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1 Can blood pressure decrease after maximal exercise test predict the blood pressure lowering effect of
2 aerobic training in treated hypertensive men?

3

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12

13

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What is known about this topic

- Significant correlations have been reported between the reductions in blood pressure observed after a maximal exercise test and after a period of aerobic training in healthy individuals.
- Blood pressure decrease observed after a maximal exercise test may be used to predict the blood pressure lowering effect of aerobic training in hypertensives.

What this study adds

- The decrease in blood pressure observed 30 min after a maximal exercise test was not associated with the blood pressure reduction induced by aerobic training in treated hypertensive men.
- The blood pressure reduction observed 30 min after a maximal exercise test cannot be used to predict hypertensives responders or non-responders to the blood pressure lowering effect of aerobic training.

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39

40 **Abstract**

41

42 The acute decrease in blood pressure (BP) observed after a session of exercise (called post-exercise
43 hypotension) has been proposed as a tool to predict the chronic reduction in BP induced by aerobic
44 training. Therefore, this study investigated whether post-exercise hypotension observed after a maximal
45 exercise test is associated to the BP-lowering effect of aerobic training in treated hypertensives. Thirty
46 hypertensive men (50 ± 8 years) who were under consistent anti-hypertensive treatment underwent a
47 maximal exercise test (15 watts/min until exhaustion), and post-exercise hypotension was determined
48 by the difference between BP measured before and at 30 min after the test. Subsequently, the patients
49 underwent 10 weeks of aerobic training (3 times/week, 45 min/session at moderate intensity), and the
50 BP-lowering effect of training was assessed by the difference in BP measured before and after the
51 training period. Pearson correlations were employed to evaluate the associations. Post-maximal exercise
52 test hypotension was observed for systolic and mean BPs (-8 ± 6 and -2 ± 4 mmHg, all $P < 0.05$). Aerobic
53 training reduced clinic systolic/diastolic BPs (-5 ± 6 / -2 ± 3 mmHg, both $P < 0.05$) as well as awake and
54 24h mean BPs (-2 ± 6 and -2 ± 5 mmHg, all $P < 0.05$). No significant correlation was detected between
55 post-exercise hypotension and the BP-lowering effect of training either for clinic or ambulatory BPs (r
56 values ranging from 0.00 to 0.32, all $p > 0.05$). Post-exercise hypotension assessed 30 min after a
57 maximal exercise test cannot be used to predict the BP-lowering effect of aerobic training in treated
58 hypertensive men.

59

60 **Keywords:** Aerobic exercise; Maximal Exercise Test; Post-Exercise Hypotension; Clinic Blood
61 Pressure; Ambulatory Blood Pressure; Hypertension.

62

63

64 INTRODUCTION

65 Hypertension is an idiopathic chronic disease, affecting 31% of adults worldwide, and indirectly
66 responsible for about 14% of the all-cause deaths [1]. Although pharmacological treatment decreases
67 blood pressure (BP), rates of BP control are still low (approximately 30%) [2], and a better control may
68 be obtained by its association with aerobic training (AT) [3–5]. Strong evidence shows that AT reduces
69 clinic and ambulatory BPs in hypertensives [6] with the magnitude of reduction being similar to the
70 pharmacological treatment [7]. Therefore, AT is recommended for hypertension treatment [3–5], but
71 approximately 25% of the hypertensives may not respond to AT with BP decrease [8], being important
72 to find tools to detect these non-responder patients.

73 A single session of aerobic exercise induces an acute and long lasting decrease in BP during the
74 post-exercise period that has been called post-exercise hypotension (PEH) [9–11]. It has been proposed
75 that PEH may be used to predict the chronic BP-lowering effect of AT [10, 11]. Therefore, for clinical
76 application, it would be useful if PEH after a maximal exercise test, a procedure already used in the pre-
77 training screening of hypertensives [3, 12], could predict the BP-lowering effect of AT.

78 Some studies reported strong correlations between the BP decrease observed after a maximal
79 exercise test and the BP reduction obtained after a period of AT in healthy individuals [13, 14]. However,
80 this association was not found in patients with chronic kidney disease who were receiving
81 antihypertensive drugs [15], suggesting that it might not happen in treated hypertensives, which needs
82 to be checked. Additionally, the studies reporting significant associations have employed the same initial
83 BP to calculate both, PEH and the BP-lowering effect of AT [13, 14]. This procedure might result in a
84 mathematical coupling known as regression to the mean that is a well-known experimental pitfall, and
85 can lead to spurious significant correlations [16, 17]. Thus, a more robust experimental design is still
86 needed to confirm the association.

87 Therefore, the present study investigated the association between PEH after a maximal exercise
88 test and the BP-lowering effect of AT in hypertensive men receiving antihypertensive medication and
89 used different initial BPs to calculate PEH and the BP-lowering effect of AT.

90

91 **METHODS**

92 This study employed secondary data from a randomized controlled trial designed to compare
93 the BP-lowering effects of morning and evening AT in treated hypertensive men. The main results were
94 published elsewhere [18]. The study was approved by the Research Ethical Committee of the School of
95 Physical Education and Sport (no. 966.072) and registered in the Brazilian Clinical Trials platform
96 (RBR-7q7pz7). All patients signed a written consent form before enrollment.

97

98 *Subjects*

99 The patients were recruited through printed and digital media. As study's criteria, patients
100 should: i) be male; ii) age between 30 and 65 years old; iii) present hypertension and be taking
101 antihypertensive medications with classes and doses constant for at least the last 4 months; iv) have
102 resting systolic/diastolic BP \leq 160/105 mmHg; v) present neither chronotype (i.e. scores between 41
103 and 59 in the Horne and Ostberg morningness-eveningness questionnaire); vi) not be taking β -blockers
104 or dihydropyridine calcium channel blockers; (vii) be nonactive (practicing $<$ 150 min/week of physical
105 activity according to the International Physical Activity Questionnaire); and viii) not have physical
106 limitations to perform aerobic exercise. The patients were excluded if they presented: i) obesity at stage
107 2 or higher (i.e. body mass index \geq 35 kg/m²); ii) diabetes with complications or in use of insulin; iii)
108 hypertensive target-organ damage; iv) other cardiovascular diseases besides hypertension; and v)
109 electrocardiogram abnormality at rest or during an exercise test.

110

111 *Preliminary Exams*

112 To check accomplishment to the study's criteria, the patients underwent preliminary
113 evaluations. They were interviewed regarding their health history, medication use and physical activity
114 practice, and answered the Horne and Ostberg's morningness-eveningness [19] and the International
115 Physical Activity [20] questionnaires. They underwent a clinical exam performed by a physician, and
116 their body mass and height were measured. Their BP was measured three times after 5 min of seated
117 rest on two different occasions. Finally, blood and urine samples were collected to evaluate the presence

118 of secondary hypertension and target-organ damage according to the Brazilian Guideline for
119 Hypertension [3].

120

121 *Procedures*

122 Before and after 10 weeks of AT, the patients who fulfilled the study's criteria attended to the
123 laboratory for two different visits conducted with an interval of at least 48h. One visit was dedicated to
124 evaluate PEH by measuring BP before and at 30 minutes after a maximal exercise test. The other visit
125 was used to evaluate the chronic BP-lowering effect of AT by measuring clinic and ambulatory BP.
126 After the training period, the visits were conducted at least 48 hours after the last training session.

127

128 *Assessment of PEH after the maximal exercise test*

129 Maximal exercise test was conducted in a temperature controlled (20-22°C) laboratory between
130 7 and 9 a.m. The patients were instructed to have a light meal two hours before, to avoid caffeinated
131 beverages and smoking in the testing day, and to avoid alcoholic drinks and vigorous physical efforts in
132 the previous 24 hours. The test was carried out on a cycle ergometer (Lode Medical Technology,
133 Corival, Groningen, Netherland) with a ramp protocol of 15 watts increment each minute until the
134 patients were unable to keep pedaling frequency at 60 rpm. The test was preceded by a 3-min warm-up
135 at 30 watts and followed by a 5-min cool-down period pedaling at 30 watts. During the test, auscultatory
136 BP (Unitec, São Paulo, Brazil) was measured every two minutes, electrocardiogram (EMG System,
137 030110/00B, São Paulo, Brazil) was continuously recorded, and breath-by-breath oxygen consumption
138 (VO_2) was continuously analyzed by a metabolic card (CPX Ultima, Medical Graphics Corporation, St.
139 Paul, MN). VO_2 peak was considered as the highest value achieved during exercise in means of 30s. For
140 10 min before and 30 min after the test, the patients rested seated on a comfortable chair. At the end of
141 each of these moments, BP was measured three times with an interval of 1 min, and the mean value was
142 calculated. The measures were taken by an experienced evaluator, using the auscultatory method and a
143 mercury column sphygmomanometer (Unitec, São Paulo, Brazil). PEH was calculated by the difference

144 between the BP measured after (at 30 min) and before the maximal exercise test conducted before the
145 training period.

146

147 *Assessment of the effect of AT on clinic and ambulatory BPs*

148 Before and after the training period, in a visit different from the maximal test, clinic BP was
149 measured using the auscultatory method and a mercury column sphygmomanometer (Unitec, São Paulo,
150 Brazil). The measurements were performed 3 times after 5 min of seated rest and with an interval of 1
151 min between the measures. The mean of the three measures was considered as the clinic BP. In the same
152 day, an oscillometric ambulatory BP monitor (Spacelabs Healthcare, 90207, USA) was positioned on
153 the non-dominant arm of the patients, and they left the laboratory being instructed to perform their
154 normal daily activities and to come back to the laboratory after 24h. The monitor was programmed to
155 take measures every 15 min for 24 hours, and the patients were instructed to avoid physical efforts
156 during the monitoring. Additionally, they should record their daily activities and take notes regarding
157 the time of sleeping and awaking. In the monitoring conducted after the training period, the patients
158 were asked to keep the same daily activities as in the pre-training monitoring. For analyses, only records
159 that presented at least 85% of the measures valid were considered. Twenty-four hour, asleep and awake
160 BP were calculated, respectively, by the average of all measures taken during whole monitoring period,
161 the period that the patient reported to be sleeping and the period that he reported to be awake. The clinic
162 BP-lowering effect of AT (Δ clinic BP) was determined by the difference in clinic BP measured after
163 and before the training period, while the ambulatory BP-lowering effect of AT (Δ ambulatory BP) was
164 determined by the difference in 24-h, awake and asleep BP assessed after and before the training period.

165

166 *AT protocol*

167 AT was performed on cycle ergometer (CEFISE, Biotec 2100, Campinas, Brazil), 3 times per
168 week for 10 weeks. Training duration and intensity progressed along the training period. Exercise
169 duration increased from 30 to 45 min in the first two weeks of training and this duration was maintained
170 until the end of the training period. Exercise intensity was set at the heart rate of the anaerobic threshold

171 during weeks 1 to 4 and increased progressively to achieve 10% below the heart rate of the respiratory
172 compensation point at weeks 9 and 10. The maximal exercise test conducted before the training period
173 was used to establish the anaerobic threshold and the respiratory compensation point according to
174 literature criteria [21]. During the training sessions, heart rate was monitored (POLAR 800cx, Kempele,
175 Finland) to keep intensity within the desirable range.

176

177 *Statistical Analysis*

178 Since this study used a database from a bigger study [18], sample size was originally calculated
179 for the main variable of the bigger study and accepted by convenience for this investigation. Normality
180 of data was evaluated by Shapiro-Wilk test. Paired t-test were used to confirm the occurrence of PEH
181 (pre- vs. post-maximal exercise test) and the effect of AT (before vs. after training). Pearson correlations
182 and linear regressions were used to analyze the association between PEH and the clinic and ambulatory
183 BP-lowering effect of AT. The analyses were performed in SPSS software (SPSS for windows; IBM,
184 Chicago, IL). Data were expressed in mean \pm standard deviation, and the level of significance adopted
185 was $p \leq 0.05$.

186

187 **RESULTS**

188

189 A total of 68 patients signed the informed consent form to participate. After checking for the
190 study criteria, 32 were excluded. Therefore, 36 patients were enrolled in the experimental protocol, but
191 during the training phase, 6 patients dropped out. Thus, 30 patients finished the study's protocol and had
192 their data analyzed (Figure 1).

193

194

[FIGURE 1 ABOUT HERE]

195

196 The sample was composed by middle-aged hypertensive men, taking different types of
197 antihypertensive drugs, mostly as monotherapy (Table 1). Maximal exercise tests were interrupted by
198 fatigue in all patients.

199

200

[TABLE 1 ABOUT HERE]

201

202 Adherence to training sessions was $96 \pm 4\%$. VO_2 peak increased significantly after AT
203 (VO_2 peak = 21.4 ± 3.3 vs. 23.1 ± 4.2 mL.kg⁻¹.min⁻¹, $p = 0.04$), while weight did not change (88.6 ± 13.3
204 vs 88.3 ± 13.0 kg, $p = 0.21$).

205 Maximal exercise test promoted PEH, significantly reducing systolic and mean BPs, but not
206 diastolic BP (Table 2). AT decreased clinic systolic, diastolic, and mean BPs (Table 3). Considering
207 ambulatory BP, AT significantly reduced 24h and awake mean BPs; tended to reduce 24h and awake
208 diastolic BPs; and did not significantly change 24h, awake and asleep systolic BPs nor asleep diastolic
209 and mean BPs (Table 3).

210

211

[TABLE 2 AND 3 ABOUT HERE]

212

213 Considering the main objective of the study, no significant association was observed between
214 the systolic or diastolic BP changes observed after the maximal exercise test (PEH) and the changes in
215 clinic or ambulatory BPs observed after AT (Table 4, Figure 2).

216

217

[TABLE 4 AND FIGURE 2 ABOUT HERE]

218

219 DISCUSSION

220 This study investigated the association between PEH assessed 30 min after a maximal exercise
221 test and the chronic BP reduction induced by AT in treated hypertensive men using an experimental
222 design that overcame previous limitations. The existence of such association would have supported the

223 use of BP reduction observed after a maximal exercise test as a clinical tool to identify those
224 hypertensives who would mostly respond to AT with BP reduction. However, contrary to this
225 expectation, the main finding of the present study was that there was no association between PEH
226 assessed 30 min after a maximal exercise test and either the clinic or the ambulatory BP reduction
227 induced by 10 weeks of AT.

228 In the present study, maximal exercise test induced PEH, decreasing systolic BP by -7.6 ± 5.7
229 mmHg, which is in accordance with the previous studies that also reported PEH after maximal exercise
230 tests in health individuals [13, 14]. Additionally, as expected, AT increased VO_2peak as previously
231 reported [18], and promoted significant reductions in clinic systolic/diastolic BPs ($-4.6 \pm 6.4 / -1.8 \pm 3.2$
232 mmHg) as well as in some parameters of ambulatory BP (24h and awake mean BPs, -2.1 ± 4.9 and -2.3
233 ± 6.0 mmHg, respectively). These BP reductions were lower than those reported in a recent meta-
234 analysis [6], but may have clinical importance since a -5 mmHg decrease in clinic systolic BP may be
235 associated with a reduction of 14% in the risk of death from stroke and 9% from coronary heart disease
236 [22].

237 Regarding the use of PEH after a maximal test to predict the BP-lowering effect of AT, the
238 present findings do not support this application in treated hypertensive men as no significant association
239 was observed between the acute and chronic responses of BP to aerobic exercise. This absence of
240 association was also reported in patients with chronic kidney disease [15], but differs from prior findings
241 of strong associations reported in healthy individuals [13, 14]. Some factors may be raised to explain
242 the discrepancy among the studies. First, the time after the maximal exercise test when PEH was
243 assessed may influence the association. The previous studies that have reported significant associations
244 assessed PEH at 7 [14] and 60 min [13] after the maximal exercise test, while the present study assessed
245 PEH at 30 min, a midpoint between these periods, which suggests that the time of measurement may
246 not have been the reason for the absence of association. However, a recent review conducted by our
247 group [23] reported that in many studies the greatest PEH happened after 30 min of recovery, being
248 possible that the use of other specific times points or the greatest reduction in BP after the exercise test
249 could reveal a different result from using the assessment at 30 min of recovery. Nevertheless, this time

250 point was employed in the present study based on the previous studies that have employed maximal
251 exercise tests and on the feasibility in clinical routine, where a long-term assessment after a maximal
252 exercise test is difficult. Another possible reason for the difference in the results of the present study in
253 comparison with those that found significant correlations is the use of antihypertensive medication that
254 may affect the relationship between the acute and the chronic responses of BP to exercise. Along this
255 line, a recent meta-analysis concluded that PEH is less evident in patients receiving anti-hypertensive
256 drugs [9], while the BP-lowering effect of AT is greater in patients receiving medication [24, 25].
257 Finally, an important explanation, as cited before, may be the mathematical approach adopted in the
258 previous studies [13, 14] that considered the same initial BP for calculating both PEH and the BP-
259 lowering effect of AT, which may have caused spurious significant correlations [16, 17].

260 The absence of association (i.e. a null result) between PEH assessed 30 min after a maximal
261 exercise test and the BP-lowering effect of AT might seem an inconsequential finding. However, it may
262 have important clinical impact considering the readiness to generalize the positive previous results
263 obtained in healthy individuals [13, 14] to other populations. Therefore, despite the importance of
264 maximal exercise test to guide AT for hypertensives, the findings of the present study do not support
265 the use of the BP response measured after this test to identify responder and non-responders to AT
266 among treated hypertensives. Therefore, other tools should be identified for this specific purpose. Along
267 this line, in pre-hypertensives, PEH after a submaximal session of aerobic exercise (30 min at 65% of
268 VO₂ peak) has been reported to be associated with the BP-lowering effect of AT [26], however, this
269 relationship needs to be tested in treated hypertensives by future research.

270 Finally, we would like to highlight some of the strengths and limitations of the present study.
271 The assessment of PEH and the BP-lowering effect of AT using different initial BP values reduces the
272 chances for mathematical bias. Additionally, as all patients were under consistent anti-hypertensive
273 treatment for 4 months or more, their clinical condition was stable, reducing any possible influence of
274 medication changes. On the other hand, the results are limited to the study cohort's characteristics.
275 Inactive middle-aged men under antihypertensive treatment were investigated. So, results cannot be
276 generalized to women, physically active patients, other age groups, and untreated patients. These

277 specific populations need to be studied in the future. Additionally, maximal tests were conducted in the
278 morning. As BP presents daily variations, results could be different if tests were conducted at other times
279 of day, which also should be tested in the future. As discussed before, PEH was assessed at 30 min after
280 the maximal exercise test, and future research should test other times points and the association with the
281 greatest PEH. Finally, a lack of statistical power due to a small sample may be a concern. However, the
282 previous studies [13, 14] that revealed strong correlations used samples smaller than the present study
283 (i.e. 12 and 23 subjects) for these calculations. In addition, if the sample size for this study had been
284 calculated *a priori* based on the data of these studies and considering an alpha error of 5% and a power
285 of 90%, the smaller number needed would be 20 subjects.

286 In conclusion, although a maximal exercise test generates PEH and AT decreases clinic and
287 ambulatory BPs in medicated hypertensive men, these acute and chronic BP changes were not
288 correlated. Thus, in this population, BP response assessed 30 min after a maximal exercise test cannot
289 be used to predict the chronic BP-lowering effect of AT.

290

291 **Data Availability Statement**

292 Additional data will be provided by the corresponding author on reasonable request.

293

294 **References**

295

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368

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371

372 **Author Contributions**

373 LA and LCB collaborate to the study design, collected data, carried out the statistical analysis,
374 contributed to the interpretation of results, and drafted the initial manuscript; TP, RF, RR collected data,
375 and revised the manuscript; GS, AA, DMJ were responsible for patients clinical evaluation and follow-
376 up, and revised the manuscript; JH contributed to the interpretation of results and revised the manuscript;
377 CF designed the study, get grants for the study, supervised data collection, contributed to the
378 interpretation of results and revised the manuscript. All authors gave final approval of the manuscript
379 version submitted for publication.

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386

387 **Ethical Approval**

388 All patients signed a written consent form. The study from which data of the present
389 investigation was derived was approved by the Research Ethical Committee of the School of Physical
390 Education and Sport (no. 966.072) and registered in the Brazilian Clinical Trials platform (RBR-
391 7q7pz7), and its procedures followed the standards proposed by the Helsinki Declaration.

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393 **Competing Interest**

394 The authors declare no competing interests.

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410 **Figure 1** – Study Flowchart.

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412 **Figure 2** – Associations between the changes clinic and ambulatorial systolic (SBP), mean
413 (MBP) and diastolic (DBP) blood pressures assessed after a maximal exercise test (Δ after Max
414 test) and after a period of aerobic training (Δ after AT).

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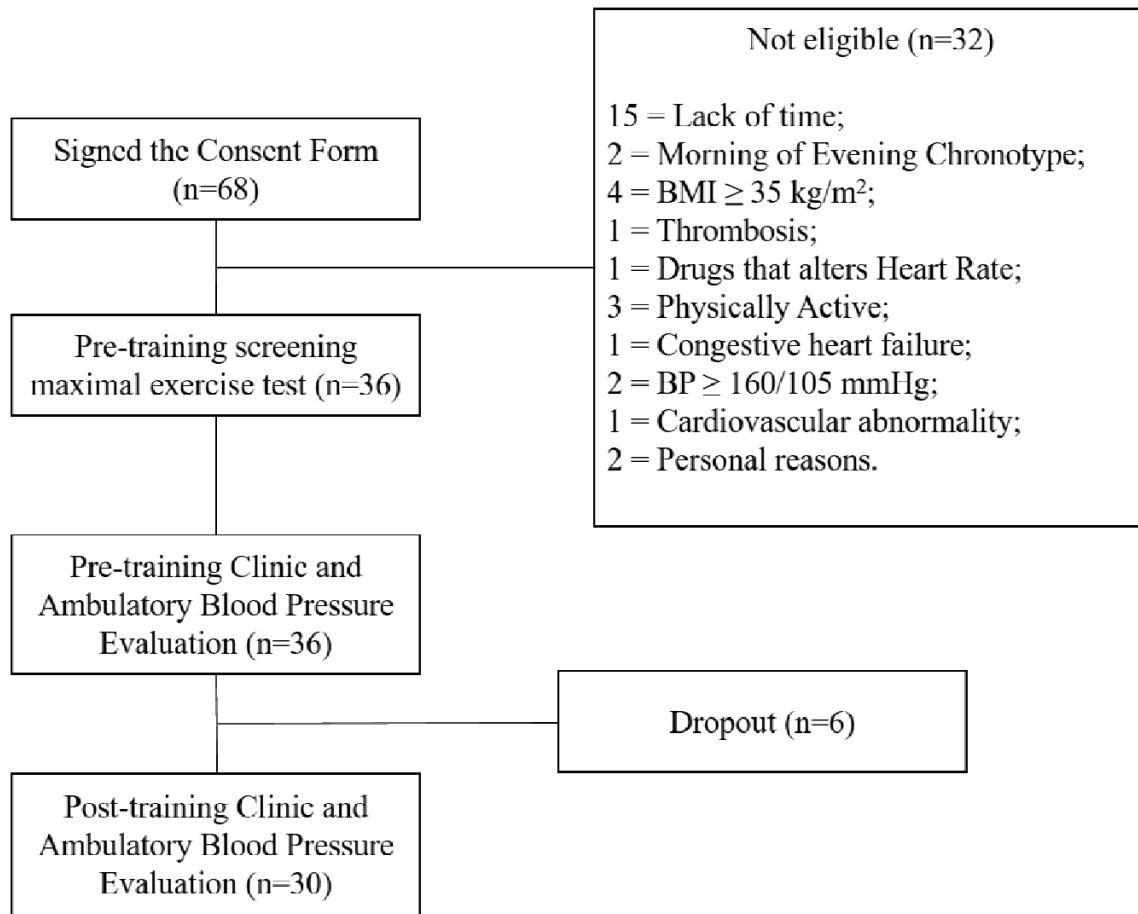


Figure 1 – Study Flowchart.

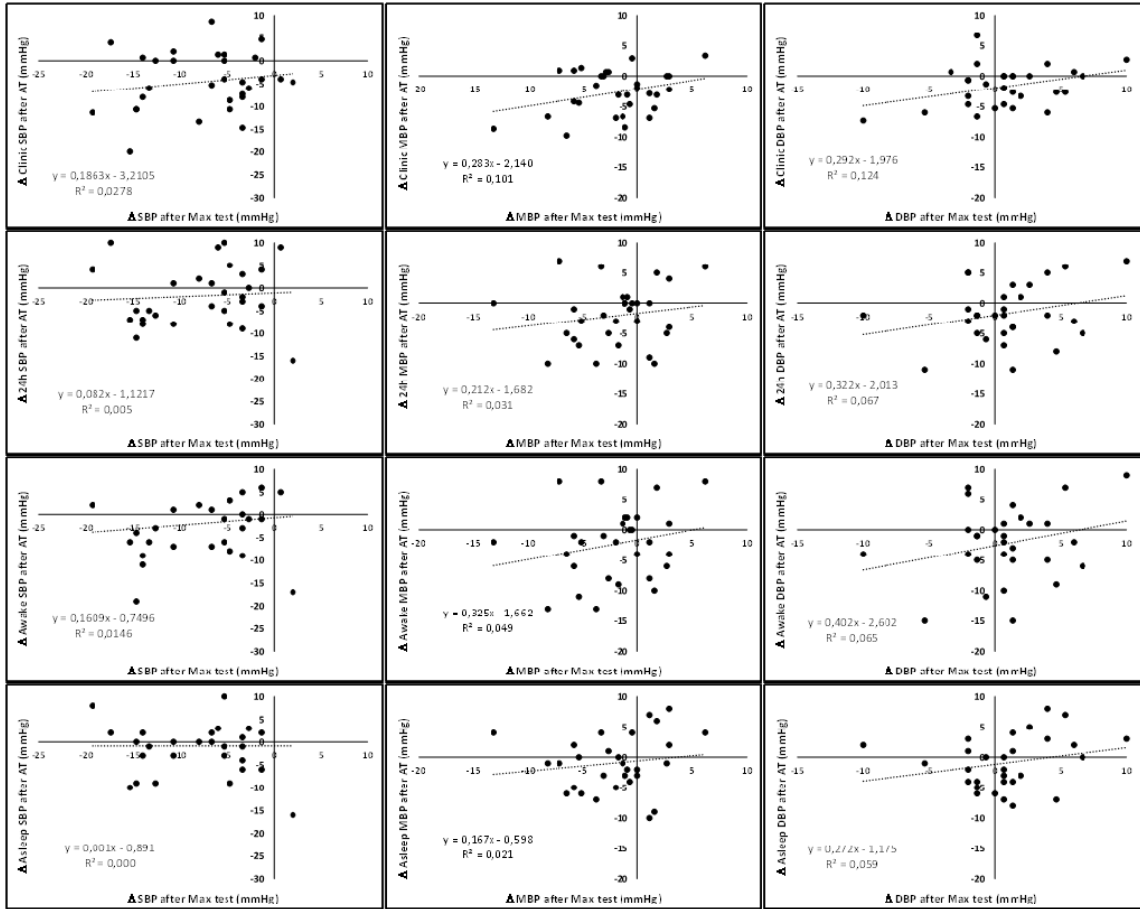


Figure 2 – Correlations between changes (Δ) in systolic (SBP), diastolic (DBP) and mean (MBP) blood pressures assessed after a maximal exercise test (Max test) and after a period of aerobic training (AT).

Table 1 – Sample characteristics (n = 30).

Characteristic	Mean ± SD
<i>General</i>	
Age (years)	50 ± 8
Body mass index (kg/m ²)	29.9 ± 4.3
Systolic blood pressure (mmHg)	133 ± 7
Diastolic blood pressure (mmHg)	90 ± 6
<i>Antihypertensive Drugs</i>	
	<i>n (%)</i>
<i>Angiotensin II receptor blockers</i>	15 (50)
<i>Angiotensin converting enzyme inhibitors</i>	11 (37)
<i>Dihydropyridine calcium channel blockers</i>	7 (23)
<i>Diuretics</i>	9 (30)
<i>Antihypertensive Strategy</i>	
	<i>n (%)</i>
<i>Monotherapy</i>	21 (70)
<i>Polytherapy</i>	9 (30)

Table 2. Post-exercise hypotension evaluated by systolic, mean, and diastolic blood pressures (BP) measured before and at 30 min after the maximal exercise test.

	Pre-test	Post-test	P
Systolic BP (mmHg)	131 ± 14	123 ± 15 *	< 0.01
Mean BP (mmHg)	104 ± 9	102 ± 10 *	0.01
Diastolic BP (mmHg)	90 ± 8	91 ± 8	0.29

* Significantly lower than pre-test

Table 3. Aerobic training blood pressure lowering effect assessed by clinic and ambulatory BPs measured before and after 10 weeks of aerobic training.

	Before training	After training	P
<i>Clinic BP</i>			
Clinic systolic BP (mmHg)	131 ± 12	126 ± 11 †	< 0.01
Clinic mean BP (mmHg)	104 ± 8	102 ± 8 †	< 0.01
Clinic diastolic BP(mmHg)	91 ± 6	89 ± 6 †	0.01
<i>Ambulatory BP</i>			
24h systolic BP (mmHg)	129 ± 9	127 ± 8	0.17
24h mean BP (mmHg)	100 ± 8	97 ± 6 †	0.03
24h diastolic BP(mmHg)	85 ± 7	83 ± 6	0.06
Awake systolic BP (mmHg)	134 ± 10	132 ± 7	0.17
Awake mean BP (mmHg)	104 ± 8	102 ± 6 †	0.05
Awake diastolic BP(mmHg)	90 ± 8	87 ± 6	0.06
Asleep systolic BP (mmHg)	119 ± 10	118 ± 9	0.45
Asleep mean BP (mmHg)	88 ± 7	88 ± 7	0.29
Asleep diastolic BP (mmHg)	73 ± 7	72 ± 7	0.25

† Significantly different from before training.

Table 4. Correlations between blood pressure change after the maximal exercise test (Δ BP after Max test) and clinic and ambulatory blood pressure changes observed after the aerobic training (Δ BP after AT).

	Δ BP after Max test		Δ BP after AT	n	r	p
Systolic BP (mmHg)	-7.6 ± 5.7	Clinic	-4.6 ± 6.4	30	0.17	0.38
		24 hour	-1.8 ± 6.7	29	0.07	0.72
	-7.8 ± 5.7	Awake	-2.0 ± 7.6	29	0.12	0.53
		Asleep	-0.9 ± 6.4	29	0.00	1.00
Diastolic BP (mmHg)	$+0.8 \pm 3.8$	Clinic	-1.8 ± 3.2	30	0.35	0.06
		24 hour	-1.7 ± 4.8	29	0.26	0.18
	$+0.9 \pm 3.8$	Awake	-2.2 ± 6.0	29	0.25	0.18
		Asleep	-0.9 ± 4.3	29	0.24	0.20
Mean BP (mmHg)	-2.0 ± 4.0	Clinic	-2.7 ± 3.6	30	0.32	0.09
		24 hour	-2.1 ± 4.9	29	0.18	0.36
	-2.0 ± 4.1	Awake	-2.3 ± 6.0	29	0.22	0.25
		Asleep	-0.9 ± 4.6	29	0.15	0.45

Data: Mean \pm standard deviation.