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

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Abstract

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

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

Design: Two groups, repeated-measures design.

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

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

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

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

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

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

Level of evidence: II

INTRODUCTION

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

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

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

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

METHODS

Experimental Design

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

Subjects

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

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

Procedures and Instrumentation

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

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

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

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

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

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

Statistical Analyses

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

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

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

RESULTS

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

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

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

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

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

DISCUSSION

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

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

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

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

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

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

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

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

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

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

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

Conclusions

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

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CONFLICT OF INTEREST

The authors declare no conflicts of interest

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Figure legends

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

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 ± SE. †
441 significantly different from PD (P<.05). ‡ significantly different from pre (P<.05).
442
443

444 **Figure 3:** Systolic blood pressure (ΔSBP, panel A) and heart rate (ΔHR, 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 ± 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 ± SE.
457

Table

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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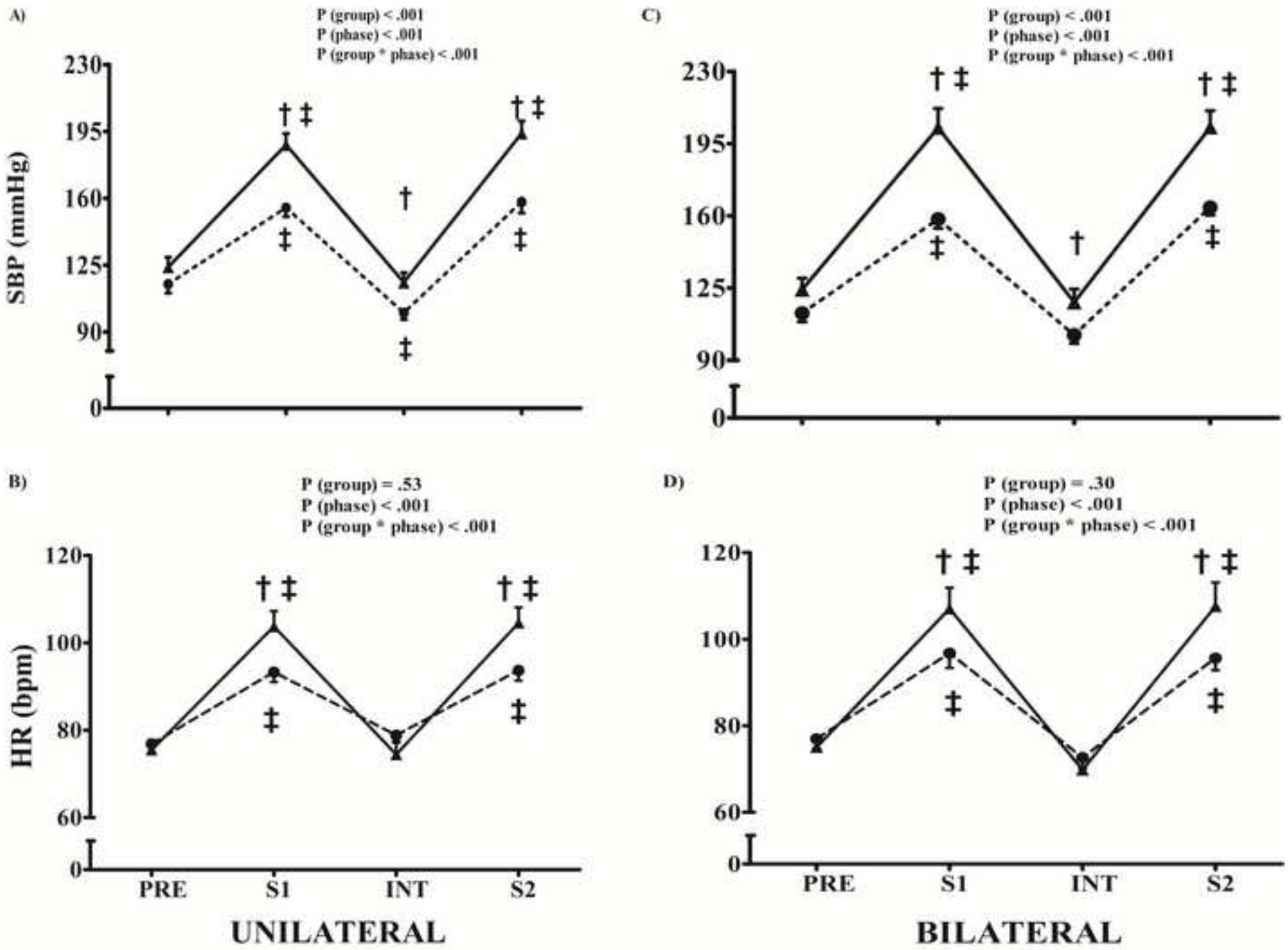

Figure 3

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