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Title: CARDIOVASCULAR RESPONSES DURING RESISTANCE EXERCISE IN PATIENTS WITH PARKINSON DISEASE

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1 **Abstract**

2 **Background:** Patients with Parkinson disease (PD) present cardiovascular autonomic
3 dysfunction which impairs blood pressure control. However, cardiovascular responses
4 during resistance exercise are unknown in these patients.

5 **Objective:** Investigate the cardiovascular responses during resistance exercise
6 performed with different muscle masses, in patients with PD.

7 **Design:** Two groups, repeated-measures design.

8 **Setting:** Exercise Hemodynamic Laboratory, School of Physical Education and Sport,
9 University of São Paulo.

10 **Participants:** Thirteen patients with PD (4 women, 62.7 ± 1.3 years, stages 2-3 of
11 modified Hoehn and Yahr scale; "on" state of medication) and thirteen paired controls
12 without PD (7 women, 66.2 ± 2.0 years)

13 **Interventions:** Both groups performed, in a random order, bilateral and unilateral knee
14 extension exercises (2 sets, 10–12 RM, 2 min of interval).

15 **Main Outcome Measurements:** Systolic blood pressure (SBP) and heart rate (HR)
16 were assessed before (pre) and during the exercises.

17 **Results:** Independent of set and exercise type, SBP and HR increases were significantly
18 lower in PD than the control group (combined values: $+45 \pm 2$ vs. $+73 \pm 4$ mmHg and
19 $+18 \pm 1$ vs. $+31 \pm 2$ bpm, $P = .003$ and $.007$, respectively). Independently of group and set,
20 the SBP increase was greater in the bilateral than the unilateral exercise (combined
21 values: $+63 \pm 4$ vs $+54 \pm 3$ mmHg, $P = .002$), while the HR increase was similar. In
22 addition, independently of group and exercise type, the SBP increase was higher in the
23 2nd than the 1st set (combined values: $+56 \pm 4$ vs $+61 \pm 4$ mmHg, $P = .04$), while the HR
24 increases were similar.

25 **Conclusions:** Patients with PD present attenuated increases in SBP and HR during
26 resistance exercise in comparison with healthy subjects. These results support that
27 resistance exercise is safe and well tolerated for patients with PD from a cardiovascular
28 point of view supporting its recommendation for this population.

29 **Level of evidence:** II

30

31

32 **INTRODUCTION**

33 Parkinson's disease (PD) is a neurodegenerative progressive disease of the
34 central nervous system mainly characterized by motor dysfunction symptoms, such as
35 rigidity, resting tremor, bradykinesia, akinesia and postural instability[1]. In addition,
36 patients usually present with autonomic dysfunction, including cardiovascular
37 dysfunction[2] that often occurs in the latter stages of the disease but sometimes
38 earlier[3]. The cardiovascular autonomic dysfunction in PD is mainly characterized by
39 reductions in sympathetic and parasympathetic activities, as well as in baroreflex
40 sensitivity[4]; which impairs blood pressure (BP) control[5].

41 Physical training is highly recommended to attenuate motor dysfunction and
42 physical deconditioning in patients with PD[6]. In addition, it improves cognitive
43 function, drug efficacy and sleep pattern, as well as prevents depression and
44 cardiovascular complications[6]. In particular, resistance training is especially important
45 to improve muscle strength, gait speed and gait initiation in these patients, which
46 decreases motor disability, increasing the ability to perform activities of daily living and
47 improving quality of life [7,8]. Our group has also demonstrated that resistance training
48 improves cardiovascular autonomic dysfunction in PD[7]. However, cardiovascular
49 responses during resistance exercise are largely unknown in patients with PD, requiring
50 further investigation, since abnormal responses may acutely increase cardiovascular
51 risk[8] and/or increase the risk of orthostatic intolerance symptoms[9].

52 In healthy individuals, heart rate (HR) and systolic BP (SBP) present a huge
53 increase during resistance exercise that is proportional to the active muscle mass
54 required to perform the exercise[10]. As patients with PD can present with autonomic
55 dysfunction, atypical cardiovascular responses may be expected when they perform

56 these kind of exercises, and these responses might be more evident when the stimulus is
57 greater, such as during exercise involving a large muscle mass. In the limited amount of
58 previous studies on cardiovascular responses to aerobic exercise (leg cycling), preserved
59 [11] or blunted[12] responses have been reported in PD patients with either presumably
60 intact[13], impaired[14] or unreported autonomic function[12]. Thus, the objective of
61 this study was to compare, patients with PD and age-matched healthy controls, HR and
62 SBP responses during resistance exercise requiring different amounts of active muscle
63 mass.

64

65 **METHODS**

66 **Experimental Design**

67 The hypothesis of this study was that patients with PD present abnormal
68 cardiovascular responses during resistance exercise, and that the abnormality of these
69 responses are greater during exercise that recruits a larger muscle mass. To test this
70 hypothesis, patients with PD and healthy controls underwent an experimental session, in
71 which they performed, in a random order, two resistance exercises (i.e. unilateral and
72 bilateral knee extension exercises) with an interval of, at least, 10 minutes between
73 them. During each exercise, they performed 2 sets of 10-12RM with a 2 min interval,
74 and SBP and HR were continuously measured.

75

76 **Subjects**

77 Thirteen patients with PD and 13 control subjects were studied. Groups were
78 similar regarding age, gender distribution, body mass index (BMI), BP, HR and leg-
79 extension 10-12 RM load (all $P > .05$, Table 1). Patients with PD were recruited from the
80 Brazilian Parkinson Association and had PD for 8.8 ± 1.2 years. To participate in the

81 study, they had to: i) present a diagnosis of idiopathic Parkinson's disease as diagnosed
82 by an experienced specialist in movement disorders, following the UK Brain Bank
83 criteria[15], and ii) be at stages 2 to 3 of the modified Hoehn and Yahr Scale [16]. In
84 addition, subjects without any known neurological disease matched to the PD patients
85 for age, gender, body mass index (BMI), resting BP and strength were used as a control
86 group. The exclusion criteria for both groups were: i) presence of arterial hypertension;
87 ii) presence of cardiovascular disease; iii) presence of orthopedic disease that could
88 limit exercise performance; iv) use of medications that could directly affect
89 cardiovascular system, except for the medications used for the treatment of PD; v)
90 participate on in any regular exercise program, except for physiotherapy for the
91 treatment of PD; and v) any previous experience with resistance training in the last 6
92 months. All volunteers signed an informed written consent form approved by the Ethics
93 Committee of the School of Physical Education and Sport, University of São Paulo
94 (2011/42), and the study was registered at the Brazilian Clinical Trials (U111-1129-
95 0762).

96

97 **Procedures and Instrumentation**

98 As a preliminary evaluation, all patients with PD were examined by a
99 specialized physician to confirm the diagnosis of PD and the Hoehn and Yahr stage. In
100 addition, patients with PD and control subjects were interviewed for the presence of
101 other diseases, physical activity level and medication use. Auscultatory seated resting
102 BP was measured in triplicate on two occasions following the hypertension guidelines
103 for both groups[17]. Subjects were excluded if mean resting systolic/diastolic BP were
104 $\geq 140/90$ mmHg, or if the interview revealed the presence of any of the exclusion
105 criterion.

106 Volunteers (patients with PD and control subjects) who fulfilled the study
107 criteria performed a familiarization session to learn the technique of the
108 unilateral(conducted with the more affected leg of the patients with PD and with the
109 non-dominant leg in the control subjects) and bilateral knee-extension exercises
110 (Nakagym, NK-5060 São Paulo, Brazil), and to allow the estimation of the workload
111 corresponding to 10 to 12 RM for both exercises. This session was conducted with the
112 PD patients during the *on-state* of medication (i.e. they took the medication 20 minutes
113 prior to the beginning of the session). The session initiated with a 5-min warm-up on a
114 cycle ergometer (Lifefitness, 5500,São Paulo, Brazil)with zero watts and was followed
115 by the unilateral and bilateral knee extension exercises (random order). The work load
116 corresponding to 10-12 RM on each exercise (unilateral and bilateral) was estimated by
117 gradually increasing the workload on each set. At the end of each set, rating of
118 perceived exertion was assessed using the OMNI-REP scale[18]. If the rate was lower
119 than 8-10, the exercise workload was increased and an additional set was performed. A
120 2 min interval was allowed between the sets and 10min interval between the exercises.

121 At least 7 days after the familiarization session, subjects reported to the
122 laboratory for the experimental session. They were instructed to refrain from exercise
123 for the previous 48 hours, to avoid the ingestion of stimulants (e.g., coffee, tea,
124 caffeinated drinks and soda) in the previous 12 hours, and to have a light meal 2 hours
125 before the experimental session. In addition, patients with PD were instructed to take
126 their PD medications 20 minutes before the beginning of the protocol (i.e. *on-state* of
127 medication). The session was conducted in a temperature-controlled laboratory (21 to
128 23°C).

129 During the experimental session (Figure 1), all volunteers warmed-up for 5 min
130 on a cycle ergometer (Lifefitness, 5500, São Paulo, Brazil) with a comfortable

131 workload, and then, performed a specific warm-up in the unilateral and bilateral knee-
132 extension exercises (2 sets of 5 repetitions on each exercise: first set with a comfortable
133 workload, a 2-min rest interval, and second set with the estimated workload
134 corresponding to 10-12 RM). After 10 min, the experimental protocol was initiated. The
135 volunteers performed the unilateral or bilateral knee-extension exercises in a counter
136 balanced random order and for 2 sets of 10-12 RM with a 2-min interval between the
137 sets and a 10-min rest between the exercises. For each exercise, BP and HR were
138 recorded at rest (for the 3 min before the exercise) and during the exercise protocol
139 (during both sets and during the interval between sets).

140 BP was measured beat-by-beat by photoplethysmography using the Finometer
141 (Finapres Measurement System, Finometer, Arnhem, Netherlands) on the left arm and
142 HR was monitored by a 3-lead electrocardiographic system (Cardio Perfect, model ST
143 2001, Netherlands). Both signals were digitalized and recorded online using a data
144 acquisition system (Windaq, DI-720, Ohio, USA) with a sampling frequency of 500
145 Hz/channel.

146

147 **Statistical Analyses**

148 A previous study[19] showed that only SBP responses during resistance exercise
149 corresponded to intra-arterial BP responses when assessed by the
150 photoplethysmographic method. Thus, in the present study, diastolic BP responses were
151 not analyzed. Pre-exercise SBP and HR values were assessed as the mean of the 2
152 minutes before the beginning of exercise. Exercise SBP and HR values were established
153 as the highest values achieved during each set (S1 and S2) at samples of 40-48 seconds
154 and the lowest value obtained during the 2 minutes rest interval between sets (INT). The

155 changes in the responses (Δ) were calculated by subtracting the values obtained during
156 exercise from pre-exercise.

157 The normality of data were confirmed by Shapiro–Wilk tests (IBM SPSS
158 Statistics version 20). Chi-square and T tests were used for comparing descriptive data
159 between groups (patients with PD and control subjects). SBP and HR responses to each
160 exercise (i.e. bilateral and unilateral) were firstly analyzed using a two-way ANOVA,
161 considering group (patients with PD and control subjects) as a between main factor and
162 exercise phase (Pre, S1, INT and S2) as a within main factor. Afterwards, the changes
163 (Δ) to both exercise in both groups were compared using a three-way ANOVA, with
164 group (patients with PD and control subjects) as a between main factor, and exercise
165 (unilateral or bilateral) and set (S1 and S2) as within main factors. Newman Keuls post-
166 hoc tests were applied when necessary (Statistica version 5.0). Significance level was
167 defined as $P \leq .05$. Data are presented as mean \pm SE.

168

169 **RESULTS**

170 Thirteen volunteers initiated the protocol with the unilateral exercise; while the
171 other 13 performed bilateral exercise first. Pre-exercise SBP and HR were not different
172 between unilateral and bilateral exercises (119 ± 17 vs. 116 ± 17 mmHg, $P=.16$ and 77 ± 8
173 vs. 76 ± 8 bpm, $P=.27$).

174 During the unilateral knee extension exercise, SBP and HR analyses presented
175 significant interactions between group and exercise phase in ANOVA ($P<.001$ for both).
176 Newman Keuls post-hoc comparisons showed that SBP and HR increased significantly
177 during both sets and returned to pre-exercise levels during the rest interval in both
178 groups, except for SBP that decreased below pre-exercise during the rest interval in the
179 PD group (Figure 2A and 2B). In addition, SBP was significantly higher in the control

180 group compared to PD throughout the protocol (S1: 188 ± 6 vs. 156 ± 5 , INT: 116 ± 5 vs.
181 100 ± 4 , and S2: 195 ± 6 vs. 159 ± 6 mmHg, respectively), while HR was higher in the
182 control group in both sets (S1: 104 ± 4 vs. 95 ± 3 , and S2: 105 ± 4 vs. 95 ± 3 bpm,
183 respectively), but was similar between the groups in the rest interval.

184 During the bilateral knee extension exercise, SBP and HR analyses presented
185 significant interactions between group and exercise phase in ANOVA ($P < .001$ for both).
186 Newman Keuls post-hoc comparisons showed that SBP and HR increased significantly
187 during both sets and returned to pre-exercise values during the rest interval in both
188 groups (Figure 2C and 2D). In addition, SBP was significantly higher in the control
189 group compared to PD throughout the protocol (S1: 203 ± 9 vs. 158 ± 4 , INT: 118 ± 6 vs.
190 102 ± 4 , and S2: 203 ± 8 vs 164 ± 4 mmHg, respectively). HR was also significantly higher
191 in the control group during both sets (S1: 107 ± 5 vs. 97 ± 3 and S2: 108 ± 6 vs. 96 ± 3 bpm,
192 respectively), but was similar between the groups during the rest interval.

193 There were no significant interactions for Δ SBP and Δ HR as assessed by the 3-
194 way ANOVAs. However, for Δ SBP, there were significant main effects for group
195 ($P = .003$), exercise ($P = .002$), and set ($P = .04$) (Figure 3, panel A). Thus, independent of
196 group and set, SBP increase was greater during bilateral than unilateral exercise (mean
197 values: $+63\pm 4$ vs $+54\pm 3$ mmHg). Furthermore, independent of group and exercise type,
198 SBP increase was higher in S2 than S1 ($+61\pm 4$ vs. $+56\pm 4$ mmHg), and independent of
199 exercise type and set, the SBP increase was greater in the control group compared to
200 patients with PD (mean values: $+73\pm 4$ vs $+45\pm 2$ mmHg). For Δ HR, only the main factor
201 of group presented a significant main effect ($P = .007$) (Figure 3, panel B), showing that
202 independent of exercise type and set, the HR increase was lower in PD than the control
203 group (mean values: $+18\pm 1$ vs. $+31\pm 2$ bpm).

204

205 **DISCUSSION**

206

207 The main finding of this study was that patients with PD presented blunted SBP
208 and HR increases during unilateral and bilateral knee extension exercise in comparison
209 with control subjects without PD. To the best of our knowledge, this is the first study to
210 describe the cardiovascular responses to resistance exercise in patients with PD. As
211 resistance training has been widely recommended for individuals with PD to improve
212 motor symptoms and functionality[20,21], the understanding of cardiovascular
213 responses to resistance exercise is important. Due to autonomic and cardiovascular
214 abnormalities in PD[2,22], the main hypothesis of this study was that patients with PD
215 would present altered responses during resistance exercise. The findings of the present
216 study support this hypothesis, as patients with PD presented blunted cardiovascular
217 responses during resistance exercise, regardless of the size of the active muscle mass.
218 Accordingly, peak values of absolute as well as increases in SBP and HR during
219 exercise were lower in the PD relative to the control group. These findings are in
220 agreement with other studies that have also reported blunted cardiovascular responses in
221 patients with PD during aerobic exercise[12,23].

222 The mechanisms responsible for the lower responses to resistance exercise in PD
223 were not assessed in the present study, and these mechanisms remain to be elucidated.
224 BP and HR increases during resistance exercise have been attributed to the stimulation
225 of central and peripheral regulatory mechanisms (central command, mechanoreflex and
226 metaboreflex) that deactivate cardiac vagal activity and stimulate cardiac and peripheral
227 sympathetic activities[24,25]. Thus, it is possible that the autonomic dysfunction
228 typically present in PD, which is mainly characterized by sympathetic

229 dysfunction[9], could be responsible for the blunted HR and SBP increases observed in
230 the present study. Accordingly, Haensch et al.[9] showed the presence of cardiovascular
231 dysfunction in PD with loss of sympathetic innervation to the heart and an associated
232 reduction in sympathetic release of norepinephrine in response to a stimulus[14]. As
233 norepinephrine increases HR, peripheral vascular resistance and BP[26], it is reasonable
234 to suggest that sympathetic activation during resistance exercise may be blunted in
235 patients with PD, mitigating HR and BP increases. Similar findings have been reported
236 in other similar neurodegenerative disorders with autonomic dysfunction (e.g., Multiple
237 System Atrophy, Pure Autonomic Failure)[2,27].

238 The present data do not support the hypothesis that activating a larger muscle
239 mass during resistance exercise results in a greater blunting of SBP and HR increases in
240 PD. This response suggests that the consequences of blunted sympathetic activation is
241 likely to occur even with the recruitment of a small muscle mass. In fact, even with a
242 weak sympathetic stimulus, such as a head-up tilt test, many patients with PD show
243 large decreases in BP, reflecting the blunted capacity to increase sympathetic
244 activity[28].

245 It is interesting to observe that the SBP increase during resistance exercise was
246 higher during the larger relative to the smaller muscle mass, while HR increased
247 similarly in both exercise types. This result is similar to others[10], but needs to be
248 explained. The increment in BP during resistance exercise is partially promoted by the
249 mechanical obstruction of blood flow around the contracting muscle, which is doubled
250 in bilateral exercise[10]. In addition, the contraction of a greater muscle mass enhances
251 mechanoreflex and metaboreflex stimuli[10,29]. All these mechanisms may explain the
252 greater increase in SBP during the bilateral exercise. On the other hand, the increment in
253 HR during resistance exercise is mainly attributed to the central command reduction in

254 vagal activity[24,25], which may not differ so much between bilateral and unilateral
255 resistance exercise. In addition, the HR increase may be partially blunted by baroreflex
256 stimulation due to the increase in BP during exercise, and this blunted response might
257 be greater with a greater muscle mass since the BP increase was higher with bilateral
258 resistance exercise. The balance among these mechanisms might explain the absence of
259 a greater increase in HR during bilateral compared to than unilateral exercise.

260 A similar explanation might be responsible for the fact that the SBP, but not the
261 HR, increase was higher in the second than in the first set of resistance exercise. During
262 resistance exercise, central command, mechano and metaboreflexes are progressively
263 activated throughout the repetitions within each set due to the increase in fatigue and
264 metabolite accumulation[24,25], which explains the increase in SBP from S1 to S2.
265 Once more, the higher increase in SBP might produce a greater stimulus for baroreflex
266 activation, therefore blunting an assumed greater increase in HR in the second set.

267 Resistance training is recommended for patients with PD for improving
268 muscular and motor functions[21]. In addition, in a previous study, we reported that
269 resistance training produces cardiac autonomic benefits in this population[7]. However,
270 as a huge and sharp increase of BP is usually observed during the execution of
271 resistance exercise [10], there is some concern among physicians regarding the
272 possibility of occurrence of acute cardiovascular events (e.g. a stroke or sudden death)
273 during the execution of this type of exercise in clinical populations that have high
274 cardiovascular risk [30], including patients with PD. Thus, the main clinical implication
275 of the present study is the demystification of the possible acute cardiovascular risk of
276 executing resistance training in patients with PD. As the present results showed that BP
277 and HR presented smaller increases during resistance exercise execution in patients with
278 PD than in control subjects, and no adverse effect has been observed during the

279 experimental protocol (e.g., dizziness, fainting or marked falls in BP or HR), the present
280 study supports that resistance exercise is safe and well tolerated for patients with PD
281 from a cardiovascular point of view; supporting its recommendation for this population.
282 However, it is also important to note that despite the lower BP and HR increases during
283 resistance exercise, patients with PD still have greater increases in BP and HR when
284 larger muscle masses were employed and when exercise is performed with more sets;
285 which should be considered when designing a resistance training protocol for this
286 population.

287 This study presents some limitations. As the study design required subjects to be
288 able to perform resistance exercise without external help, only patients in stages 2 and 3
289 of the modified Hoehn and Yahr scale were able to participate. In addition, as the aim of
290 the present study was to investigate cardiovascular responses in PD without the
291 influence of other diseases, the participants did not present with hypertension or any
292 other cardiovascular disease. However, it is usual to detect cardiovascular disease in
293 patients with PD in different stages of the disease. These patients might have greater
294 dysautonomia and respond differently to resistance exercise. Future studies are required
295 to understand cardiovascular responses to resistance exercise in patients with Parkinson
296 and cardiovascular disease and varying levels of dysautonomia. Regarding usage of PD
297 medication, patients were taking different drugs and doses, which did not allow the
298 determination of the effects of each PD medication but it does increase the external
299 validity of the present results as patients with PD regularly take different
300 pharmacotherapies. Considering the exercise protocol, this study employed only one
301 dynamic resistance exercise performed with one or two legs; and used two sets of 10-12
302 repetitions. The magnitude of cardiovascular responses might be different with different
303 exercises, volumes and intensities. However, it is unlikely that modifications in the

304 exercise protocol would eliminate the differences in cardiovascular responses observed
305 between subjects with and without PD.

306

307 **Conclusions**

308 Patients with PD present blunted SBP and HR increases during resistance
309 exercise in comparison with healthy subjects, showing that this type of exercise is safe
310 and well tolerated for patients with PD from a cardiovascular point of view and
311 supporting its recommendation for this population.

312

313

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318

319

320 **CONFLICT OF INTEREST**

321 The authors declare no conflicts of interest

322

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432 **Figure legends**

433 **Figure 1:** Experimental Protocol. HR = Heart Rate, SBP = Systolic Blood Pressure, RM

434 = maximal repetition

435

436 **Figure 2:** Systolic blood pressure (SBP, panels A and C) and heart rate (HR, panels B
437 and D) measured before (pre) and during the first set (S1), the interval (INT) and the
438 second set (S2) of the unilateral (panels A and B) and the bilateral (panels C and D)
439 knee extension exercise in Parkinson disease patients (PD, dotted lines with circles) and
440 control subjects (CONTROL, solid line with triangles). Data are shown as mean \pm SE. †
441 significantly different from PD ($P < .05$). ‡ significantly different from pre ($P < .05$).

442

443

444 **Figure 3:** Systolic blood pressure (Δ SBP, panel A) and heart rate (Δ HR, panel B)
445 increases during the first (S1) and second (S2) sets of the unilateral (UNI) and bilateral
446 (BI) knee extension exercises in patients with Parkinson disease (PD) and control
447 subjects (CONTROL). Results of group, exercise and set main effects. Data is presented
448 as mean \pm SE. [] Main effect of ANOVA. † Different from PD group. ‡ Different from
449 S1. § Different from unilateral

450

451

452 Table 1. Characteristics of the patients with Parkinson disease (PD) and the control
453 subjects.

454 BMI – Body mass index, SBP – systolic blood pressure, DBP– diastolic blood pressure,
455 HR- heart rate, RM – repetition maximum, H&Y – modified Hoehn-Yahr stage. Data =
456 mean \pm SE.

457

Table 1. Characteristics of the patients with Parkinson disease (PD) and the control subjects.

	PD	CONTROL	P
N	13	13	
Age (years)	62.7±1.3	66.2±2.0	.16
Gender (F/M)	9/4	7/6	.42
BMI (kg/m ²)	25.9 ±1.1	25.6±1.0	.86
SBP (mmHg)	119.0±3.1	122.7±1.8	.33
DBP (mmHg)	79.8±1.8	81.7±1.3	.41
HR (bpm)	69.7±1.4	69.4±2.3	.89
Workload 10-12 RM BI (kg)	36.1±3.5	36.9±2.9	.86
Workload 10-12 RM UNI (kg)	18.8±1.7	20.7±1.4	.40
H & Y 2/2.5/3 (n)	4/6/3	-----	-----

BMI – Body mass index, SBP – systolic blood pressure, DBP– diastolic blood pressure, HR- heart rate, RM – repetition maximum, H&Y – modified Hoehn-Yahr stage. Data = mean ± SE.

Figure 2
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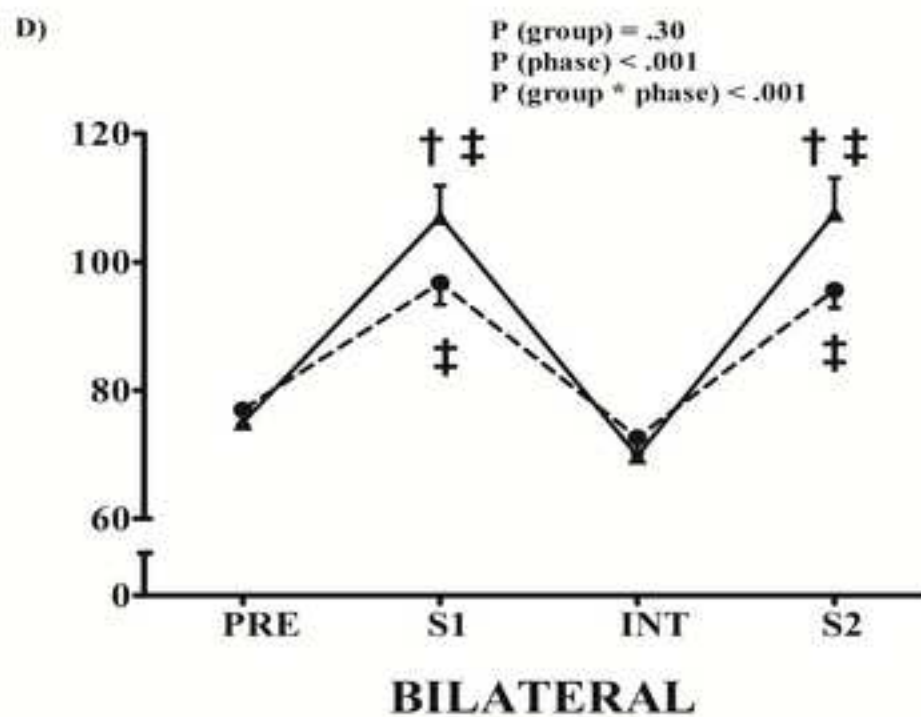
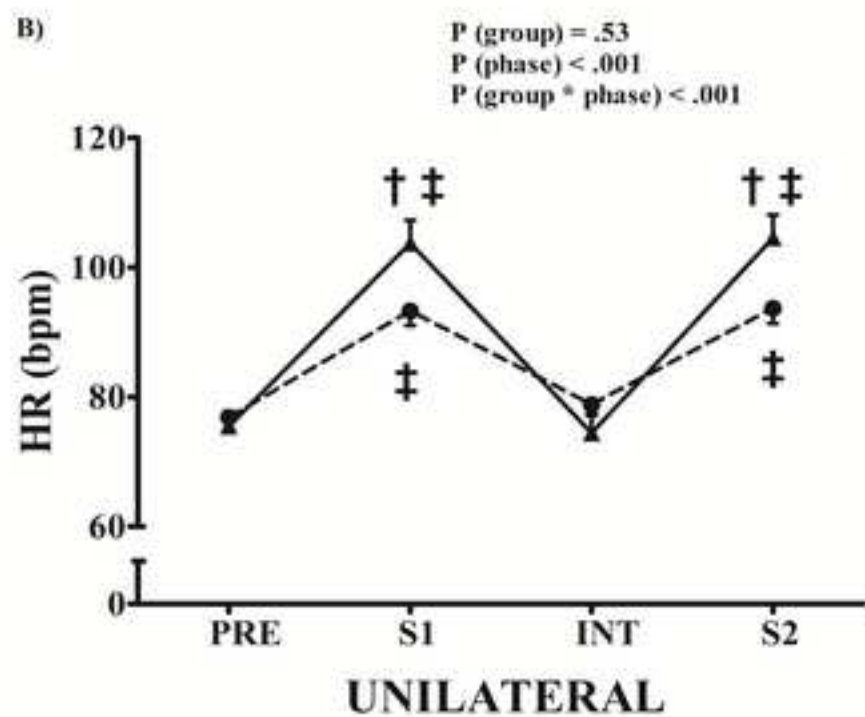
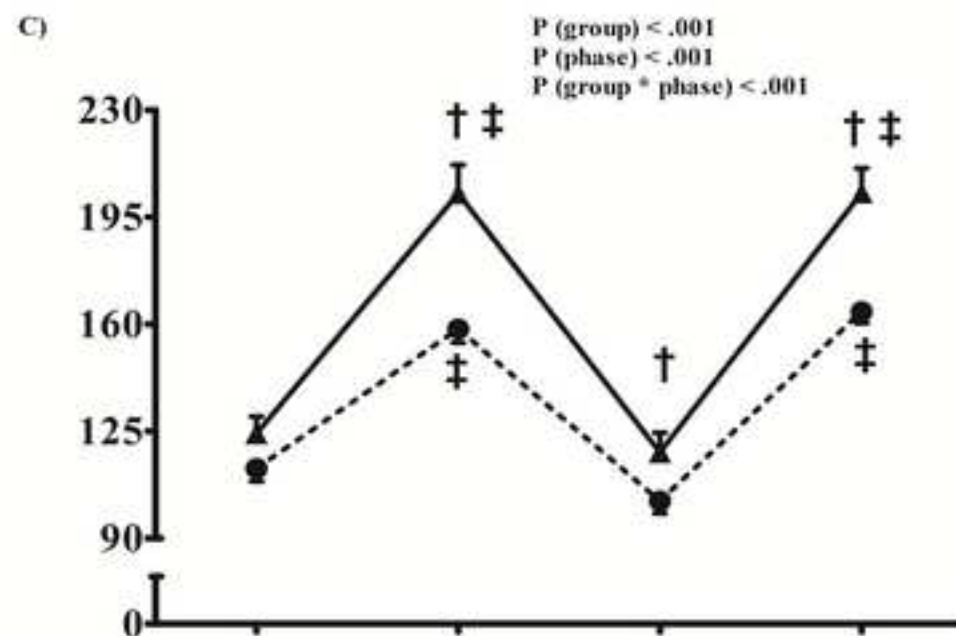
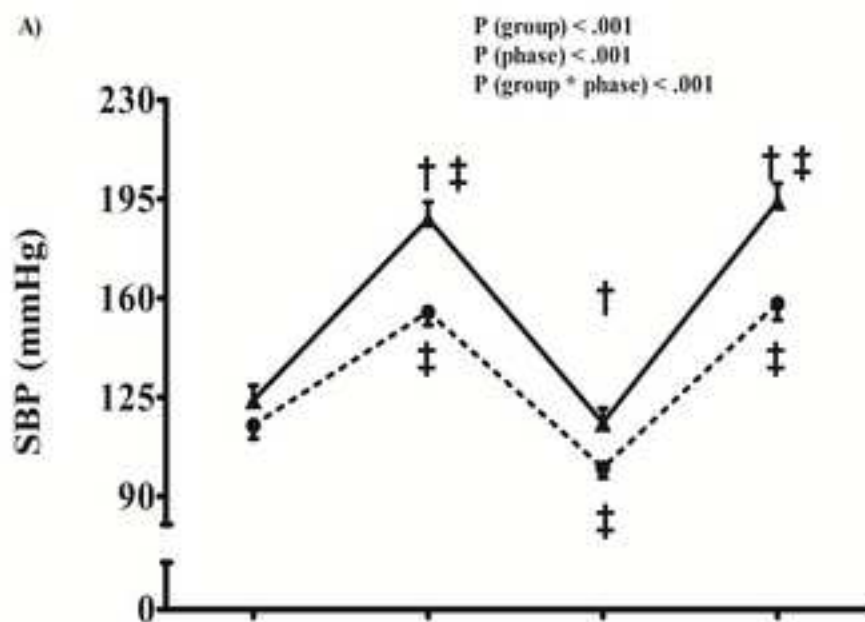


Figure 3
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