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# A Gender comparison of Cardiovascular Responses to Lower Body Negative Pressure Exposure

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**Abstract** The purpose of this study was to compare the LBNP tolerance between genders. Twenty healthy subjects (8 men, 12 women) were exposed to 10 min of 45mmHg LBNP. Baseline was taken in the sitting and supine positions. Finger blood pressure and heart rate (HR) were recorded continuously. Stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR) were calculated by a pulse contour method. Baseline cardiovascular variables were similar in all females, independently of the menstrual cycle phase and they were considered as one group. Seven of 8 men and 7 of 12 women completed the 10 min of LBNP. Non-finishers (n=6) increased heart rate, decreased systolic blood pressure, mean blood pressure, calculated SV and CO in comparison with the Finisher (n=14) group ($p<0.05$). Both groups, however, maintained TPR unchanged during the exposure to LBNP. This suggests the tolerance to LBNP is related to the capability of both avoiding too large a decrease in SV, and inducing an adequate vasoconstriction response.

***Keywords:*** *gender differences; menstrual cycle; LBNP tolerance; cardiovascular response*

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## 1. Introduction

Lower body negative pressure (LBNP) is the application of sub-atmospheric pressure to the lower portion of the body below the iliac crests. Independently of gravity, the negative pressure applied translocates blood and interstitial fluid to the lower body, stresses the cardiovascular system by reducing venous return and contributes to increase the vascular tone in the legs [8]. The application of LBNP partially reverses the headward shift of blood and body fluids occurring in microgravity, which may contribute to the reduction of cardiovascular deconditioning. Therefore, it has been successfully applied as a countermeasure during space flights [7] and also in ground-based microgravity simulation studies [8]. In fact, physical exercise performed in combination with the LBNP for 40 min, 6 days a week, is an effective way of maintaining maximal oxygen consumption after 30 days of bed rest [17].

It has also been used to detect changes in orthostatic tolerance after head-down bed rest studies [2], to predict the degree of post-flight orthostatic instability and to explore the underlying mechanisms after space flights [1].

Johnston et al. [11] were the first to report LBNP evidence of reduced orthostatic tolerance in-flight, which was demonstrated by an increase in heart rate and a decrease in blood pressure. LBNP has been used extensively over the last 25 years in investigations dealing with blood pressure control, since it can lower both central venous and arterial pressures. It has also been used in resting and in exercising subjects on bicycle ergometers or treadmills [12] and during isometric handgrip exercises [10].

Orthostatic tolerance is reported to be lower in women than in men [5], since women are more likely to become pre-syncopal after spaceflight than men. However, it does not necessarily occur after head-down tilt bed rest [19]. These authors suggest that post-flight pre-syncope being greatest in women can be ascribed to a combination of inherently low-resistance responses, a strong dependence on volume status and a relative hypoadrenergic response.

Differences in adrenergic responses at maximal LBNP exposure have also been thought to be responsible for the marked discrepancies between men and women in LBNP tolerance as central venous pressure, cardiovascular and baroreflex responses to graded LBNP are similar in men and women [5].

Convertino [3] found evidence partially opposing these findings, suggesting that women have less responsiveness in mechanisms that underlie blood pressure regulation under orthostatic challenge. In his experiments, lower LBNP tolerance in females was associated with reduced

baroreflex heart rate responsiveness and greater decline in cardiac output, with increased beta1-adrenoreceptor responsiveness and stronger vasoconstriction with lower levels of circulating norephinephrin at pre-syncope.

Another aspect is the usefulness of being able to predict tolerance to LBNP, as a low tolerance thereof is also associated with low orthostatic tolerance. Indeed, 40% of the variability in LBNP tolerance can be predicted by easy to measure variables, with the male gender, increased chronotropic response to LBNP, high resting total peripheral conductance, advanced age and lower body fat all being associated with increased tolerance to LBNP [20].

Fu et al. [6] found an adequate vascular response and concluded that decreased cardiac filling rather than reduced responsiveness of vascular resistance during orthostatic challenges might explain gender differences in LBNP tolerance. However, in a study conducted by Custaud et al. [4], no gender differences were shown in LBNP tolerance after head-down tilt bed rest. Their results suggest that there is an impaired vasoconstriction in women, but neither endocrine responses nor alterations in the cardiac baroreflex can fully explain gender differences in the responses to LBNP after head-down tilt bed rest.

It is clear that experimental results are contradictory and that the possible mechanisms involved in gender differences, if any, in LBNP tolerance are still a matter of discussion.

The present non-invasive study aimed at contributing to a better understanding of male and female cardiovascular responses to a 10 min exposure to 45 mmHg of lower body negative pressure. LBNP tolerance is discussed considering genders, the possible influence of menstrual cycle phases and the role of total peripheral resistance and cardiac output.

# 2. Methods

## 2.1. Subjects

Twenty subjects (12 women and 8 men) were studied. All subjects were non-smokers and healthy on the basis of medical history and physical examination, presenting normal ECG, resting arterial blood pressure < 140/90 mmHg and body mass index < 27 kg/m$^2$ during selection procedures. They had no history of lower limb venous insufficiency or intake of medications that could affect the autonomic nervous or cardiovascular systems. No women were pregnant and 9 of them were taking oral contraceptives. Female subjects were divided into two groups according to their menstrual cycle phase history (1$^{st}$ and 2$^{nd}$ phases), as no hormonal blood exams were performed.

The research protocol was approved by the Pontifical Catholic University of Rio Grande do Sul (PUCRS) Ethics and Scientific Research Committees. All subjects signed a consent form prior to the beginning of the experiment, which complied with the recommendations as set out in the declaration of Helsinki.

## 2.2. LBNP Box

The LBNP box used in this experiment was developed by the Microgravity Centre/PUCRS-Brazil in cooperation with the Institute of Aerospace Medicine, German Aerospace Centre/DLR. This LBNP box consists of five carbon steel ribs in the shape of a cylinder (length 124 cm x diameter 80 cm), with the ribs being wrapped in a transparent vinyl, highly resistant to pressure. There are neither ports nor windows in the vinyl cover structure. The front and back plates are made of carbon steel. The subject reclines to a horizontal position with legs out straight on a cushioned bed, mounted over a trolley system. Inner and outer-wheeled trolleys were developed to safely, comfortably, rapidly and easily move the subject in and out of the LBNP box. Before the beginning of the LBNP session, the subject was asked to wear a custom-made skirt designed to act as a waist seal. Airflow, negative pressure, temperature and humidity were continuously monitored and controlled during LBNP sessions [16].

## 2.3. Protocol

In preparation for the LBNP session, selected subjects were instructed to sleep 8 hours the night before the study, to drink an extra 1 L of water during the preceding day, and to refrain from drinking coffee and/or alcohol for at least 12 hours prior to the experiment. All tests were conducted in the morning and subjects were asked to have only a light breakfast.

A familiarization phase was conducted prior to the main study day. Subjects were placed inside the LBNP box to experience different negative pressure levels for a total of 6 min. The main study day began with the instrumentation of the subject, consisting of the placement of ECG electrodes and the Portapres$^{TM}$ finger cuff. The subject was subsequently asked to remain in a sitting position for 10 min. At the end of this period, the subject was placed in the LBNP box in the supine position for 20 min and a 2 mmHg negative pressure was applied for an additional 15 min. The box pressure was then decreased to - 45 mmHg for 10 min or until pre-syncope symptoms arose. A 5 min recovery period then followed with negative pressure inside the box at 2 mmHg.

Besides the medical evaluation of clinical signs and symptoms of pre-syncope, such as intense paleness accompanied by dizziness and sweating, the main criteria for determining LBNP tolerance were based on clearly defined changes in heart rate and blood pressure: 1) Mean blood pressure decrease either amounting to 40% of its supine value before intervention or its reaching an absolute value < 60 mmHg without an increase in heart rate within 10 s; 2) during the first minute of - 45 mmHg LBNP or reaching an absolute value < 50 bpm during more than 10 s; 4) a continuous, simultaneous decrease of both heart rate and mean arterial pressure, either for more than 15 s or until one of them reach the minimum levels reaching a heart rate > 70% of its theoretical maximum during more than 10 s; 3) decrease in heart rate either amounting to less than 50% of the values measured.

## 2.4. Measurements

Beat-by-beat values of systolic (SBP-P), diastolic (DBP-P), pulse (PBP-P), and mean (MBP-P) arterial pressures were derived from continuous recordings of finger arterial blood pressure (Portapres$^{TM}$), and heart rate was measured from a standard ECG. The signals were digitized (Biopac System®) and the physiological parameters extracted with custom software (PhysData®,

Synaptek, Bonn, Germany). Outliers were identified and eliminated from beat-to-beat time series. These were divided in one minute periods and reduced to one data point (mean value/minute).

Stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR) were calculated using the Wesseling et al. (1993) method (W), with PSA being the area under the systolic pressure curve, MBP-P being the finger mean blood pressure, HRT the heart rate and age being the age of the subject in years.

As a safety medical procedure, blood pressure (BP) was also measured manually by an oscillometric method (BOSO®) at predetermined intervals, and heart rate and heart rhythm were also continuously monitored by an independent ECG (Instramed®, Miniscope 1).

### 2.5. Statistical Analysis

Data was analyzed using the last 2 min at sitting position (control), 10 min in the supine position (baseline –2 mmHg), throughout the –45 mmHg pressure exposure and during the 5 min recovery period. The computer software used for the analysis was Statistica® Version 8, Stat Soft, Hamburg, Germany. The data is presented as mean (SD). The tests applied were ANOVA (repeated measures), Tukey HSD test, and t-test (independent, by groups). The level of significance used was $p \leq 0.05$.

## 3. Results

The male (n=8) and female (n=12) subject characteristics are presented in Table 1.

No significant difference was found between the two female groups, which consisted of the 1st (n=7) and 2nd (n=5) phases of the menstrual cycle, for all cardiovascular variables during sitting (control position) and baseline (supine position), except for a higher heart rate in the supine position in the 1st phase group.

The comparison between the male and female groups (Table 2) showed that women had a higher heart rate, calculated stroke volume and cardiac output for both sitting and supine positions. Systolic, diastolic and mean blood pressures were not significantly different. Men presented a higher calculated total peripheral resistance in both positions.

Men and women were then combined and further divided into two groups, Finishers (n=14, 7 men and 7 women) and Non-finishers (n=6, 1 man and 5 women) depending on the LBNP tolerance.

Figure 1 shows the results for the two groups, comparing mean values obtained during sitting (control), supine and end of LBNP exposure for all cardiovascular variables measured or calculated. Table 3 demonstrates the comparison between finishers and Non-finishers only in relation to the end of the 10 min exposure to –45 mmHg, since there were no significant differences between all the supine and sitting variables for the Finishers and Non-finishers groups.

**Table 1. Descriptive characteristics of subjects**

| **Measurement** | **Females** n=12 mean (SD) | **Males** n=8 mean (SD) | **P Value** |
|---|---|---|---|
| Age (yr) | 23.8 (2.7) | 22.8 (2.3) | 0.41 |
| Height (cm) | 163 (6.0) | 179 (7.0) | 0.0 |
| Weight (kg) | 59.2 (6.7) | 75.9 (7.3) | 0.0 |
| BMI (kg/m$^2$) | 22.3 (2.5) | 23.8 (1.7) | 0.003 |
| HR (bpm) | 88.7 (8.2) | 74.0 (11.3) | 0.87 |
| SBP (mmHg) | 123.3 (6.4) | 123.9 (10.1) | 0.49 |
| DBP (mmHg) | 77.6 (3.9) | 79.4 (7.5) | 0.17 |

**Table 2. Comparison between male and female groups during sitting (control) and supine (baseline) positions**

| Measurement | Male n=8 mean (SD) | Female n=12 ean (SD) | P Value |
|---|---|---|---|
| Sitting Position | | | |
| HR (bpm) | 73.2 (7.2) | 92.5 (11.0) | 0.0004 |
| SBP (mmHg) | 111.2 (12.8) | 117.1 (12.9) | 0.33 |
| DBP (mmHg) | 69.7 (8.1) | 71.4 (8.8) | 0.67 |
| MBP (mmHg) | 83.6 (9.5) | 86.6 (10.0) | 0.5 |
| SV-W (ml) | 56.9 (6.3) | 67.13 (13.2) | 0.05 |
| CO-W (l/min) | 4.2 (0.5) | 6.2 (1.3) | 0.00008 |
| TPR (dyne.s.cm$^{-5}$) | 1657.5 (316.8) | 1171.2 (118.4) | 0.0004 |
| Supine Position | | | |
| HR (bpm) | 61.9 (3.5) | 78.0 (9.0) | 0.00 |
| SBP (mmHg) | 111.9 (13.2) | 114.4 (9.8) | 0.63 |
| DBP (mmHg) | 62.2 (6.6) | 65.2 (9.9) | 0.46 |
| MBP (mmHg) | 78.8 (8.6) | 81.6 (9.1) | 0.50 |
| SV-W (ml) | 71.6 (6.8) | 79.7 (10.8) | 0.08 |
| CO-W (l/min) | 4.4 (0.5) | 6.1 (1.0) | 0.00 |
| TPR (dyne.s.cm$^{-5}$) | 1438.7 (131.3) | 1089.9 (183.9) | 0.00 |

**Table 3. Comparison between Finishers (F) and Non-finishers (NF) at the end of the LBNP session**

| Measurement | End of LBNP – F n=14 mean (SD) | End of LBNP – NF n=6 mean (SD) | P Value |
|---|---|---|---|
| HR (bpm) | 88.7 (16.6) | 110.8 (31.1) | 0.05 |
| SBP (mmHg) | 110.0 (16.8) | 83.0 (13.2) | 0.002 |
| DBP (mmHg) | 66.9 (12.9) | 53.8 (14.2) | 0.059 |
| MBP (mmHg) | 81.3 (13.7) | 64.0 (13.5) | 0.02 |
| SV-W (ml) | 61.0 (7.9) | 33.9 (5.9) | 0.000001 |
| CO-W (l/min) | 5.2 (1.0) | 3.7 (0.8) | 0.004 |
| TPR (dyne.s.cm$^{-5}$) | 1379.5 (342.1) | 1421.8 (145.2) | 0.78 |

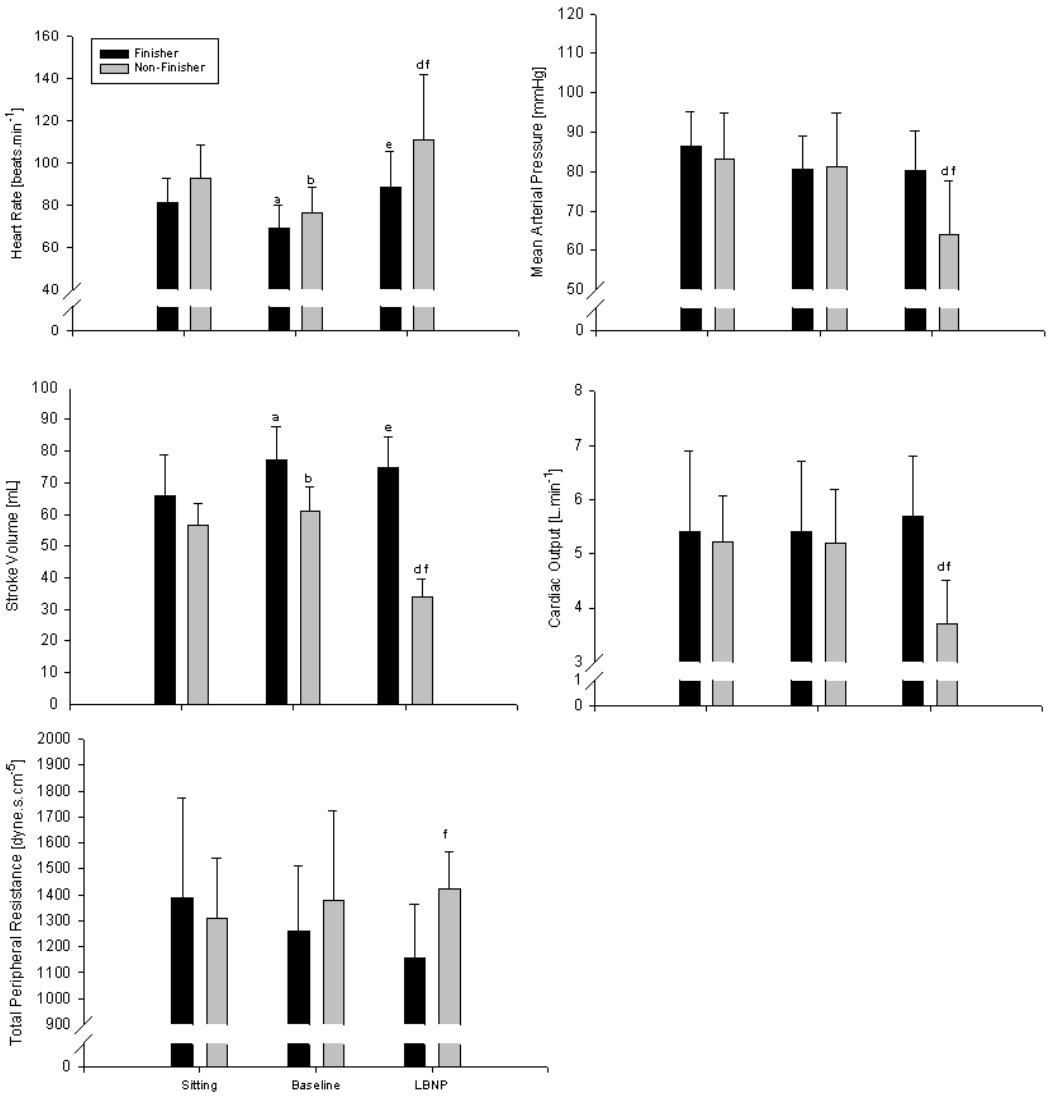


**Figure 1**. Finishers (F) and Non-finishers (NF): cardiovascular responses $p<0.05$: a = sitting vs. baseline (F); b = sitting vs. baseline (NF); c = sitting vs. LBNP (F); d = sitting vs. LBNP (NF); e = baseline vs. LBNP (F); f = baseline vs. LBNP (NF). Heart rate decreased from sitting to supine for Finishers ($p=0.02$) and Non-Finishers ($p=0.05$), and decreased at the end of the LBNP exposure only for the Non-Finishers ($p=0.02$). Heart rate increased at the end of LNBP exposure for Finishers ($p<0.01$) and Non-finishers ($p=0.01$).

Mean arterial blood pressure remained unchanged from sitting to supine in both groups. It also remained unchanged in the Finishers group when sitting and supine values were compared with the value obtained at the end of 10 min of –45 mmHg. The Non-finishers, however, presented a decrease from both sitting ($p=0.0$) and supine ($p=0.01$) to the end of the LBNP session.

Calculated SV increased from sitting to supine in both groups ($p<0.05$). It remained unchanged from sitting to the end of LBNP exposure for Finishers, but decreased for Non-finishers ($p=0.0$). It decreased in both groups from supine to the end of the LBNP session ($p<0.05$).

Calculated CO was unchanged from sitting to supine in both groups. However, it decreased only in the Non-finishers from sitting at the end of LBNP ($p<0.0001$).

Calculated TPR remained unchanged in both groups from sitting to supine mean. For the supine to the end LBNP session, mean values remained unchanged for the Finishers group, but increased for the Non-finishers ($p=0.01$).

All participants (n=20) fully recovered after LBNP exposure to the pre-experiment physiological data, regardless of being male or female and Finishers or Non-finishers.

**Table 4. Comparison between male Finishers (F) and female Finishers, and female Finishers and female Non-finishers (NF) in relation to cardiac output and total peripheral resistance during the three experimental conditions**

| Measurement | Male - F n=7 mean (SD) | Female - F n=7 mean (SD) | Female - NF n=5 mean (SD) | P Value female - F vs. male - F | P Value female -F vs. female - NF |
|---|---|---|---|---|---|
| CO-W (l/min) | | | | | |
| Sitting | 4.2 (0.5) | 6.6 (1.1) | 5.5 (0.6) | 0.003 | 0.32 |
| Supine | 4.5 (0.4) | 6.2 (1.2) | 6.2 (0.7) | 0.008 | 0.99 |
| End of LBNP | 4.4 (0.4) | 6.0 (0.8) | 3.9 (0.7) | 0.02 | 0.009 |
| TPR (dyne.s.cm$^{-5}$) | | | | | |
| Sitting | 1661.5 (341) | 1117.1 (172) | 1246.9 (186) | 0.009 | 0.86 |
| Supine | 1423.0 (133) | 1099.3 (237) | 1076.8 (88.6) | 0.24 | 0.99 |
| End of LBNP | 1537.4 (366) | 1221.7 (247) | 1403.1 (154) | 0.26 | 0.62 |

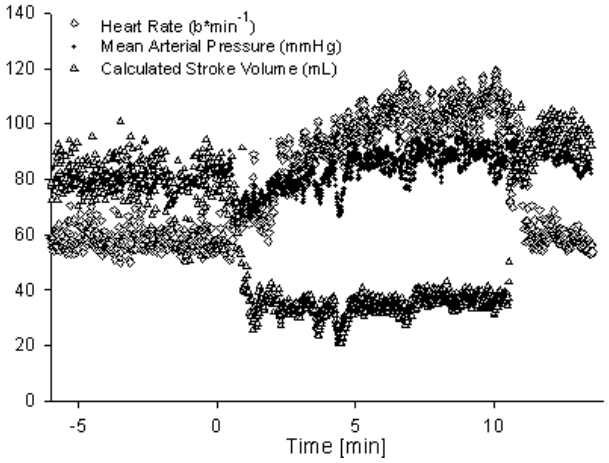


**Figure 2.** Hemodynamic response to 45 mmHg LBNP for a Finisher

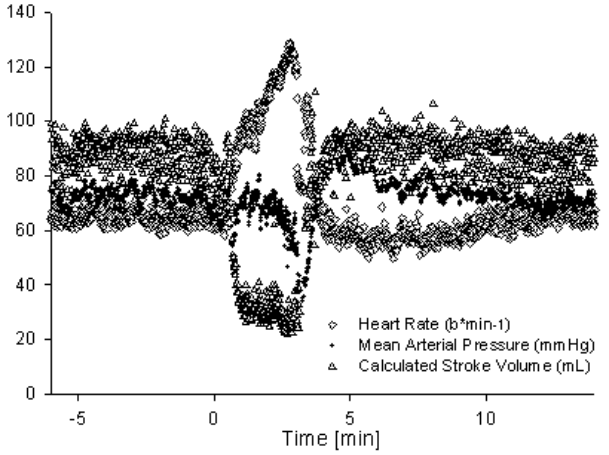


**Figure 3.** Hemodynamic response to 45 mmHg LBNP for a Non-finisher

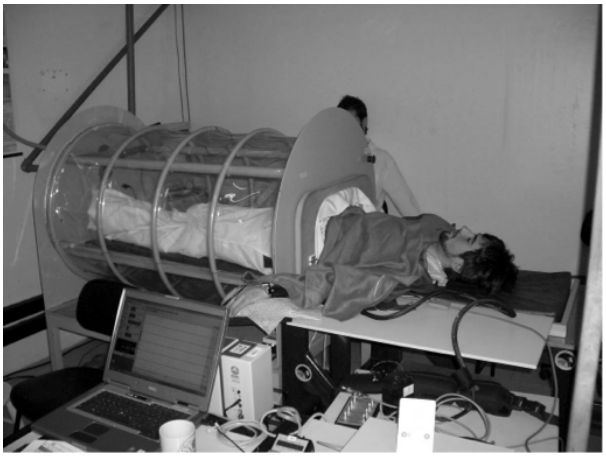

**Figure 4.** Male subject during LBNP exposure

# 4. Discussion

## 4.1. Female Responses

Gender differences in orthostatic tolerance have been described but the physiological mechanisms involved are still uncertain. It has been reported several times that women present greater susceptibility to orthostatic intolerance following spaceflight [3,6,18] and after head-down tilt experiments [4]. The present study addressed the issue of spontaneous tolerance by comparing the tolerance to –45 mmHg during 10 min between women and men. All participants were from the same age group and had no alterations in their cardiovascular baseline variables that were measured for selection purposes, with blood pressure and heart rate being within the normal range. Men were taller and heavier than women ($p<0.05$), and both groups had an adequate BMI for their age (Table 1).

It is known that the female hormones estrogen and progesterone affect several physiological variables that may alter orthostatic tolerance [14] and thus, the female group was initially divided into two groups, women in the 1st phase and the 2nd phase of the menstrual cycle. In the present study, no significant differences were found between the two female groups for all variables, except for a higher heart rate in the supine position in the 1st phase group (mean of 83.1 (5.9)) in relation to the 2nd phase group (mean of 70.9 (10.3)) ($p=0.03$). Heart rate is a cardiovascular variable that can be affected by many different factors, including stress, and based on this assumption we did not take it into account as it was an isolated finding. It was also corroborated by the fact that there was no difference in the heart rate measurement during the control period when the women's 1st and 2nd phases of menstrual cycle were considered. Therefore, the lack of difference between these two groups of women allowed us to merge them into one, referred to as the female group (n=12).

These findings are in accordance with the study from Meedering et al. [14] in which the influence of the menstrual cycle and gender on hemodynamic responses to combined orthostatic and heat stress was evaluated. They found that orthostatic intolerance in the heating remained unchanged regardless of menstrual cycle phases. Although they found a clear gender difference in orthostatic tolerance, they concluded that it was not attributable to fluctuating hormone profiles during the menstrual cycle.

When looking at Table 2, it is important to note that women - in contrast to our expectations - presented a higher heart rate, calculated stroke volume and cardiac output than men, which might indicate an emotional driven response to the experiment itself. Although all subjects were submitted to a familiarization protocol, the male group members for this study were more familiar with the equipment used and the physiological responses to a cardiovascular stress test than the female group members, in that most of the male subjects were professionally linked to the laboratory in which the experiment was conducted. It is believed that this has created a bias in the results as the male subjects were actually expected to have a higher stroke volume and cardiac output than the women. The calculation of the cardiac index corroborated these findings, since it was also higher in the female group than in the male during the 3 experimental conditions ($p<0.05$). However, these findings proved unimportant regarding the tolerance to the LBNP stress.

## 4.2. Male Responses

Total peripheral resistance was higher in the male group for both sitting ($p=0.01$) and supine positions than in the female group ($p=0.01$). It was possible to assume that it could provide a better tolerance to the 10 min exposure to -45 mmHg in male group. Men indeed coped better with the LBNP imposed cardiovascular stress, since 7 out of 8

finished the 10 min run, which contrasted with the results found in the women's group where 7 out of 12 completed the experiment. It demonstrated that there was a gender difference in the response to the LBNP stress, which seems to be independent of the menstrual cycle phase. These findings are in accordance with the literature [3,4,6,18].

In this regard, an important aspect that should be assessed more appropriately is whether there are differences between genders in the vasoconstrictor responses of the lower limbs during LBNP. Hachiya et al. [9] examined this issue and found that men have greater vasoconstrictor responses in the legs during gradual exposure to LBNP, judging from the greater slopes in oxygenated Hb at given blood pooling and at each negative pressure in the male subjects.

Additionally, venous compliance in the lower limbs and their gender differences need to be taken into account. Lower limb venous compliance significantly affects peripheral venous pooling during orthostatic stress, such that a high venous compliance can contribute to a reduced orthostatic tolerance. At rest, venous compliance in the legs appears to be lower in women than men and when they are exposed to LBNP, this variable appears to reduce in male subjects but not in females. It seems, therefore, that gender affects this variable both in situations of low sympathetic activity, such as when resting, as well as conditions of high sympathetic activity, as in LBNP. Nevertheless, these results do not explain the gender differences in orthostatic tolerance and, therefore, tolerance to LBNP [15].

## 4.3. LBNP Tolerance

With regards to LBNP tolerance, subjects in our study were divided into Finishers (F) and Non-finishers (NF). The Finishers group comprised of a total of 14 subjects that completed the experiment (7 out of 8 men or 87.5% and 7 out of 12 women or 58.3%), and the Non-finishers group had a total of 6 subjects who did not complete the 10 min of LBNP session (1 out of 8 men or 12.5% and 5 out of 12 women or 41.7%).

Heart rate decreased for both groups from sitting to supine, which is a typical physiological response to this postural change ($p<0.05$). It increased by 20 bpm from a mean of 70 bpm in the supine position to around 90 bpm by the end of the LBNP session for the Finishers group. However, this increase was much more pronounced in the Non-finishers ($p=0.05$), increasing from 76 bpm to 110 bpm (around 40 bpm) (Figure 1, Table 3).

Although mean blood pressure remained unchanged at the end of the LBNP exposure for the Finishers, it decreased for the Non-Finishers ($p=0.0$). The calculated stroke volume presented an expected response when subjects moved from sitting to supine position, increasing mean values for both groups ($p<0.05$). The Non-finishers group also showed a decrease in stroke volume from sitting to the end of LBNP test, which differs from the Finishers group whose SV remained unchanged. This already indicated a less effective physiological reaction of the Non-finishers to the cardiovascular stress. It then decreased in both groups from the supine position to the end of the LBNP session by around 20% and 50% in the Finishers and Non-finishers, respectively, again reinforcing the view that the Non-finishers were not able to cope with to the 10 min of –45 mmHg in the same way as did the Finishers (Figure 1, Table 3).

Calculated cardiac output was unchanged from sitting to supine in both groups, however, it decreased from sitting to the end of LBNP in the Non-finishers group only ($p=0.0$). It remained the same when the mean supine value (5.4 L/min) was compared with the mean value obtained at the end of the LBNP exposure (5.2 L/min) for the Finishers, and decreased from 5.7 L/min to 3.7 L/min for the Non-finishers ($p=0.004$) (Figure 1, Table 3). These findings show that the increase in heart rate was not large enough to compensate for the decrease in stroke volume, resulting in a marked reduction in NF cardiac output. Additionally, total peripheral resistance in the NF group did not increase sufficiently to compensate for the decline in cardiac output, and thus blood pressure dropped.

The calculated total peripheral resistance is not significantly different when both groups are compared with a mean value of approximately 1400 dyne.s.cm$^{-5}$ (Table 3). Calculated total peripheral resistance did not change when supine values were compared with mean values at the end LBNP session for the Finishers. However, it increased for the Non-finishers ($p=0.01$) (Figure 1). We believe that the difference in calculated total peripheral resistance between both groups at the end of LBNP exposure was not enough to counterbalance the decrease of 35% in the calculated cardiac output.

There seem to be two components in the response of Non-finishers: (a) a large decrease in stroke volume and (b) a lack of adequate compensation by increase in heart rate and in total peripheral resistance. Both can be seen as an inadequate sympathetic response to the LBNP challenge. We suggest the lack of an adequate sympathetic response could also be affecting the capacitance vessels and contributing to a marked decrease in venous return and, consequently, the stroke volume in the Non-finishers. Figure 2 and Figure 3 illustrate it by showing the hemodynamic response to 45 mmHg LBNP of a Finisher and a Non-finisher, respectively.

## 4.4. Specific Gender Differences

A comparison between female F and NF (Table 4) showed clearly an important difference in the mean value of around 6.0 L/min of CO for the F in relation to the NF, who had a mean value of approximately 4.0 L/min. We also found a significant decrease in the calculated CO within the female NF group from either sitting or supine to the end of the LBNP session ($p<0.05$). There was, however, no significant difference between the female F and NF in relation to the calculated TPR for the three experimental conditions, which once more indicates a lack of response of the peripheral vasculature in order to compensate for the important decrease in cardiac output during the exposure to the LBNP stress. Interestingly, if only the female NF group is considered, a significant increase in the calculated total peripheral resistance was found ($p=0.03$) from the supine position (mean of 1077 dyne.s.cm$^{-5}$) to the end of the LBNP session (mean of 1400 dyne.s.cm$^{-5}$). However, this increase in peripheral resistance was insufficient to compensate for the decrease in cardiac output and failed to maintain blood pressure within clinically acceptable limits.

Analyzing the only male subject that was not able to complete the experiment, we could see that he presented the same pattern of calculated CO as the female NF group, which was an important decrease in a mean value of sitting and supine of around 3.8 L/min to a value of 2.6 L/min at the end of the LBNP session.

The same analysis was performed considering only male and female Finishers (Table 4). Female F presented a higher calculated CO for the three experimental conditions (mean of 6.5 L/min) in comparison to male F (mean of 4.3 L/min) ($p<0.05$). Although female F started the experiment with a higher calculated CO, a proportionally larger number of male subjects were able to finish the experiment, which implies that the tolerance to the cardiovascular stress imposed by the LBNP is more related to the ability to maintain an appropriate SV and to increase total peripheral resistance than to the actual initial value of these variables.

Differently for the calculated CO values that were in accordance with the female NF group, the only male subject who was unable to finish the LBNP session showed a decrease of heart rate, mean blood pressure and stroke volume, without an increase in TPR. This difference from the female NF implies a distinction between the autonomic reaction patterns, since the male NF presented a typical vaso-vagal pre-syncope. The difference between F and NF will rely on an adequate sympathetic response. Meck et al. [13] suggested that the etiology of orthostatic hypotension and pre-syncope after spaceflight includes low alfa-1-adrenergic receptor responsiveness before flight and a remodeling of the central nervous system during spaceflight such that sympathetic responses to baroreceptor input become impaired. Our findings are also corroborated by the study of Waters et al. [21], which suggests that post-flight pre-syncope is greatest in women and it can be caused by the combination of inherently low-resistance responses, a strong dependence on volume status, and a relative hypoadrenergic response.

Seven of 8 men and 7 of 12 women completed the 10 min of LBNP. Non-finishers (n=6) increased heart rate, decreased systolic blood pressure, mean blood pressure, calculated SV and CO in comparison with the Finisher (n=14) group ($p<0.05$). Since both CO and TPR are affected in non-finishers and, even being aware of the limitations imposed by using only non-invasive methods, we suggest that this is due to an inadequate sympathetic response to LBNP affecting heart rate, peripheral resistance, and capacitance vessels. This inadequate sympathetic response seems to be more frequent in women than in men but is not specifically gender dependent, nor is it modulated by the menstrual cycle.

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