization.

Therefore, hemodynamic data analysis was performed on 12 animals, 6 in either group. Changes in hemodynamic parameters in the RDN and SHAM groups are presented in Table 2.

When hemodynamic parameters were compared between the groups after the procedures (RDN or sham, according to allocation), there were significant differences

Table 1: Angiographic characteristics of renal arteries and number of RF ablation points in each animal.

Animal #	Group	Main RA diameter (mm)	RA branch diameter (mm)	Number of ablation points
1	RDN	4.1	2.9	22
2	RDN	3.7	2.8	23
3	SHAM	4.0	2.9	—
4	RDN	3.3	2.3	16
5	SHAM	3.7	2.6	—
6	RDN	3.6	3.3	22
7	RDN	3.9	2.8	22
8	SHAM	3.9	2.7	—
9	RDN	4.9	3.8	23
10	SHAM	3.6	2.4	—
11	SHAM	4.2	2.8	—
12	RDN	4.2	2.5	18
13	SHAM	3.9	2.8	—
	Total	3.9 ± 0.4	2.8 ± 0.4	20.3 ± 2.9

in the following parameters: systolic blood pressure (sBP), mean arterial pressure (MAP), and systolic right ventricle (sRV) pressure (Table 2).

Additionally, in the RDN group, when hemodynamic parameters were compared before and after ablation, a statistically significant drop in diastolic pulmonary pressure (dPAP) was identified (13.0 ± 4.4 vs. 10.0 ± 3.0 mmHg; $P = 0.04$) (Table 2). Five out of six pigs in the RDN group showed a significant decrease in MAP. When these five animals were analyzed separately, statistically significant changes were revealed after RDN in the following parameters: a decrease in the mean sBP, when compared with the baseline values (98.8 ± 17.8 vs. 90.2 ± 12.6 mmHg, $P = 0.04$), and a decrease in MAP (74.2 ± 14.2 vs. 65.2 ± 10.6 mmHg, $P = 0.04$) and in mean PVR (291.0 ± 77.4 vs. 228.5 ± 63.8 dyn $*$ sec $*$ cm^{-5}, $P = 0.03$) (see Figure 2). The sham procedure did not result in any hemodynamic change.

The total average volume of blood loss did not differ between both groups and ranged from 30 to 40 ml.

3.2. Electrical Stimulation of the Renal Arteries. There was no detectable influence of RA stimulation on BP or heart rate (HR) during stimulation and within 5 minutes after stimulation. The mean sBP before and immediately after electrical stimulation was 104.0 ± 14.2 mmHg vs. 103.7 ± 12.6 mmHg and diastolic BP (dBP) 67.0 ± 6.4 mmHg vs. 67.3 ± 7.2 mmHg ($P > 0.05$). The mean HR was 107.7 ± 10.5 bpm and 108.3 ± 10.3 bpm, respectively, $P > 0.05$. No BP reaction to RA stimulation was noted after RDN.

3.3. Angiographic Assessment of the Renal Arteries after Denervation. Local narrowing of the RA lumen was detected in 3 out of 7 pigs after RDN, and the narrowing was partly released after additional selective nitrate injection. According to their transient appearance and pharmacological response, these changes fulfilled the criteria of artery spasm. In the SHAM group, after balloon inflation, local artery changes were not detected. In total, angiographically detected RA lumen changes were detected in 23% of cases and were all attributed to radiofrequency ablation.

3.4. Autopsy Study. Gross anatomical evaluation of the RA showed a greater number of lesions in the RDN group compared to the SHAM group. In total, in the RDN group, twenty-three artery intimal dissections were found (3.3 ± 1.4 per animal; 0.5 ± 0.6 per artery: in trunk 0.4 ± 0.6 and in branches 0.6 ± 0.6, $P > 0.05$). Thin thrombotic masses attached to the RA wall were identified on 9 sections (1.28 ± 1.38 per animal). One case of hemorrhage in the kidney parenchyma and one parietal hematoma of the RA were identified. There was one case of total thrombosis of the left main PA.

Following RDN, in two of three cases with suspected artery spasm, dissections of the RAs were found on histological preparations at the anticipated sites of artery lumen narrowing.

There were lesions of the RA detected in 6 SHAM group animals: the mean number of artery wall lesions was lower than in the RDN group: 5 dissections (0.83 ± 0.75 per animal; $P < 0.05$) and 3 blood clots (0.5 ± 0.84 per animal; $P < 0.05$).

A positive correlation was found between the number of RF ablation points and the number of dissections ($R = 0.84$; $P < 0.05$), as well as between the number of RF ablation points and the number of blood clots ($R = 0.88$; $P < 0.05$).

The shape of artery dissections was different between groups: pinpoint-like dissections in the SHAM group and larger dissections in the RDN group, with a length up to 5 mm. In the RDN group, blood clots were found in the area of the distal branches of the RA, which completely occluded the vessel lumen in one case. An example of macroscopically visible dissection and blood clotting after RDN is presented in Figure 3; a RA wall dissection detected under microscopy is shown in Figure 4.

The expression of TH was determined in both groups in all evaluated nerve fibers, in 100% of cells. The level of TH expression ranged from 3 to 4 points, and there was no difference between the groups.

4. Discussion

The main finding of our study is that we have identified the potential impact of extended RDN on pulmonary hemodynamics, the effect beyond systemic blood pressure reduction. In animals with a significant BP lowering after RDN, a statistically significant decrease in PVR, but not SVR, was found.

The other interesting finding is a high number of both, RF-induced and cannulation-related RA wall damage, detected on autopsy study. The majority of these lesions are not usually seen on angiography. Moreover, angiographically detected local artery narrowing following radiofrequency application can be a sign of RA dissection. The reversibility of artery narrowing after nitrate injection does not rule out the presence of microdissection.

Table 2: Hemodynamic changes in the RDN and SHAM groups.

	RDN group ($N = 6$)		SHAM group ($N = 6$)		P, between groups, when parameters were analyzed after procedures	A subgroup of RDN animals with MAP drop: delta in parameters after ablation, median [IQR], $N = 5$	P, five RDN cases with MAP drop, comparison of parameters before and after ablation
	Before RDN, mean ± SD	After RDN, mean ± SD	Before sham, mean ± SD	After sham, mean ± SD			
HR (min^{-1})	116.7 ± 15.1	118.2 ± 21.8	95.8 ± 11.7	102.2 ± 19.1	0.24	3 [-2; 12]	0.34
sBP (mmHg)	97 ± 16.5	90.8 ± 11.4	88.3 ± 7.5	93.2 ± 8	0.03	-6 [-14; -6]	0.04
dBP (mmHg)	60.3 ± 11.6	56 ± 8.2	54.5 ± 6.4	60.2 ± 6	0.05	-7 [-9; -4]	0.14
MAP (mmHg)	72.7 ± 13.2	66 ± 9.6	65.7 ± 6.4	71.2 ± 6.6	0.04	-7 [-10; -6]	0.04
sPAP (mmHg)	19.5 ± 4.3	18.3 ± 5.2	15.7 ± 4	15 ± 3.4	0.24	-1 [-1; 0]	0.27
dPAP (mmHg)	13 ± 4.4	10 ± 3	11.8 ± 3.8	10.7 ± 2.4	0.82	-2 [-5; -1]	0.06
mPAP (mmHg)	15.1 ± 4.1	13.3 ± 2.9	13 ± 3.9	12.2 ± 2.9	0.48	-1 [-4; 0]	0.11
sRV (mmHg)	18.5 ± 6.6	19.3 ± 5.2	13.8 ± 4.3	13.3 ± 3.1	0.04	-1 [-3; 3]	0.89
dRV (mmHg)	5 ± 2.6	4.5 ± 2.6	6.5 ± 3.3	6 ± 1.3	0.48	0 [-1; 0]	0.18
mRV (mmHg)	9.3 ± 2.8	9.3 ± 2.2	8.8 ± 3.7	8.2 ± 1.7	0.31	-1 [-1; -1]	0.22
PWP (mmHg)	4.7 ± 1.8	4 ± 1.1	5 ± 2.4	4.7 ± 1.9	0.39	-1 [-2; 0]	0.47
RAP (mmHg)	3.8 ± 2.7	2 ± 1.7	4.4 ± 2.4	3.2 ± 1.6	0.24	-3 [-3; -2]	0.07
SVR ($dyn * sec * cm^{-5}$)	1747.7 ± 726.1	1544.9 ± 725.8	1113.4 ± 520.3	1193.1 ± 589.7	0.24	-252.9 [-591.7; 96.0]	0.22
PVR ($dyn * sec * cm^{-5}$)	261.9 ± 99.3†	215.1 ± 65.9	136.9 ± 58.5†	133.7 ± 86.3	0.06	-88.0 [-92.4; -36.5]	0.03
CO (l/min)	3.6 ± 1.5	3.7 ± 1.2	5 ± 1.8	5.4 ± 2.3	0.24	0.2 [-0.3; 0.5]	0.68

HR: heart rate; sBP: systolic blood pressure; dBP: diastolic blood pressure; MAP: mean arterial pressure; sPAP: systolic pulmonary artery pressure; dPAP: diastolic pulmonary artery pressure; mPAP: medium pulmonary artery pressure; sRV: systolic right ventricle pressure; dRV: diastolic right ventricle pressure; mRV: medium right ventricle pressure; PWP: pulmonary wedge pressure; RAP: right atrial pressure; SVR: systemic vascular resistance; PVR: pulmonary vascular resistance; CO: cardiac output. $^{\dagger}P = 0.03$ in baseline parameters between the groups.

4.1. Acute Blood Pressure Dynamics after Denervation. RDN is used as a method for the management of resistant systemic hypertension. The long-term clinical effects of RDN on BP have been shown in earlier and recent studies, and the major effects of RDN have been detected after several weeks following the procedure [3, 5, 11]. The acute impact of RDN on BP has been described in a number of clinical and experimental studies and is mainly explained by the change in sympathetic nervous tone after RA nerve ablation [12–14].

We suggest that when the procedure is being performed under general anesthesia the acute effects might be different from those obtained when it is conducted under light sedation. In the clinical settings, during RF energy delivery, many patients describe severe lumbar pain. It is believed that the development of pain is associated with the heating of vascular adventitia [15]. To reduce the pain in clinical practice, different approaches are used to anesthetize patients, for example, administering opioids at least 2 minutes before RF exposure and conducting combined anesthesia [16]. General anesthesia in experimental studies allows standardizing the conditions and possible hemodynamic changes after the intervention.

In our study, all procedures were performed under the same conditions, namely, all animals were of about the same age and similar morphometric indicators, and general anesthesia with intubation was performed. The difference between groups was the only RF application.

We have found a significant decrease in BP in only five out of six animals, which might be explained by the nonfully reproducible extent of catheter-based sympathetic denervation, which depends on the individual nerve distribution and artery anatomy.

There was a difference in the level of CO between the RDN and SHAM groups. This fact can be explained by a difference in the mean animals' weight in two groups.

4.2. Pulmonary Vascular Resistance Decrease after Denervation. The acute effect of RDN on PVR has been identified in 5 out of 6 pigs and in none of the animals from the SHAM group.

Our findings regarding the impact of RDN on pulmonary vasculature are in line with a previous report demonstrating the effects of denervation on pulmonary vascular and RV wall remodeling in chronic experiments with induced PAH [7]. In the latter study, the authors identified that PAP and

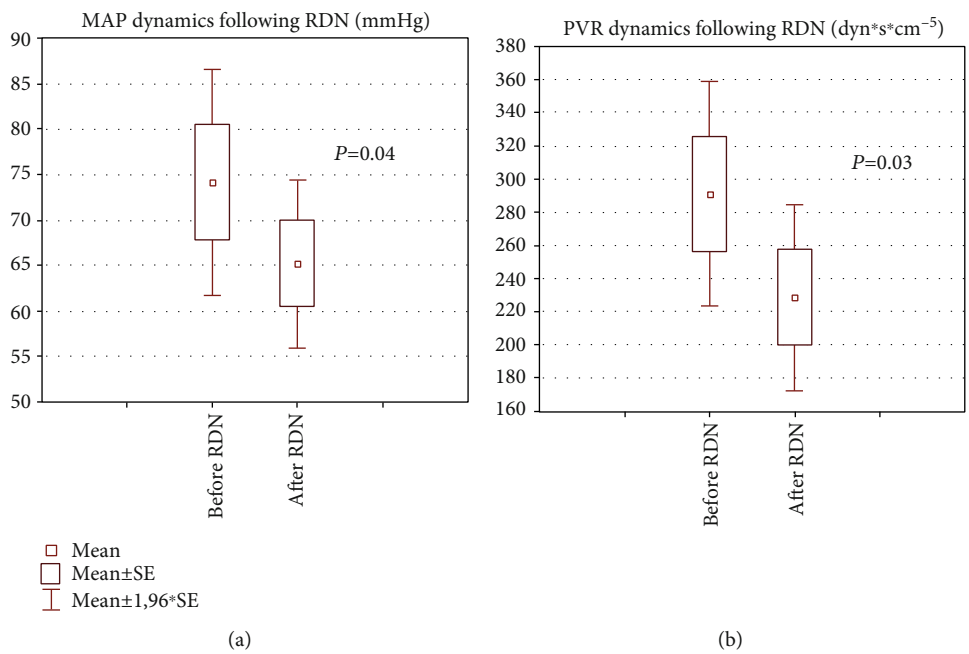

Figure 2: Hemodynamic parameters before and after RDN in five animals with a decrease in MAP values. (a) Mean arterial pressure before and after ablation. (b) PVR before and after ablation. RDN: renal artery denervation; PVR: pulmonary vascular resistance.

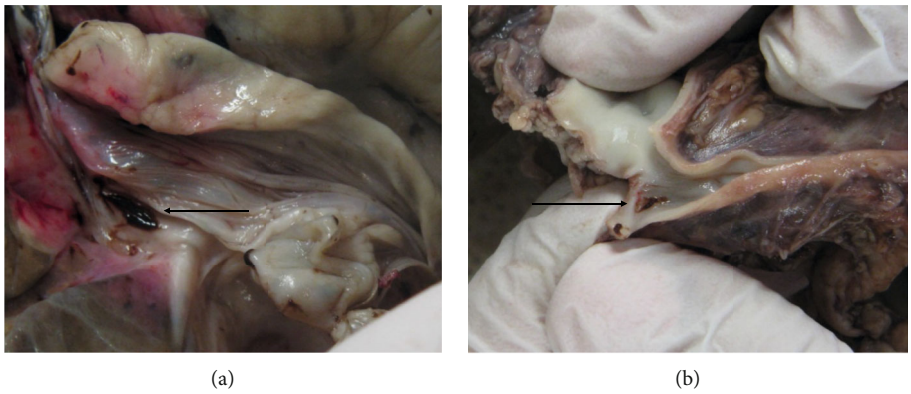

Figure 3: Pig #4. RA gross anatomical evaluation after RDN. (a) RA thrombosis. (b) RA dissection. RA: renal artery; RDN: renal artery denervation.

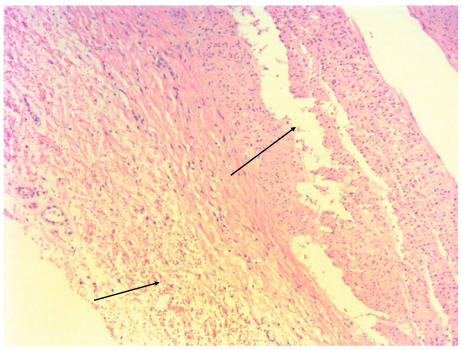

Figure 4: Pig #4. The arrows indicate renal artery wall dissection and hemorrhagic impregnation after RF ablation. Hematoxylin-eosin, 100x.

the RV pressures with induced PAH were lower in animals with RDN.

4.3. Renal Artery Stimulation. Recently, RA electrical stimulation has been tested as an approach to BP elevation and in defining an endpoint of RDFтвN procedures [9, 10, 17]. Indeed, detecting sites within the RA that correspond to the most extensive innervation is desirable. Theoretically, electrical stimulation at those sites might elicit a sympathetic response and subsequent BP elevation. On the other hand, effective ablation of the site would have resulted in the non-reproducibility of the elicited reactions. We cannot exclude the difference in the stimulation protocols between our study and previous studies. However, a very similar stimulation approach protocol was affective in provoking autonomic reactions when used in other large vessels [18]. We suggest that pain perception during RA stimulation might be

responsible for some BP elevation. In our study, the procedure was conducted under deep sedation and analgesia, precluding pain feeling. According to our findings, RA high-frequency stimulation does not elicit BP rise before and after RDN.

The absence of pain feeling under general anesthesia alleviates the possible bias of pain-associated BP elevation and effects of ablation-related pain on the measured parameters. On the other hand, acute BP and pulmonary hemodynamic reactions following extended RDN under deep anesthesia may reflect the real impact of the procedure on hemodynamics.

4.4. Autopsy Data. Damage to the vascular wall and/or renal parenchyma was detected in 12 (92%) animals. Although artery wall dissection was found in both groups of experimental animals, RDN was associated with more dissections, than in the SHAM group.

Previous studies compared the safety of single-electrode and multielectrode RDN systems [19]. The authors have shown that damage to both the walls of the RA and renal nerves was more prominent in the group where a multielectrode RDN system was used. However, none of the two systems led to the complete destruction of the renal nerves. We suggest that remarkable damage to the RA in our study can be associated with the use of the balloon ablation system developed for application in humans. Therefore, we cannot exclude the overstretching of the RA, which, in combination with a RF application, predispose to damage.

We have found no difference in the expression of TH between the animal groups. This finding is in line with a previous report showing that no significant TH expression decrease can be found shortly after RDN, and this might be explained by a delayed axonal degeneration in the necrotic nerves [20]. In the latter study, the authors stated that the level of TH expression cannot reflect the effectiveness of RDN in the acute phase.

4.5. Study Limitations. We evaluated the acute cardiovascular effects of extended RDN and did not intend to assess long-term effects. The remote effects should be addressed in a chronic experimental study.

Another limitation is the limited sample size. However, the study was exploratory and showed the effects of RDN on PVR in the majority of experimental animals. Randomized study design with a SHAM group and the conduction of the procedure under standardized conditions make the conclusions more solid.

The experiments were conducted on normotensive animals without systemic or pulmonary hypertension modeling. Different extent of effects might be expected in animals with induced hypertension or PAH.

5. Conclusions

In normotensive swine, extensive RDN leads to a rapid and significant decrease in BP and PVR in the majority of cases. At the same time, no significant dynamics in SVR can be detected. Extended RDN is frequently associated with artery wall dissection and thrombus formation, which seem underdiagnosed by angiography. The results of our experimental study provide a rationale for further investigation of extended RDN effects on pulmonary circulation in chronic PAH models.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Combined Aerobic and Resistance Exercises Evokes Longer Reductions on Ambulatory Blood Pressure in Resistant Hypertension: A Randomized Crossover Trial

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Aim. The present study compared the acute effects of aerobic (AER), resistance (RES), and combined (COM) exercises on blood pressure (BP) levels in people with resistant hypertension (RH) and nonresistant hypertension (NON-RH). *Methods*. Twenty patients (10 RH and 10 NON-RH) were recruited and randomly performed three exercise sessions and a control session. Ambulatory BP was monitored over 24 hours after each experimental session. *Results*. Significant reductions on ambulatory BP were found in people with RH after AER, RES, and COM sessions. Notably, ambulatory BP was reduced during awake-time and night-time periods after COM. On the other hand, the effects of AER were more prominent during awake periods, while RES caused greater reductions during the night-time period. In NON-RH, only RES acutely reduced systolic BP, while diastolic BP was reduced after all exercise sessions. However, the longest postexercise ambulatory hypotension was observed after AER (~11 h) in comparison to RES (~8 h) and COM (~4 h) exercises. *Conclusion*. Findings of the present study indicate that AER, RES, and COM exercises elicit systolic and diastolic postexercise ambulatory hypotension in RH patients. Notably, longer hypotension periods were observed after COM exercise. In addition, NON-RH and RH people showed different changes on BP after exercise sessions, suggesting that postexercise hypotension is influenced by the pathophysiological bases of hypertension.

1. Introduction

Hypertension refers to a highly prevalent multifactorial condition characterized by chronic elevations in blood pressure (BP) that is strongly associated with negative health-related outcomes [1, 2]. When hypertension occurs in the absence of other diseases (e.g., obesity) and without apparent cause, it is clinically denominated as primary hypertension (NON-RH) [2]. In this case, lifestyle changes and pharmacological therapy are commonly effective to blood pressure control [2, 3].

However, approximately 20% of the patients clinically diagnosed with NON-RH may present an inability to achieve BP levels lower than proposed cut-offs, regardless of the optimal dose of 3 or more antihypertensive drugs, including 1 diuretic, a condition denominated as resistant hypertension

(RH) [4–6]. In the recent years, an increasing attention to RH has been paid by health professionals, given that these patients are at higher risk of cardiovascular events and death in comparison to people with NON-RH [4–6].

Hence, experts in the field [7] have suggested that complementary therapies may be important supporting actors in the management of RH patients, although no specific guidelines have been proposed. Physical exercise is a well-established strategy to control BP in NON-RH patients [8–15] and recognized as part of the hypertension therapy according to different medical associations [16, 17]. Indeed, findings from randomized clinical trials reported reduced BP levels in middle-aged and older adults after different exercise training protocols [8–15].

Notably, the beneficial effects of physical exercise are not restricted to its chronic practice since reduced BP levels may be observed after an acute session of exercise, a phenomenon denominated postexercise hypotension (PEH) [10, 13, 18]. PEH is found after aerobic (AER) and resistance (RES) exercises in NON-RH and normotensive people [19–22]. Furthermore, PEH may predict the success of exercise protocols [21, 22] and likely contribute to low cardiovascular risk during the performance of activities of daily living [23, 24].

The effects of physical exercise in RH are still poorly explored. A previous seminal study found postexercise ambulatory hypotension after AER exercise in patients with RH [25]. However, the effects of other regimes of exercise, such as RES, still seem to be elucidated. In addition, although no further cardiovascular benefits were observed in normotensive and hypertensive people after exercise sessions that combined (COM) AER plus RES exercises [26–28], this kind of exercise is recommended by experts in the field for people who aim to improve cardiorespiratory, musculoskeletal, and neuromotor fitness [29] and for hypertensive patients who intend to reach optimum blood pressure values [30].

Based on these premises, the present study investigated the acute effects of AER, RES, and COM on 24-hour ambulatory BP monitoring (ABPM) in people with RH and NON-RH. In addition, postexercise ABPM were compared between RH and NON-RH. Our hypothesis is that AER, RES, and COM might cause different patterns of PEH in RH and NON-RH.

2. Methods

2.1. Sample and Recruitment. This was a randomized controlled crossover trial that investigated the acute effects of AER, RES, and COM exercises on 24-hour ABPM in people with RH and NON-RH. Concealed randomized allocation into one of four experimental sessions was performed by an independent researcher using a simple computer-generated list of random numbers and an allocation ratio of 1 : 1 : 1 : 1. All researchers, including evaluators, exercise supervisors, and those responsible for statistical analysis, knew where participants were allocated. Participants were also aware of exercise session but were blind to study hypothesis.

Recruitment was carried out through the Outpatient Resistant Hypertension Clinic of University of Campinas (Campinas, SP, Brazil). Twenty patients agreed to participate in the study protocol: 10 subjects with stage 2 hypertension (NON-RH) and 10 subjects clinically diagnosed with RH. RH was defined as an uncontrolled BP despite the use of ≥3 antihypertensive medications at optimal doses, including a diuretic if possible, or patients with controlled BP using ≥4 antihypertensive medications [4–6]. The diagnosis of RH was assessed following a 6-month protocol for screening of secondary causes of hypertension (primary hyperaldosteronism, renal artery stenosis, pheochromocytoma, and obstructive sleep apnea) and pseudo-RH (counting pills and ABPM). The subjects carrying one or both conditions were properly excluded from the study. Patients who showed significant changes on electrocardiogram trace under resting or physical stress test; who dropped out from the investigation; who presented changes on antihypertensive medication in the past 6 months prior to inclusion in the study; who had cardiac or cerebrovascular diseases, heart failure, or renal dysfunction; who are practicing regular physical exercise over the 6 months preceding the beginning of the study; who are using hormonal replacement therapy; and who are smokers were excluded. We included male and female aged 40 to 80 years old able to practice physical exercises.

Sample size was estimated using G∗Power version 3.1.9.2. on the basis of the magnitude of the mean differences in SBP levels [25] among the three sessions in two repeated measures. Considering an ES set at 0.45 [25], a power of 80%, and a level of significance set at 5%, the sample size was estimated to be 10 participants per group.

This study was approved by the Research Ethics Committee of the Faculty of Medical Sciences, University of Campinas (Campinas, Brazil) (Protocol 1638486; registered at ClinicalTrials.gov under ID number NCT02987452), and all patients that met the eligibility criteria gave their informed written consent before participation. The investigation was performed according to the Helsinki Declaration of 1975 (as revised in 1983).

2.2. Procedures. Experiments were performed in a quiet air-conditioned room (22-24°C) always in the mornings (07:00-12:00 am) in the Laboratory of Cardiovascular Pharmacology of the University of Campinas. Experiments were separated into two distinct phases. In the first phase, participants completed a familiarization period to familiarize them with the proper technique of the physical exercises utilized in the present study. Afterwards, the optimal exercise load to AER, RES, and COM was determined. The familiarization period took place in 4-6 alternate days. In the second phase, participants were requested to come five times to the laboratory after a 12 h overnight fast, including water, energetic beverages, and alcohol consumption, and without performing intense physical activity for 24 h.

In the first visit, a Bioimpedance Analyzer 450 (Biodynamics Corporation, Seattle, USA) was used for anthropometric measurements [31–33]. Bioimpedance assessed body mass index, fat-free mass, fat mass, basal metabolic rate, and total body water content. In the following visits, participants performed an acute session of exercise (i.e., AER, RES, or COM) or control (CONT) according to prior randomization at least 1 h after a standardized light breakfast (i.e., 40 g chocolate mini-cookie (Bauducco, São Paulo, Brazil; 132 kcal,

18 g of carbohydrate, and 2.1 g of protein; 5.7 g of fat), 200 mL chocolate box milk (Toddynho, PepsiCo, São Paulo, Brazil; 167 kcal, 27 g of carbohydrate, and 3.7 g of protein; 5.1 g of fat), and 144 g brown crackers pack (Club Social Nabisco, São Paulo, Brazil; 110 kcal, 16 g of carbohydrate, and 1.9 g of protein; 4.4 g of fat)). Approximately one hour after the end of the exercise session, participants were lying comfortably in the supine position, instrumented to ABPM, and were discharged.

2.3. Primary Outcome

2.3.1. Ambulatory Blood Pressure Monitoring. ABPM was recorded for a 24-hour period using the Spacelabs equipment 90217 (Spacelabs Inc., Redmond, WA, USA). Awake-time was considered the interval between the first and tenth hours after the experimental sessions, while night-time referred to the period between the eleventh and eighteenth hours after the experimental sessions. Participants were instructed to maintain and record normal daily activities in a personal diary.

2.3.2. Exercise Session Protocols. Exercise protocols were based on American College of Sports and Medicine (ACSM) guidelines [15, 29]. AER, RES, and COM exercises were used in the present study. Exercise protocols were equalized according to the total session time.

A minimum interval of 96 hours was required between exercise sessions. AER exercise was performed in a treadmill for 45 minutes at 50-60% of maximal heart rate (HRmax) obtained from the ergometric stress test. HR was monitored continuously across the exercise session using a cardiac monitor (Polar RS800 CX, Polar Electro Oy, Kempele, Finland). RES exercise consisted of 6 exercises with 4 sets of 12 submaximal repetitions performed at moderate intensity (3-5 on the adapted Borg scale) [34] (i.e., 1st chair squat, 2nd vertical bench press, 3rd seated knee raise, 4th seated row, 5th dorsiflexion and plantar flexion, and 6th shoulder abduction). A 1-minute interval was adopted between sets and exercises. All exercises were performed in the total range of motion and muscle contractions—concentric and eccentric—and were performed at moderate velocity (2 sec for each). Participants were instructed to avoid the Valsalva maneuver during the entire muscle contraction. COM exercise consisted of a session of AER exercise performed at 50-60% HRmax for 25 minutes plus a session of RES based on 6 exercises with 2 sets of 12 submaximal repetitions at moderate intensity according to the modified Borg scale [34]. An experienced exercise physiologist supervised all exercise sessions.

The optimal loads for exercise sessions were determined the familiarization period. RES was acquired using the rating of perceived exertion (RPE) method [35] based on the resistance of the elastic bands proposed by Uchida et al. [36]. A maximal exercise stress test on a treadmill using an individualized incremental protocol was used to determine the intensity of AER exercise. Before exercise testing, participants remained seated for 20 min. A resting electrocardiogram was performed, and BP, HR, and lactate levels were assessed. Afterwards, the incremental test using an electronic treadmill (Life Fitness®, model 9700HR®, Fort Mill, Tennessee, USA) was initiated, according to a modified Bruce protocol, which included six stages with 3 min each, characterized by increasing speed (2.7-6.8 km/h) and grade (0-16%). The HRmax were considered the highest HR recorded at the exhaustion moment. Electrocardiograph patterns were registered and accompanied by a cardiologist throughout the whole test.

2.3.3. Control (CONT) Session. CONT session involved the continuous monitoring of blood pressure to over 60 minutes. This evaluation was considered the baseline values for all comparisons. Afterwards, the ABPM was removed, and the participants remained seated, but not exercising, in the machines for another 60 minutes.

2.4. Statistical Analysis. Normality of data was tested using the Shapiro-Wilk test. Baseline comparisons among groups were performed using unpaired Student's *t*-test. A two-way ANOVA followed by a Bonferroni post hoc test was performed to identify differences among the different times of evaluations in the experimental sessions. The area under the curve (AUC) was calculated. Peaks less than 10.0% of the distance from minimum to maximum Y were ignored. ANOVA followed by a Bonferroni post hoc test was performed to identify differences among experimental sessions. Categorical variables were presented in frequencies and/or percentages and compared by chi-squared test. All statistics analyses were performed using the GraphPad Prism 6.0 (GraphPad Prism Inc., 2000). All statistical methods are two-tailed, P values were calculated, and statistical significance was set at ≤ 0.05.

3. Results

Participant recruitment and experimental sessions were conducted from January 2017 to December 2017. No exclusions or dropouts occurred after randomization, and no patients reported changes in antihypertensive medication during the follow-up examination. Participants completed all experimental sessions.

Characteristics of study participants are shown in Table 1. No differences in clinical characteristics were observed among the groups. Higher glucose levels were observed in NON-RH, while people with RH had higher HDL-c levels. As expected, all patients with RH were under diuretic treatment. However, diuretic was only taken by 5 participants in the NON-RH group and it was lower in RH ($P = 0.03$). No other differences were found between the groups.

3.1. Effects of an Acute Session of Exercise on 24-Hour ABPM of RH Patients. Figure 1 shows 24-hour ABPM in RH patients. There were no significant within- and between-group differences in systolic (Figure 1(a)) and diastolic (Figure 1(b)) ABPM at baseline and after experimental sessions. Systolic BP was significantly reduced in all exercise groups when compared to baseline. AER reduced systolic BP from the 2nd to 7th ($\Delta = -17.6$ mmHg), 12th to 13th ($\Delta = -15.4$ mmHg), and 15th to 16th ($\Delta = -18.0$ mmHg) hours after exercise. A shorter PEH period was observed after RES, given that significant

Table 1: General characteristics of resistant hypertensive (RH) subjects and non-resistant hypertensive (NON-RH) subjects according to clinical and biochemical data and antihypertensive (anti-HT) drugs used by the subgroups.

	RH ($n = 10$)	NON-RH ($n = 10$)	P value
Clinical data			
Age (years)	60 ± 9	54 ± 13	0.66
Female gender, n (%)	6 (60)	5 (50)	1
Diabetes mellitus, n (%)	10 (100)	5 (50)	0.09
BMI (kg/m^2)	31 ± 5	32 ± 7	0.18
Fat-free mass (kg)	54 (43-71)	61 (47-82)	0.40
Fat mass (kg)	25 ± 10	26 ± 14	0.32
Total body water (L)	75 ± 2	75 ± 3	0.17
Basal metabolic rate (cal/day)	1765 ± 482	1996 ± 540	0.39
Biomarkers			
HbA1C (%)	7 ± 2	6 ± 0.7	0.13
Glucose (mg/mL)	97 (89-139)	98 (94-134)*	0.07
Creatinine (mg/mL)	0.8 (0.1-1.1)	0.8 (0.7-0.9)	0.81
Aldosterone (pg/mL)	100 ± 141	132 ± 95	0.64
Creat clear (mL/min/1.73m^2)	83 ± 66	89 ± 65	0.86
Cholesterol (mg/mL)	188 ± 48	175 ± 40	0.55
HDL-c (mg/mL)	44 ± 9	38 ± 7*	0.07
LDL-c (mg/mL)	109 ± 35	106 ± 46	0.88
Triglycerides (mg/mL)	135 (90-214)	143 (105-205)	0.97
Anti-HT drugs			
Number of classes	4 ± 1	2 ± 1	0.13
Diuretics, n (%)	10 (100)	5 (50)*	0.03
Spironolactone, n (%)	2 (20)	2 (20)	1
Beta-blockers, n (%)	8 (80)	6 (60)	0.63
ACEIs and ARBs, n (%)	5 (50)	7 (70)	0.65
CCBs, n (%)	8 (80)	3 (30)	0.07
Others, n (%)	0	0	1

Values are expressed as mean ± standard deviation or median (1st, 3rd quartiles), according to data distribution. RH: resistant hypertensive; NON-RH: non-resistant hypertensive; BMI: body mass index; HbA1C: glycated hemoglobin; Creat clear: creatinine clearance; LDL and HDL: low- and high-density lipoproteins, respectively; anti-HT: antihypertensive drugs; ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; CCBs: calcium channel blockers.

reductions were only found from the 14th to 15th ($\Delta = -19.5$ mmHg) and 17th to 18th ($\Delta = -15.3$ mmHg) hours after exercise. On the other hand, the longest PEH period was observed after COM, so that significant reductions were observed from the 2nd to 6th ($\Delta = -19.5$ mmHg), 13th to 17th ($\Delta = -18.6$ mmHg), and 19th ($\Delta = -14.3$ mmHg) periods. Diastolic BP was also reduced after acute exercise protocols. PEH was observed after AER from the 4th to 6th ($\Delta = -11.6$ mmHg), 11th to 13th ($\Delta = -12.0$ mmHg), and 15th to 17th ($\Delta = -14.1$ mmHg) hours after exercise. RES caused significant PEH from the 14th to 15th ($\Delta = -11.3$ mmHg), 18th ($\Delta = -8.5$ mmHg), and 20th ($\Delta = -3.2$ mmHg) hours after exercise. As observed in systolic BP, COM caused the longest PEH period: from the 3rd to 6th ($\Delta = -11.5$ mmHg) and 10th to 19th ($\Delta = -11.7$ mmHg) hours after exercise. There were no significant differences in systolic and diastolic BPs after CONT.

3.2. Effects of an Acute Session of Exercise on 24-Hour ABPM of NON-RH Patients. Figure 2 shows 24-hour ABPM in NON-RH patients. No significant differences in systolic and diastolic BPs were observed among the groups at baseline or after exercise. AER and COM did not cause significant reductions on systolic BP (Figure 2(a)). On the other hand, RES reduced systolic BP in the 18th moment relative to baseline ($\Delta = -18.0$ mmHg). Diastolic BP (Figure 2(b)) was reduced after the exercise protocols. AER caused significant PEH from the 10th to 20th ($\Delta = -13.3$ mmHg) and 21st to 22nd ($\Delta = -12.9$ mmHg) hours after exercise. A shorter PEH period was observed after RES: from the 12th to 20th ($\Delta = -12.9$ mmHg) periods. COM reduced diastolic BP from the 12th to 16th ($\Delta = -11.8$ mmHg) hours after exercise. There were no significant differences in systolic and diastolic pressures after CONT.

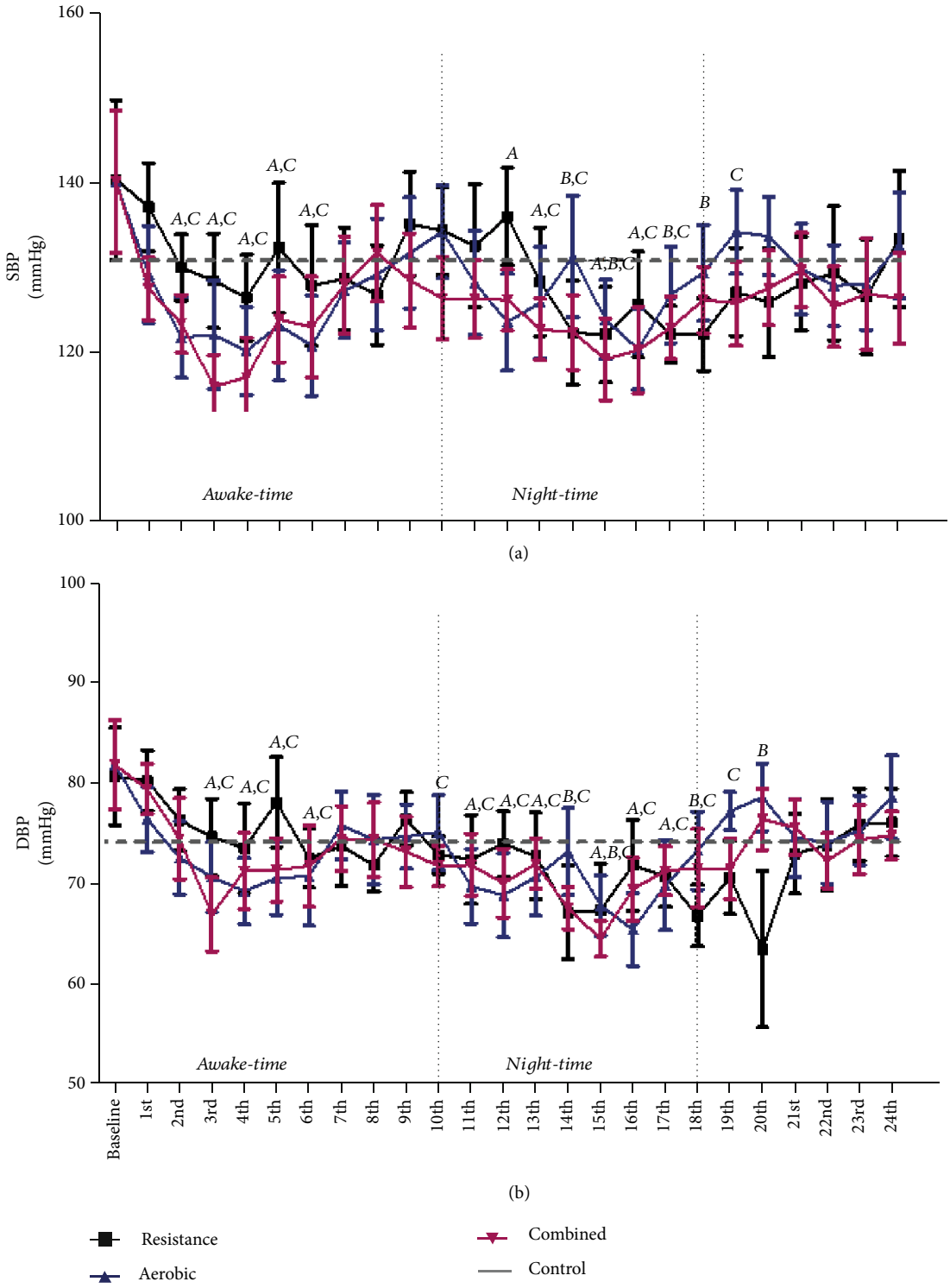

Figure 1: Ambulatory systolic blood pressure (a) and diastolic blood pressure (b) levels after aerobic, resistance, and combined exercises in RH. $^{a}P < 0.05$ aerobic in comparison to baseline values; $^{b}P < 0.05$ resistance in comparison to baseline values; $^{c}P < 0.05$ combined in comparison to baseline values.

3.3. Area under the Curve. Table 2 shows the results of AUC. In RH, SBP had a significantly lower AUC after COM relative to AER and RES in the 24 h period, awake-time, and night-time. RES had a lower AUC of SBP during the night-time period in comparison to AER. The AUC of DBP was lower in COM relative to AER and RES in the 24 h and awake-time periods and lower in RES when compared to AER over 24 hours. On the other hand, lower AUC of DBP was

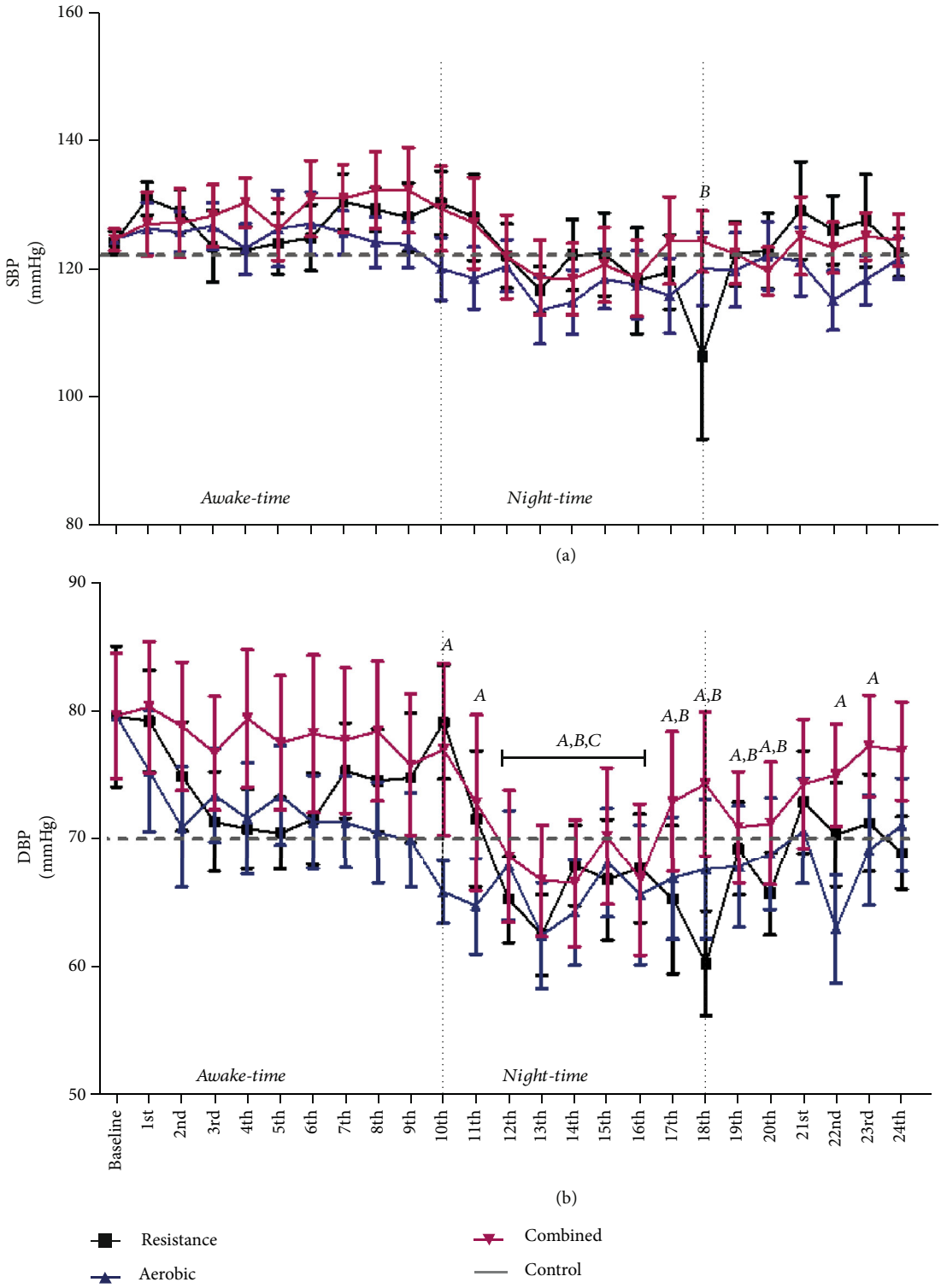

Figure 2: Ambulatory systolic blood pressure (a) and diastolic blood pressure (b) levels after aerobic, resistance, and combined exercises in NON-RH. [a]$P < 0.05$ aerobic in comparison to baseline values; [b]$P < 0.05$ resistance in comparison to baseline values; [c]$P < 0.05$ combined in comparison to baseline values.

observed after AER relative to RES during awake-time. Regarding NON-RH, the AUC of SBP and DBP was higher in COM compared to AER and RES in all periods. In addition, the AUC of SBP in the 24 h and awake-time periods, as well as the AUC of DBP in the awake-time period, was lower in AER relative to RES.

Table 2: Area under the curve of the experimental sessions.

	RES		AER		COM	
	Mean	SD	Mean	SD	Mean	SD
Resistant hypertension						
24 h						
SBP	2618	18.2	2610	15.2	2535ab	15.2
DBP	1049	11.5	1070a	11.7	1052b	9.8
Awake-time						
SBP	1871	18.5	1798	19.4	1778ab	16.3
DBP	787	12.0	771a	13.0	752ab	16.1
Night-time						
SBP	1356	17.2	1361a	18.2	1320ab	19.8
DBP	469	12.9	468	13.2	468	17.7
Nonresistant hypertension						
24 h						
SBP	1796	16.1	1767a	14.1	1823ab	16.5
DBP	1019	12.0	1004	13.3	1081ab	16.3
Awake-time						
SBP	1781	12.0	1741a	12.0	1816ab	15.6
DBP	1045	10.9	1005a	12.1	1090ab	17.1
Night-time						
SBP	954	17.3	947	15.6	976ab	19.8
DBP	365	11.4	373	12.8	397ab	17.7

SBP = systolic blood pressure; DBP = diastolic blood pressure; SD = standard deviation; [a]$P < 0.05$ vs. strength; [b]$P < 0.05$ vs. aerobic.

3.4. Comparisons between RH and NON-RH. There were no significant differences in systolic and diastolic BPs between RH and NON-RH after acute exercise sessions.

3.5. Harms. There were no harms or other unintended effects of the intervention.

4. Discussion

The main findings of the present study indicate that an acute session of AER, RES, and COM exercises significantly reduced ambulatory BP in RH patients. Notably, longer reductions in systolic and diastolic BPs were observed after COM (~12 h) relative to AER (~6 h) and RES (~3 h) exercises. According to AUC analysis, COM reduced SBP in both awake-time and night-time periods in comparison to AER and RES. AUC analysis also indicated that the effects of AER exercise were more predominant in the awake-time period, while lower DBP was observed after RES in the night-time period. People with NON-RH showed different BP responses to exercise sessions. Indeed, systolic BP was only significantly reduced after RES. Diastolic BP was reduced after all exercise sessions, but the longest reductions were observed after AER (~11 h) in comparison to RES (~8 h) and COM (~4 h). AUC indicated that the lower diastolic BP values after AER were mainly observed in the awake-time period. Although different BP responses were observed between RH and NON-RH, no significant differences were observed among groups.

Findings of the present study are partially supported by Santos et al. [25], who reported that an acute session of AER exercise (45 minutes at 50% HRmax) reduced systolic ($\Delta = -4.7$ mmHg) and diastolic ($\Delta = -4.0$ mmHg) BPs in RH patients. Particularly, a greater and longer reduction is observed in the present study relative to Santos et al. [25].

These different results do not seem to occur due to baseline BP levels or designs of AER exercise, given that participants of both studies showed similar baseline ABPM values (~145 mmHg) and performed AER exercise sessions with similar volume and intensity. Hence, a possible explanation for these distinct results may be the amount of exercising muscle mass [37, 38]. In fact, the current AER session was performed in a treadmill, while Santos et al. [25] used a cycle ergometer. Nevertheless, these assumptions are only speculative and should be further investigated in future studies.

This is the first study that investigated the acute effects of different types of exercise on ABPM. Our findings bring new light to the exercise cardiology field by demonstrating that COM exercise elicits longer reductions in systolic and diastolic BPs compared to AER and RES. COM reduced ABPM over 24 hours, including awake-time and night-time periods. On the other hand, the effects of AER exercise occurred predominantly in the awake-time period, while larger and longer blood pressure reductions were observed in the night-time period after RES. Taken as a whole, these findings suggest that COM exercise might provide further benefits relative to AER or RES exercise alone in RH patients.

Earlier studies [26–28] in normotensive people and patients with NON-RH reported different results. Ferrari

et al. [28], for example, found greater PEH in the awake-time after AER exercise when compared to COM exercise. Similarly, NON-RH patients of the present study showed longer PEH after AER in comparison to RES and COM. These findings suggest that different mechanisms are underlying the effects of physical exercise in RH and NON-RH.

A possible explanation for the greater blood pressure reductions observed after AER exercise is based on the fact that this kind of exercise reduces cardiac output (CO) without changing peripheral vascular resistance (PVR) [27, 39, 40]. By contrast, PVR seems to remain elevated after RES and COM exercises, suggesting that RES may reduce the postaerobic exercise hypotension [27, 39, 40].

On the other hand, RES seems to potentiate postaerobic blood pressure reductions in RH. Only one study investigated the possible mechanisms underlying blood pressure changes after exercise in RH, and researchers [25] reported discrete changes in vascular responses after AER exercise. This phenomenon would imply reduced systolic volume (SV) due to a reduced preload and, consequently, decreased CO. In addition, a decreased vascular resistance certainly implies reduced PVR. In this context, it is possible to suggest that RES not necessarily causes additional reductions on CO and PVR but preserves their changes in response to AER for a long period.

Nevertheless, these inferences must be interpreted with caution because they were based on different populations and in mechanisms that were investigated in the first hour after exercise sessions. In addition, CO and PVR have demonstrated an important intersubject variability [40], which indicates that specific studies are necessary to investigate the effects of different regimes of exercise on hemodynamic parameters of RH patients.

The cellular mechanisms underlying blood pressure reduction after exercise sessions were not investigated in the present study. However, many of them may likely have influenced our findings. The role of the activation of H1 and H2 histamine receptors on blood pressure control during [41] and after [42–44] AER exercise has been described in the literature. According to experts in the field, blockade of both histamine H1 and H2 receptors may inhibit post-AER hypotension in normotensive people [42, 43] and contribute to greater diastolic blood pressure values after exercise in black people [44]. This phenomenon seems to occur due to the fact that histamine receptor blockers significantly reduce vascular conductance in response to physical stress [43, 44]. Contrarily, blockade of H1 and H2 receptors seems not to affect blood pressure responses to RES [43].

Acute improvements in cardiac autonomic modulation are another possible mechanism mediating exercise-induced blood pressure reduction, although studies have reported conflicting results. Liu et al. [21] reported that an acute session of AER caused rebalancing of the sympathovagal modulation to the heart in prehypertensive people, while Teixeira et al. [27] found increased sympathovagal balance after AER in normotensive people. On the other hand, no changes on cardiac autonomic modulation were observed by de Brito et al. [45] after AER performed both in the morning and in the evening in prehypertensive men.

On the other hand, studies have reported increased sympathetic activity and sympathovagal balance in the first hour after RES in untrained normotensive [19, 39, 46] and hypertensive [39] people, as well as RES-trained people with hypertension [47, 48]. Although this phenomenon might contribute to increase CO and inhibit blood pressure reduction, studies [19, 39, 46–48] reported significant PEH, which might occur due to a compensatory reflex vasodilation [48].

Only a few studies investigated the effects of COM on autonomic modulation. Teixeira et al. [27] and Saccomani et al. [49] found increased sympathovagal balance after COM in normotensive people. Notably, Teixeira et al. [27] reported that COM caused a greater and longer increase in sympathetic activity and reduction in vagal activity relative to AER and RES. In hypertensive people, COM did not change autonomic modulation [50].

Taken together, this information might suggest that histamine and cardiac autonomic modulation are mediating PEH after COM in RH, while reduction on blood pressure after RES in NON-RH is at least predominantly mediating by a compensatory reflex vasodilation. Nevertheless, generalizations are inappropriate and future studies are needed to confirm our premises.

A question that remains unanswered is why RES and AER exercises reduced BP in different periods of the day in patients with RH. The behavior of BP throughout the day after exercise performance is still under debate. According to Nishiguchi et al. [2], reduced ambulatory BPs after AER are commonly observed during waking periods. In contrast, the effects of RES are heterogeneous [2]. Tibana et al. [51] support the findings of the present study by reporting significant blood pressure reduction during the night-time period in older women with metabolic syndrome after an acute session of RES.

These findings might indicate that RES and AER exercises affect differently the circadian cycle and the release of possible mechanisms associated with blood pressure reduction (e.g., neurohumoral factors, autonomic modulation) [51], thus causing reductions in BP in different periods of the day in people with RH. However, these inferences should be further investigated and tested in future studies.

The divergent blood pressure responses to exercise sessions between RH and NON-RH may also occur due to antihypertensive medication, given that all patients with RH were under diuretic treatment, while this class of antihypertensive medication was only taken by five participants in the NON-RH group. Indeed, authors have proposed that acute exercise combined with antihypertensive medication may cause greater PEH than exercise alone.

Anunciação et al. [50] observed that an acute session of supramaximal interval AER exercise combined with angiotensin receptor blockers caused greater hypotension at the night period in people with metabolic syndrome relative to exercise alone. However, other studies have refuted this hypothesis testing the same [52] or other medication [53] in hypertensive people, indicating the more evidence is needed. In addition, no studies with diuretics have been conducted.

We acknowledge some limitations of the present study. First, our findings are based on a small sample size. Second, obesity was not controlled as an eligibility criterion. Third, the possible mechanisms responsible for PEH were not assessed. Fourth, although exercise sessions were equalized by time, different caloric expenditures were likely provided by RES (124 kcal), AER (160 kcal), and COM (139.0 kcal) exercises [2]. Fifth, PEH was significant when postexercise was compared with preexercise values (PEH I), but not with the control session PEH II. Experts in the field have suggested that interpretations based on PEH II should be preferred over PEH I in studies using ABPM [54]. However, authors stated the importance of preexercise values to take into consideration day-to-day variation on BP [54]. Finally, the same baseline values were used for all comparisons.

Our findings have practical applications, given that low BP levels after acute exercise may contribute to low cardiovascular risk during the performance of ADL [23, 24]. Hence, health professionals responsible for exercise prescription in patients with RH should preferably prescribe COM exercise, instead of either AER or RES alone. In addition, acute hemodynamic responses to physical exercise may predict long-term adaptations [21, 55], suggesting that the chronic effects of COM should be tested in randomized clinical trials as tool for the management of blood pressure in people with RH.

5. Conclusion

Findings of the present study indicate that AER, RES, and COM exercises elicit systolic and diastolic postexercise ambulatory hypotension in RH patients. Notably, longer hypotension periods were observed after COM exercise. In addition, NON-RH and RH people showed different changes on BP after exercise sessions, suggesting that postexercise hypotension is influenced by the pathophysiological bases of hypertension.

Data Availability

Data are available upon reasonable request.

Disclosure

This study is part of the PhD thesis of NFP.

Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contributions

Nayara Fraccari Piresa and Helio José Coelho-Júnior contributed equally to this work. Bruno Rodrigues and Heitor Moreno Júniora are senior authors contributed equally to this work.

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