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ORIGINAL ARTICLE

# Effects of different postures on the hemodynamics and cardiovascular autonomic control responses to exercise in postural orthostatic tachycardia syndrome

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## Abstract

**Purpose** To assess the effects of two different body positions on the cardiovascular autonomic profile during a single bout of exercise in patients with postural orthostatic tachycardia syndrome (POTS).

**Methods** Thirteen patients with POTS and thirteen healthy controls (C) participated in the study. ECG, respiration, beat-by-beat arterial pressure and $O_2$ consumption ($V$O2) were continuously recorded while on a cycle ergometer in supine and upright positions, before and during exercise (6 min, 50 Watts). Spectral analysis of RR intervals and systolic arterial pressure (SAP) variability provided indexes of cardiac sympathovagal interaction (LF/HF ratio), cardiac vagal modulation ($HF_{RR}$, high-frequency component of RR variability, ~ 0.25 Hz), sympathetic vasomotor control ($LF_{SAP}$, low-frequency component of SAP variability, 0.1 Hz) and baroreflex sensitivity (BRS, $\alpha_{LF}$).

**Results** While supine, patients with POTS showed lower $HF_{RR}$ and $\alpha_{LF}$, greater heart rate (HR), LF/HF and $LF_{SAP}$, compared with C, suggesting cardiovascular sympathetic over-activity and reduced BRS. While sitting upright, POTS showed greater HR and reduced $HF_{RR}$ and $\alpha_{LF}$ compared with C. During supine exercise, SAP, HR, LF/HF increased and $HF_{RR}$ and $\alpha_{LF}$ decreased similarly in POTS and C. In POTS, upright sitting exercise was associated with slightly higher $\dot{V}O_2$, a greater increase in HR whereas $LF_{SAP}$ was lower than in C.

**Conclusion** Upright exercise was associated with excessive enhancement of HR and a blunted increase of the sympathetic vasomotor control in POTS. Conversely, supine exercise-induced hemodynamic and autonomic changes similar in POTS and C, thus making supine exercise potentially more suitable for physical rehabilitation in POTS.

**Keywords** Autonomic nervous system · Baroreflex · Posture · Orthostatic intolerance · Exercise

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### Abbreviations

| | |
|---|---|
| ANOVA | Analysis of variance |
| BMI | Body mass index |
| BP | Blood pressure |
| BRS | Baroreflex sensitivity |
| C | Controls |
| DP | Double product |
| ECG | Electrocardiogram |
| HF | High frequency |
| HR | Heart rate |
| LF | Low frequency |
| PAF | Pure autonomic failure |
| POTS | Postural orthostatic tachycardia syndrome |
| RR interval | Interval between two consecutive R waves of the ECG |
| SAP | Systolic arterial pressure |
| VO2peak | Oxygen uptake at the peak of exercise |

## Introduction

Postural orthostatic tachycardia syndrome (POTS) is characterized by excessive tachycardia upon standing (≥ 30 beats/min within 10 min of the upright position) in the absence of orthostatic hypotension (Brignole et al. 2018; Goldberger et al. 2019; Lambert and Lambert 2014). In addition, a subset of these patients, named "hyperadrenergic", presents symptoms and physical signs of reduced cardiac vagal modulation and exceeding cardiac sympathetic activity particularly in the upright posture (Furlan et al. 1998, 2000). These orthostatic symptoms include palpitation, chest pain, dyspnea and dizziness that concur in reducing exercise tolerance (Lambert and Lambert 2014; Low et al. 2009; Parsaik et al. 2012; Shibata et al. 2012). In turn, this leads to progressive physical deconditioning, resulting in substantial morbidity and reduced quality of life and work capability (Barbic et al. 2020; Dipaola et al. 2020).

Given such abnormal sympathetic nervous activity and reactivity in POTS (Lambert and Lambert 2014), physical reconditioning aimed at increasing exercise capability and consequent cardiac vagal modulation represents a crucial part of the therapeutic strategy (Fu et al. 2011). Indeed, a mild to moderate exercise training program has been found to increase orthostatic tolerance in POTS patients (Fu and Levine 2015). Fu et al. (Fu et al. 2010, 2011) showed that a 3-month exercise training program in a semi-recumbent posture, increased maximal oxygen consumption ($VO_{2peak}$), left ventricular mass and end-diastolic volume, resulting in a significant increase in physical fitness and reduced cardiac remodeling. In addition, the regular physical exercise proved to increase blood volume (Fu et al. 2010, 2011; Saltin et al. 1968; Shibata et al. 2012), enhance vagal control of the sinus node (Shibata et al. 2012) and improve baroreflex sensitivity (BRS) (Galbreath et al. 2011), all of which eventually contribute to an enhancement in orthostatic tolerance (Dorfman et al. 2007) in POTS patients. However, adherence to physical exercise is hardly achieved by the vast majority of POTS patients who often complain of unbearable worsening of orthostatic symptoms during exercise (Schondorf and Low 1993). Therefore, identifying the most favorable conditions likely to optimize hemodynamics and, consequently, the adherence to exercise-based rehabilitative programs, may be clinically relevant in POTS.

The present study aimed to assess the effects of two different body positions on the cardiovascular autonomic profile during a single bout of exercise in POTS patients. Our working hypothesis was that exercising in a supine position would provide POTS patients with a more favorable condition than sitting upright position in terms of resulting hemodynamics and autonomic changes during exercise.

## Material and methods

### Populations

Thirteen patients with POTS (12 women, 1 man) and 13 healthy control participants (12 women, 1 man), matched for age, sex and body mass index (BMI) (see Table 1) took part in the study. Size of the groups are in line with those that allowed the characterization of the response of the POTS cardiovascular control to the orthostatic stressor (Furlan et al. 2000). All participants refrained from performing any medium–high intensity physical exercise for at least 48 h before the study. The participants with regular menstrual cycles (28 ± 2 days) were assessed during the follicular phase, i.e., 7–10 days after the start of menses.

**Table 1** Demographic and hemodynamic parameters at rest of controls and postural orthostatic tachycardia syndrome (POTS) group

| | Controls ($n = 13$) | POTS ($n = 13$) |
|---|---|---|
| Age (years) | 25 ± 2 | 27 ± 8 |
| Female/Male $n$ (%) | 12/1 (92/8) | 12/1 (92/8) |
| Hyperadrenergic phenotype $n$ (%) | 0 | 5 (38%) |
| BMI (Kg/m$^2$) | 20 ± 2 | 20 ± 3 |
| HR (bpm) | 74 ± 12 | 88 ± 14* |
| SAP (mmHg) | 112 ± 11 | 116 ± 15 |
| DAP (mmHg) | 64 ± 6 | 66 ± 10 |

Data are presented as mean ± SD

*BMI* indicates body mass index, *HR* Heart rate, *SAP* systolic arterial pressure, *DAP* diastolic arterial pressure

*$p < 0.01$

Patients underwent a complete medical evaluation to exclude secondary causes of orthostatic intolerance. Drug treatment was discontinued for at least 10 days before the study. Patients were considered as POTS (Brignole et al. 2018; Goldberger et al. 2019) if they had: (1) sustained increase of heart rate (HR) of at least 30 bpm or HR ≥ 120 bpm during active standing; (2) absence of orthostatic hypotension (falls in systolic/diastolic blood pressure (BP) during standing ≤ 20 mmHg); (3) duration of symptoms longer than 6 months, and (4) daily occurrence of at least 2 of the following orthostatic symptoms: palpitations, dizziness, fatigue, lightheadedness, presyncope or syncope during upright posture. 38% of the patients with POTS had values of $HF_{RR}$ lower than 200 $ms^2$, which could reflect a POTS sub-group with a hyperadrenergic phenotype (Diedrich et al. 2018, 2021). Participants of both groups were excluded if they presented any cardiovascular, respiratory, metabolic or neurologic diseases, were smokers, engaged in any regular physical activity in the last three months, or reported to be drug abusers. In addition, only participants with white-collar jobs were included in both groups. This made the two populations habitual daily physical activities roughly similar.

All the subjects gave their written informed consent. The study was approved by the Ethics Committee of Geneva University Hospital (dossier CER: 12–263, 2013). Studies were carried out in the Laboratory of Clinical Physiology of Geneva Medical School. Data was analyzed at Humanitas University, Rozzano, Italy.

## Instrumentation procedure and exercise protocol

Electrocardiogram (Elmed ETM 2000; Heiligenhaus, Germany) and noninvasive finger BP (Portapres, TNO, Eindhoven, Netherlands) were continuously recorded during the study protocol. The BP signal was calibrated at each session using a mercury column sphygmomanometer. Signals were recorded during the entire procedure, digitized by a 16-channel A/D converter (model MP 100; Biopac Systems, Santa Barbara, CA) and stored on a computer. The acquisition rate was 1000 Hz per channel. The order of exercise postures was randomized. Participants were instructed to remain in the supine or sitting upright resting position without moving or speaking for 10 min to fully adapt to that position. Participants were then asked to perform 6 min of exercise on an electrically braked cycle ergometer at 50W, a workload previously shown to be well tolerated in a prior study (Masuki et al. 2007). In upright posture, subjects exercised on an ordinary electrically braked cycle ergometer (Ergometrics 800S, Ergoline, Bitz, Germany). In supine posture, an electrically braked arm-cycle ergometer (Ergoselect 400, Ergoline, Bitz, Germany), modified for leg pedaling supine, was used. Subjects wore race cycling shoes, allowing fixation of their feet to the pedals. The pedaling frequency was maintained between 60 and 80 rpm. After the first exercise session, participants were instructed to rest for at least 30 min and perform the second exercise session when they felt fully recovered.

## Power spectral analysis of RR interval and systolic arterial pressure variability

The methods for extraction of the RR interval (i.e. time between two consecutive R waves from ECG) and systolic arterial pressure (SAP) time series have been previously described (Porta et al. 2014; Zamuner et al. 2015). Sequences of 256 consecutive beats were considered for both hemodynamics and cardiovascular parameters analyses and were selected within the supine and sitting upright rest and exercise conditions. HR variability power spectral analysis provides two main oscillatory components: the high-frequency component (HF, at the respiratory rate), an index of the vagal efferent modulation to the heart and the low frequency (LF, about 0.1 Hz) component. The latter, when expressed in normalized units, may reflect the sympathetic efferent modulation to the heart and its changes (Barbic et al. 2007). $LF_{RR}/HF_{RR}$ ratio, a dimensionless index, assesses the reciprocal modifications of the sympathetic and vagal modulation to the sino-atrial node discharge (Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996). The LF oscillatory component of SAP variability ($LF_{SAP}$) is expressed in absolute values and is a recognized index of sympathetic vasomotor control (Malliani et al. 1991; Pagani et al. 1986).

## Baroreflex sensitivity (BRS)

BRS was estimated in the frequency domain by the $\alpha_{LF}$ index. This marker was computed as the square root of the ratio between the powers of $LF_{RR}$ and $LF_{SAP}$ (Pagani et al. 1988; Porta et al. 2013). For a reliable estimation of BRS, cross-spectral phase values $[Ph_{RR\text{-}SAP}(LF)] < 0$ and coherence between SAP and RR $[K^2_{SAP\text{-}RR}(LF)] > 0.5$ were considered as crucial prerequisites, as described by Pagani et al. (Pagani et al. 1988).

## Statistics

Data distribution and variance homogeneity were evaluated using the Shapiro–Wilk normality test and Levene's test, respectively. A mixed two-way analysis of variance (ANOVA) followed by Bonferroni's post hoc test were applied to assess group (POTS x controls) and posture (Supine x Upright) interactions regarding the Double

Product variable. The other variables did not meet the criteria for the parametric test; therefore between-group (POTS x controls) comparisons were obtained by the Mann–Whitney and within-group comparisons (Supine x Upright) were performed using the Wilcoxon test with a priori Bonferroni's correction. Analyses were performed using SPSS software, version 20.0. The significance level was set at 5%.

## Results

### Baseline characteristics

Age, BMI, SAP and DAP were similar in POTS and controls in the supine posture. Patients with POTS had greater HR values than the controls when supine ($p = 0.01$) (Table 1), as expected.

### Resting condition: POTS vs controls (between group comparisons)

Before exercise, while in supine posture, POTS patients had lower $HF_{RR}$nu ($p = 0.003$), $HF_{RR}$ ($p = 0.01$) and greater $LF_{RR}$nu ($p = 0.01$), $LF_{RR}/HF_{RR}$ ($p = 0.03$) and $LF_{SAP}$ ($p = 0.02$) compared to controls ($p < 0.05$), suggesting lower vagal modulation to the heart, and higher overall cardiovascular sympathetic drive (Table 2). $\alpha_{LF}$ was lower in POTS than in controls ($p = 0.02$), suggesting a lower cardiac BRS in POTS. In the sitting upright position, POTS patients showed a higher HR compared to controls ($p = 0.04$).

### Resting condition: supine vs sitting upright positions (within-group comparisons)

Compared to the supine position, the spectral indices of the cardiovascular autonomic profile increased similarly in POTS and controls when adopting the upright posture. On the other hand, $\alpha_{LF}$ index decreased ($p < 0.001$) only in controls (Table 2).

Regarding the HR*SAP double product (DP), no significant group*posture interaction was found (F = 0.02, $p = 0.88$). However, a significant main effect of posture was observed (F = 15.9, $p = 0.001$). Therefore, regardless of the group, the DP was significantly higher in the upright than in the supine sitting position (Table 2).

Furthermore, VO2 was higher in the upright position compared to the supine position only in the POTS group ($p < 0.05$), suggesting that the upright position imposes a greater metabolic demand on the POTS group than on the control group (Table 2).

### Exercising condition: POTS vs controls (between group comparisons)

During exercise in the supine posture, no significant differences were found between groups for any of the studied variables (Table 2). On the other hand, during exercise in the upright posture, POTS patients presented greater HR ($p = 0.04$) and lower $LF_{SAP}$ ($p = 0.05$) compared to controls (Table 2). Figure 1 illustrates an example of the HR response observed in a patient with POTS and a participant of the control group at supine and upright postures during exercise.

Regarding the DP, the two-way ANOVA showed a group main effect (F = 5.8, $p = 0.02$). Thus, regardless of the posture, POTS patients showed greater DP than controls (Table 2).

The VO2 data are shown in Tables 2. No significant differences in VO2 between POTS and controls were found during 50W exercise in both postures ($p > 0.05$).

### Effects of exercise on hemodynamics and cardiovascular autonomic control (within-group comparisons)

During supine exercise, compared to the resting supine condition, HR, SAP and $LF_{RR}/HF_{RR}$ significantly increased ($p < 0.05$; Table 2) while $HF_{RR}$ and $\alpha_{LF}$ decreased in both groups ($p < 0.05$; Table 2). Importantly, $LF_{SAP}$ ($mmHg^2$) significantly increased in both groups while exercising in a supine posture ($p < 0.05$, Table 2). However, during exercise in the sitting upright posture, $LF_{SAP}$ increased only in the control group, whereas remained unchanged in POTS patients compared to the resting condition (Table 2). Moreover, $LF_{SAP}$ during exercise significantly increased in the sitting upright posture in the control group, but not in the POTS group (Table 2). These results suggest an inability to properly activate sympathetic vasomotor control during the gravitational stimulus in the POTS group.

In addition, during exercise in the sitting upright posture (Table 2), HR, $LF_{RR}/HF_{RR}$ and SAP increased ($p < 0.05$) and $HF_{RR}$ (in $ms^2$) decreased in both groups ($p < 0.05$) compared to the supine position. Similarly, $\alpha_{LF}$ decreased in both groups ($p < 0.05$). No differences between postures were observed in both groups regarding the VO2 ($p > 0.05$).

### *Delta* changes in the cardiovascular autonomic control and hemodynamics (between group comparisons)

Cardiovascular autonomic indices delta changes from supine to exercise were calculated and compared between groups (Table 3). The POTS patients presented lower $\Delta\alpha LF$ than controls during supine ($p < 0.05$), which could be explained by the lower $\alpha LF$ at rest condition. In addition, $\Delta LF_{SAP}$

**Table 2** Hemodynamics, indices of autonomic activity, baroreflex sensitivity ($\alpha_{LF}$) and exercise functionality in Postural Orthostatic Tachycardia Syndrome (POTS) and control (C) groups while supine and in the sitting upright positions before exercise

| | Condition | Supine | | Sitting upright | |
|---|---|---|---|---|---|
| | | Controls | POTS | Controls | POTS |
| HR (bpm) | Rest | $74 \pm 12^{‡}$ | $88 \pm 14$ | $90 \pm 16^{§‡}$ | $104 \pm 17^{§}$ |
| | Exercise | $118 \pm 7^{\#}$ | $127 \pm 19^{\#}$ | $120 \pm 14^{\#‡}$ | $136 \pm 22^{\#†}$ |
| RR (ms) | Rest | $833 \pm 152^{‡}$ | $700 \pm 115$ | $685 \pm 138^{§‡}$ | $591 \pm 95^{§}$ |
| | Exercise | $512 \pm 33^{\#}$ | $482 \pm 73^{\#}$ | $504 \pm 60^{\#‡}$ | $449 \pm 64^{\#†}$ |
| $LF_{RR}$ ($ms^2$) | Rest | $928.1 \pm 1192.6$ | $488.3 \pm 625.5$ | $752.1 \pm 797.1$ | $624.4 \pm 620.8$ |
| | Exercise | $33.1 \pm 30.7^{\#}$ | $28.5 \pm 28.6^{\#}$ | $38.8 \pm 26.3^{\#}$ | $37.3 \pm 34.5^{\#}$ |
| $LF_{RR}$ (nu) | Rest | $35.4 \pm 13.0^{‡}$ | $53.3 \pm 21.5$ | $68.4 \pm 15.8^{§}$ | $65.9 \pm 19.1^{§}$ |
| | Exercise | $59.3 \pm 16.8$ | $63.1 \pm 22.0$ | $63.0 \pm 14.3$ | $59.1 \pm 22.6$ |
| $HF_{RR}$ ($ms^2$) | Rest | $1808.0 \pm 2418.3^{‡}$ | $480.0 \pm 649.7$ | $491.2 \pm 832.0^{§}$ | $318.5 \pm 342.9$ |
| | Exercise | $12.9 \pm 6.9^{\#}$ | $11.3 \pm 17.4^{\#}$ | $26.7 \pm 39.1^{\#}$ | $11.4 \pm 16.1^{\#}$ |
| $HF_{RR}$ (nu) | Rest | $58.6 \pm 16.4^{‡}$ | $37.1 \pm 16.7$ | $27.8 \pm 14.8^{§}$ | $26.6 \pm 11.7$ |
| | Exercise | $31.0 \pm 18.3$ | $22.4 \pm 10.6$ | $26.1 \pm 19.2$ | $22.3 \pm 18.7$ |
| $LF_{RR}/HF_{RR}$ | Rest | $0.7 \pm 0.4^{‡}$ | $1.9 \pm 2.0$ | $3.6 \pm 2.7^{§}$ | $3.3 \pm 2.4^{§}$ |
| | Exercise | $2.7 \pm 2.2^{\#}$ | $3.6 \pm 2.3^{\#}$ | $4.7 \pm 4.1^{\#}$ | $5.6 \pm 4.0^{\#}$ |
| SAP (mmHg) | Rest | $112 \pm 11$ | $116 \pm 15$ | $121 \pm 19^{§}$ | $130 \pm 13^{§}$ |
| | Exercise | $140 \pm 23^{\#}$ | $151 \pm 15^{\#}$ | $151 \pm 21^{\#}$ | $151 \pm 30^{\#}$ |
| $LF_{SAP}$ ($mmHg^2$) | Rest | $4.0 \pm 3.5^{‡}$ | $7.4 \pm 3.8$ | $11.5 \pm 9.0^{§}$ | $17.8 \pm 13.1^{§}$ |
| | Exercise | $8.6 \pm 8.1^{\#}$ | $10.2 \pm 3.0^{\#}$ | $19.8 \pm 15.6^{\#†‡}$ | $11.9 \pm 7.4$ |
| αLF (ms/mmHg) | Rest | $16.3 \pm 10.9^{‡}$ | $8.0 \pm 6.4$ | $8.5 \pm 6.8^{§}$ | $6.8 \pm 6.2$ |
| | Exercise | $2.4 \pm 1.8^{\#}$ | $1.4 \pm 0.8^{\#}$ | $1.8 \pm 1.0^{\#}$ | $1.8 \pm 1.3^{\#}$ |
| DP (mmHg*bpm) | Rest | $8322 \pm 551$ | $10{,}248 \pm 551$ | $11{,}028 \pm 733$ | $13{,}487 \pm 733$ |
| | Exercise | $16{,}479 \pm 905^{\#}$ | $19{,}271 \pm 905^{\#}$ | $18{,}333 \pm 1575^{\#}$ | $20{,}959 \pm 1575^{\#}$ |
| $\dot{V}O_2$($ml_* Kg^{-1}{}_* min^{-1}$) | Rest | $3.4 \pm 1.2$ | $3.4 \pm 0.8$ | $3.6 \pm 0.9^{§}$ | $3.9 \pm 0.5^{§}$ |
| | Exercise | $11.3 \pm 2.6^{\#}$ | $11.2 \pm 1.7^{\#}$ | $11.5 \pm 2.8^{\#}$ | $11.6 \pm 1.6^{\#}$ |

DP is a double product. DP indicates HR x SAP. $\dot{V}O_2$ is $O_2$ consumption at rest while supine and at 50W exercise

Data are expressed as mean ± SD

*RR* RR interval, $LF_{RR}$ low-frequency component of RR interval variability, *nu* normalized units, *HF* high-frequency component of RR variability, *LF/HF* ratio between the low and the high-frequency components of RR variability, *SAP* systolic arterial pressure, $LF_{SAP}$ low-frequency component of SAP variability, $\alpha_{LF}$ alpha index

§$p < 0.05$ supine vs upright

‡$p < 0.05$ vs POTS

#$p < 0.05$ vs Rest

during upright position was also lower in POTS patients than in control, corroborating the inability to properly activate sympathetic vasomotor control during the gravitational stimulus in the POTS group.

## Discussion

The main results of the current study were as follows: In POTS patients, as expected, the HR was higher and a cardiac sympathetic predominance was observed compared to healthy controls; 2) the sitting upright position was associated with enhanced cardiovascular sympathetic modulation and reduced cardiac vagal modulation in both groups compared with the supine position, with greater values of HR and greater increase in VO2 observed in POTS than in controls, corroborating the hypothesis that the upright posture imposes a greater metabolic demand for these patients; 3) supine exercise was characterized by similar hemodynamic and autonomic changes both in POTS and controls, compared with pre-exercise; 4) in POTS, sitting upright exercise was associated with a remarkable increase in HR and a blunted increase in $LF_{SAP}$ compared to controls. The latter observation suggests a potential inability to adequately activate sympathetic vasomotor control in POTS patients while exercising in the upright position.

The findings of the present study indicate that, when 50 W physical exercise is performed in the supine position, the

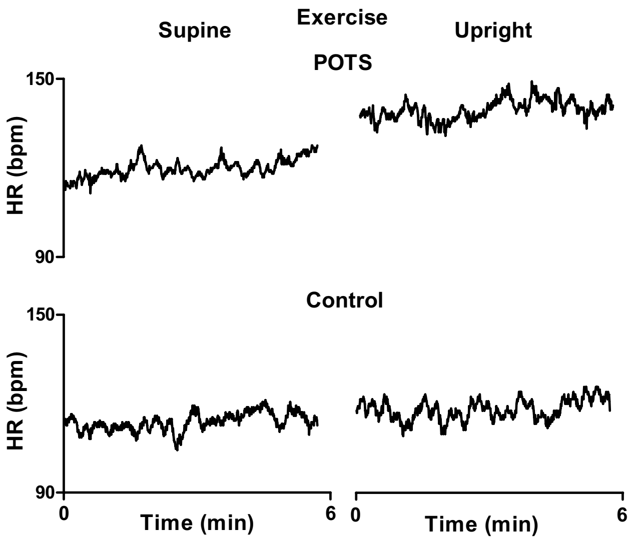


**Fig. 1** Representative example of the heart rate (HR) observed in a patient with postural orthostatic tachycardia syndrome (POTS) and a patient of the control group (control) at supine and upright postures during exercise. Notice during upright the exaggerated increase of HR in the POTS patient compared with the control subject

increase in SAP, HR, LF/HF and $LF_{SAP}$, and the reduction in $HF_{RR}$ and $\alpha_{LF}$ compared to pre-exercise, were similar in POTS and healthy individuals. The importance of the exercise position is further highlighted by the observation that even in a patient affected by pure autonomic failure (PAF), who likely has complete peripheral sympathetic denervation, cycling in the lying down position resulted in an increase in the time of exercise and in a double product that was as high as twice than that obtained during upright exercise (Costantino et al. 2011). In the current study, when comparing POTS and controls, the slightly different hemodynamics during supine exercise accounted for a slightly higher double product and $O_2$ consumption during lying down exercise in the POTS group. This finding points to a likely greater cardiovascular strain, possibly because of greater deconditioning to physical exercise, that POTS patients had to endure despite the same exercise load compared to healthy controls, even when lying down.

Another striking finding of the present study is that, compared to exercise carried out in the supine position, during exercise performed in the sitting upright posture POTS patients had a similar decrease in arterial baroreceptor control, but exhibited a greater HR and blunted increase of $LF_{SAP}$ than controls. In contrast, in healthy controls, modifications in hemodynamics, spectral parameters and BRS were similar during the two exercise protocols, suggesting that the body position was irrelevant in affecting their hemodynamics and autonomic profile at the same exercise intensity.

Overall these observations suggested the presence of discordant cardiac and vascular autonomic control in POTS during sitting upright physical activity, a finding mimicking what was previously described in this disorder during the upright position (Furlan et al. 1998) and in a POTS subgroup with legs neuropathy (Jacob et al. 2000). Several authors have reported exceedingly high HR values during exercise as

**Table 3** Hemodynamics, indices of autonomic activity and baroreflex sensitivity ($\alpha_{LF}$) changes from supine to exercise in Postural Orthostatic Tachycardia Syndrome (POTS) group and controls in supine and in the sitting upright positions

| | Δ Supine | | | Δ Upright | | |
|---|---|---|---|---|---|---|
| | Controls | POTS | *p*-value | Controls | POTS | *p*-value |
| HR (bpm) | 44 ± 11 | 39 ± 18 | 0.48 | 30 ± 12 | 33 ± 22 | 0.73 |
| RR (ms) | −321 ± 146 | −218 ± 111 | 0.05 | −182 ± 101 | −142 ± 81 | 0.28 |
| $LF_{RR}$ ($ms^2$) | −895 ± 1176 | −459 ± 628 | 0.25 | −713 ± 781 | −587 ± 617 | 0.65 |
| $LF_{RR}$ (nu) | 23.9 ± 19.5 | 9.8 ± 23.8 | 0.11 | −5.3 ± 19.7 | −6.8 ± 26.6 | 0.87 |
| $HF_{RR}$ ($ms^2$) | −1795 ± 2418 | −465 ± 650 | 0.08 | −464 ± 815 | −307 ± 333 | 0.53 |
| $HF_{RR}$ (nu) | −27.5 ± 25.5 | −14.7 ± 17.7 | 0.15 | −1.5 ± 20.7 | −4.3 ± 18.8 | 0.73 |
| $LF_{RR}/HF_{RR}$ | 2.0 ± 2.3 | 1.5 ± 1.8 | 0.48 | 1.1 ± 4.5 | 2.2 ± 4.2 | 0.53 |
| SAP (mmHg) | 27 ± 20 | 31 ± 19 | 0.61 | 30 ± 25 | 21 ± 27 | 0.26 |
| $LF_{SAP}$ ($mmHg^2$) | 4.6 ± 8.6 | 2.0 ± 5.3 | 0.72 | 8.3 ± 15.6 | −5.9 ± 16.7 | 0.01 |
| αLF (ms/mmHg) | −13.8 ± 10.5 | −6.6 ± 6.5 | 0.047 | −6.7 ± 6.4 | −5.0 ± 6.5 | 0.22 |

DP is a double product. DP indicates HR x SAP

Data are expressed as mean ± SD

*RR* RR interval, $LF_{RR}$ low-frequency component of RR interval variability, *nu* normalized units, *HF* high-frequency component of RR variability, *LF/HF* ratio between the low and the high-frequency components of RR variability, *SAP* systolic arterial pressure, $LF_{SAP}$ low-frequency component of SAP variability, $\alpha_{LF}$ alpha index

§$p < 0.05$ supine vs upright

‡$p < 0.05$ C vs POTS

#$p < 0.05$ vs Rest

well as during quiet standing in patients with POTS, hypothesizing the presence of relatively low cardiac output and stroke volume as possible underlying pathophysiological mechanisms (Fu et al. 2010; Fu et al. 2011; Masuki et al. 2007; Pianosi et al. 2016; Raj et al. 2005; Raj and Robertson 2007; Shibata et al. 2012). Stewart and Montgomery (Stewart and Montgomery 2004) reported that POTS patients exhibited inadequate peripheral vasoconstriction in both supine and upright postures, possibly as the consequence of cardiac atrophy and chronic hypovolemia (Kamiya et al. 2000; Levine et al. 2002). A blunted increase of the sympathetic neural transmission to the vessels, likely resulting in less effective sympathetic vasoconstriction, has also been described (Furlan et al. 2009), in keeping with our current finding of an insufficient increase of $LF_{SAP}$ during sitting up-right exercise. In the present study, the greater HR values observed during upright exercise in POTS patients compared with controls might reflect sympathetic compensatory mechanisms targeting the heart in the presence of an inability to properly activate the sympathetic vasomotor control during the sitting upright exercise. This is suggested by our finding of a blunted increase of $LF_{SAP}$ in POTS compared to controls during upright exercise, an observation that aligns with the presence of partial sympathetic denervation at the leg level, as previously described by Jacob et al. (Jacob et al. 2000).

An additional observation of the current study is that the decrease of the BRS during exercise, although diminished in a supine position due to a lower BRS at rest, was still preserved in the patients with POTS, suggesting that baroreflex mechanisms still maintain their functional integrity, as previously observed (Furlan et al. 1998). Furthermore, the double product during 50W cycling, a physiological index of the overall cardiovascular strain during exercise, was slightly greater in POTS than in controls. This pattern was also mirrored by VO2 values, which increased more in POTS than in controls, suggesting that the final energy expenditure for a similar workload (50W) was greater in POTS patients. It must be noted that adherence to exercise in this population is poor (George et al. 2016). Indeed, POTS patients usually complain of unbearable fatigue, lightheadedness, dizziness, palpitations, during upright posture daily activities (Schondorf and Low 1993). These symptoms tend to promote a sedentary lifestyle (Barbic et al. 2020; Dipaola et al. 2020), initiating a vicious cycle that exacerbates their physical and gravitational deconditioning. Therefore, physical re-conditioning represents a crucial part of the non-pharmacological therapeutic strategy (Brilla et al. 1998; Fu and Levine 2015; Mtinangi and Hainsworth 1998) in POTS. Physical exercise has proven to be effective in enhancing cardiac vagal modulation and arterial baroreflex function (Galbreath et al. 2011), decreasing cardiac sympathetic activity (Shibata et al. 2012), expanding blood volume (Saltin et al. 1968) and increasing cardiac size and mass (Dorfman et al. 2007), which were all abnormal in POTS. Therefore, as for clinical implications, this study suggests that exercising in supine posture could provide a better hemodynamic and physiological condition for patients with POTS to begin engaging in physical exercise programs. However, future randomized controlled trials should be performed to corroborate these results and to assess the long-term effects and adherence to supine exercise, especially when compared with traditional upright exercises such as cycling or treadmill walking.

The present study is not free from limitations. The sample size is limited, making it difficult to generalize the current results to all patients with POTS. In addition, based on reported habitual life habits, the physical activity carried out by the patients during their daily activities, including the work activity, was quite limited and similar between groups. However, quantitative differences in daily physical exercise levels between the two populations were not assessed. Finally, POTS is a disorder known to be characterized by a greater prevalence in female. Male and female participants in the current study might have had different cardiovascular responses to the postures and exercise. However, the cohort limited number did not allow us to carry out any robust gender-based sub-analyses, which could be addressed in future studies.

## Conclusions

Patients with POTS exhibited a cardiac autonomic profile consistent with sympathetic predominance while resting in a supine posture. Supine exercise was characterized by similar hemodynamic and autonomic changes in POTS and healthy individuals, whereas sitting upright exercise in POTS patients was associated with a remarkable increase in HR with blunted enhancement of sympathetic vascular modulation. The results of the present study might prompt physiotherapists and health professionals working with this population to prescribe supine or recumbent exercises instead of traditional upright exercises.

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**Authors contribution** GF and RF conceived and designed the study. CPA and ARZ contributed to the data extraction and analysis, statistical analysis and draft the manuscript. FB, NF and AB recruited the participants and performed the assessments. AP, SR and DS analyzed the data and contributed to the data interpretation. All authors contributed to the writing and reviewing of the manuscript and have read and approved the manuscript.

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## Declarations

**Conflict of interest** The authors have no competing interests to declare.

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