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Orthostatic tolerance and spontaneous baroreflex sensitivity in men versus women after 7 days of head-down bed rest

Marc-Antoine Custaud [a,*], Edmundo Pereira de Souza Neto [a], Patrice Abry [b], Patrick Flandrin [b], Catherine Millet [a], Monique Duvareille [a], Jacques-Olivier Fortrat [a], Claude Gharib [a]

[a] *Laboratoire de Physiologie de l'Environnement (EA 645), 8 Avenue Rockefeller, Lyon 69373, France*
[b] *Laboratoire de Physique, Ecole Normale Supérieure de Lyon, Lyon, France*

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Abstract

Many factors are involved in the development of orthostatic intolerance after real or simulated weightlessness. The aim of our study was to compare the effects of 7-day head-down bed rest (HDBR) in eight women and eight men on the spontaneous baroreflex sensitivity (standard spectral method and new time–frequency algorithm) during lower body negative pressure (LBNP) tests.

Results obtained before HDBR have shown in women, compared to men, higher heart rate, lower blood pressure, higher parasympathetic modulation at rest and greater decrease in baroreflex sensitivity with greater increase in sympathetic activity during LBNP. After HDBR, we observed in both men and women a dramatic decrease in orthostatic tolerance (7.0 min at R + 1 vs. 10.0 min, $p < 0.05$, at BDC-1 in men; 5.4 vs. 9.0 min, $p < 0.05$, in women) together with a decrease in plasma volume ($-9.1 \pm 0.9\%$ in men, $-9.5 \pm 1.4\%$ in women) and in spontaneous baroreflex sensitivity without gender effect. After HDBR, at the highest level of LBNP, diastolic blood pressure increased in men ($+5.6 \pm 1.3$ mm Hg) and decreased in women (-1.0 ± 2.7 mm Hg) with a gender difference ($p < 0.05$). This result suggests impaired vasoconstriction in women after HDBR.

Neither endocrine response nor alterations to the cardiac baroreflex can explain gender differences in orthostatic tolerance after HDBR as reported by previous studies. Further studies need to be conducted in order to obtain a more precise analysis of gender difference in arteriolar vasoconstriction after HDBR. The time frequency method we developed to study changes in spontaneous baroreflex might be applied to the analysis of LBNP tests.

Keywords: Orthostatic intolerance; Lower body negative pressure; Time–frequency analysis; Gender characteristics; Heart rate variability

1. Introduction

Gender differences in cardiovascular regulation induce lower orthostatic tolerance in women (Gotshall et al., 1991; Convertino, 1998). After head-down bed rest (HDBR) and space flight, cardiovascular deconditioning with orthostatic intolerance appears. Studies on cardiovascular deconditioning have frequently dealt with men, but few works have included women (Greenleaf et al., 1977; Vernikos et al., 1993; Fortney et al., 1994; Maillet et al., 2000; Millet et al., 2001; Waters et al., 2002). The effects of gender on cardiovascular deconditioning thus remain unclear.

Many authors have compared tolerance to orthostatic stress in men and women apart from HDBR. Clinical studies have shown that women are particularly prone to postural orthostatic tachycardia syndrome (POTS) (Robertson, 1999) and to vagal syncope. As reported by Convertino (1998) and Gotshall (2000), women have significantly less lower body negative pressure (LBNP) tolerance than men using a pre-syncopal LBNP protocol. Even if lower height and higher blood volume during the postovulation period are cardiovascular parameters that may improve orthostatic tolerance in women, other cardiovascular features in women may contribute to their reduced orthostatic tolerance compared to men. Some studies have shown lower baroreflex sensitivity in women (Convertino, 1998; Laitinen et al., 1998; Abdel-Rahman et al., 1994). Reduced orthostatic tolerance in women is also associated with their lower circulating

* Corresponding author. Tel.: +33-4-78-77-70-78; fax: +33-4-78-01-74-67.
E-mail address: mcustaud@club-internet.fr (M.-A. Custaud).

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blood volume (Convertino, 1998). During LBNP, women have shown greater blood pooling in the pelvic region, inducing a greater decrease in central blood volume and leading to hypotension (White and Montgomery, 1996). In women, estrogen has also been shown to induce the production of vasodilator agents, such as nitric oxide, which may prevent the correction of a decrease in blood pressure (Chowienczyk and Ritter, 2001). Women may be more sensitive to orthostatic stress than men because of contributions from any one or a combination of these mechanisms.

Both space flight and HDBR induce a cardiovascular deconditioning syndrome, the most serious symptom of which is orthostatic intolerance, with a significantly reduced capacity for exercise and an increased resting heart rate (Blomqvist et al., 1994). The parameters that have been identified and that are involved in this syndrome include hypovolemia, impairment of vasomotor functions, decrease in baroreflex sensitivity, increase in venous compliance, alterations in microcirculation, changes in hormonal secretion and changes in energy metabolism (Pavy-Le Traon et al., 1999). Other parameters cannot be excluded, however, e.g., the influence of vestibular alterations on blood pressure regulation (Convertino et al., 1997). This cardiovascular deconditioning partly occurs secondary to a fluid shift from the lower extremities towards the cardiothoracic region in the initial period of HDBR or exposure to weightlessness. Waters et al. (2002) observed a dramatic decrease in orthostatic tolerance in women (all five women were intolerant) after space flight compared to men (6 of 24 men were intolerant). Presyncopal people, especially women, had smaller vascular resistance than nonpresyncopal men, with lower increase of norepinephrine in standing and a stronger sensitivity to hypovolemia. On the other hand, ground-based experiments have revealed no major gender difference in endocrine and fluid responses to HDBR (Greenleaf et al., 1977; Vernikos et al., 1993; Fortney et al., 1994; Millet et al., 2001). There are no studies devoted to the spontaneous baroreflex changes in men and women induced by HDBR.

The aim of this protocol was to compare the effects of 7-day HDBR on orthostatic tests (LBNP and stand test) in men and women. We hypothesized that the lower orthostatic tolerance in women after HDBR could be explained in part by a more pronounced alteration of the spontaneous baroreflex sensitivity. During this study, we also compared a dynamic method we developed to monitor cardiac baroreflex regulation more accurately during LBNP with standard stationary tools.

2. Methods

2.1. Subjects

A total of eight healthy men (32.4 ± 1.9 years; 74.2 ± 2.7 kg; 177 ± 2 cm) and eight healthy women (27.8 ± 0.9 years; 56.2 ± 2.2 kg; 164 ± 1.5 cm) took part in this study. The volunteers had no history of cardiovascular or any other major disease. They were all nonsmokers and were not taking drugs. During the study, they did not ingest caffeine or alcohol. All subjects had good orthostatic tolerance as evaluated by a 10-min stand test and a 15-min 70° head-up tilt in the course of the selection period.

The women were not taking oral contraceptives prior to, or during, the study. The menstrual cycle was determined for each woman by the peak in luteinizing hormone in urine (monitor Clearplan Plus®; Unipath Diagnostics, Rueil Malmaison, France). Six volunteers were included during the first part of the menstrual cycle, one on the 13th and one on the 18th day of the cycle.

This study was approved by the Midi-Pyrénées Ethics Committee (Comité de Protection des Personnes de Midi-Pyrénnées). Written informed consent was obtained from all the volunteers before they took part in the protocol.

2.2. Experimental protocol

This experiment was composed of two periods of HDBR at a 1-year interval, one for the men and one for the women. All the subjects remained in the Institut de Médecine et de Physiologie Spatiale (MEDES, Toulouse, France) for 14 days, including four ambulatory control days (BDC-4 to BDC-1), 7 days of −6° HDBR (HDBR1–HDBR7) and three recovery days (R1–R3).

2.3. Plasma volume measurement

Plasma volume measurements were taken with Evans Blue dye dilution (Foldager and Blomqvist, 1991) in the morning before breakfast of BDC-3 and R+1.

2.4. Dynamic tests

2.4.1. Stand test

For both periods of HDBR, stand tests were performed in the morning of days BDC-1 and R+1. The stand test in the morning of day R+1 was the first time the subjects had had to stand up since the HDBR period. After 30 min in the horizontal position (20 min to set up the instrumentation and 10 min for data acquisition), the subject sat for 5 min and stood for a maximum of 10 min. The stand test was interrupted before the end of the 10 min if presyncopal or syncopal symptoms occurred (a feeling of faintness, rapid drop in systolic blood pressure (more than 25 mm Hg) or tachycardia of more than 160 beats/min).

2.4.2. LBNP

The LBNP tests were performed in the afternoon of BDC-1 and R+1 for each period of HDBR. Five to 6 h separated the stand tests and LBNP tests. During that time, subjects had no exercise but were free to walk inside the institute. Lower body suction was applied to the supine subject whose limbs and pelvis (below the iliac crest) were

enclosed in an airtight chamber. After 20 min spent setting up data collection, the test began with 10 min of baseline collection. This was followed by a graded depression of 7-min stages at −15, −30 and −45 mm Hg. The intolerance criteria were the same as for the stand test.

2.4.3. Acquisition of data

During the active stand tests and the LBNP, we recorded continuously, on a beat-by-beat basis:

- the RR interval (RRi) time in milliseconds between two R peaks on the electrocardiogram (ECG), obtained from a standard bipolar ECG lead and an R peak detection circuit with precision of 1 ms; and
- systolic blood pressure (SBP) and diastolic blood pressure (DBP) obtained by finger photoplethysmography (Portapres® TNO; Biomedical Instrumentation Research Unit, Amsterdam, the Netherlands).

During both tests, heart rate and blood pressure were also monitored independently of data collection with an ECG monitor and an automated oscillometer (Dynamap®; Criticon, Tampa, FL, USA).

2.4.4. Computation of parameters

2.4.4.1. Stationary methods. Modern approaches to the baroreflex function make it possible to evaluate the sensitivity of the spontaneous baroreflex with a noninvasive beat-by-beat measurement of arterial blood pressure and RRi. This method avoids the use of pharmacological agents for estimating baroreflex sensitivity (Parlow et al., 1995).

These techniques are used particularly in the evaluation of the sensitivity of the cardiac baroreflex by analyzing the relationship between variations in SBP and RRi. Baroreflex sensitivity is expressed in milliseconds per millimeters mercury and corresponds to the changes in RRi that are caused by changes in systolic blood pressure (Pagani et al., 1988; Hughson et al., 1993; Gerritsen et al., 2000; Persson et al., 2001; Di Rienzo et al., 2001).

Analysis of the baroreflex could be performed in time domains using the sequence technique or in frequency domains with spectral and cross-spectral analysis. The α index is computed with spectral analysis of the RRi and spectral analysis of SBP variations:

$$\alpha = \sqrt{\frac{\text{SpectralPowerRRi}}{\text{SpectralPowerSBP}}}.$$

Cross-spectral analysis makes it possible to calculate the gain in transfer function between changes in SBP and RRi:

$$\text{Gain} = \sqrt{\gamma^2} \times \sqrt{\frac{\text{SpectralPowerRRi}}{\text{SpectralPowerSBP}}}$$

with γ^2 as the squared coherence between RRi and SBP. These indices are calculated only for the frequency where the squared coherence is >0.5.

Those two indices, obtained in frequency domains, are calculated on specific frequency bands. They are usually computed in low-frequency (LF; 0.04–0.15 Hz) and high-frequency (HF; 0.15–0.4 Hz) bands. There is no consensus on which frequency band is better to use. For some authors, the LF band is more specific for the baroreflex; for other authors, HF variations in RRi and SBP also depend on the baroreflex and study more specifically the influence of respiration on the baroreflex. Computing this gain into the total frequency band (TOT; 0.04–0.4 Hz) (Piccirillo et al., 2001) has thus been recently suggested.

Finally, the α coefficient and gain of the transfer function are similar indices: they both take into account the coherence between RRi and SBP as a "cut-off" value, but only the gain is weighted by the coherence value.

In this study, we calculated the gain in transfer function for each stage of the LBNP using 5-min segments.

2.4.4.2. Nonstationary methods. The dynamic aspect of baroreflex sensitivity has become evident and new tools have been developed to study nonstationary situations using Wigner–Ville tools or parametric autoregressive methods (Cerutti et al., 2001; Barbieri et al., 2001). We developed a simple dynamic method based on a nonparametric model and derived from the cross-spectral methods between RRi and SBP to calculate dynamic gain in transfer function between RRi and SBP. This algorithm computes the evolution over time of spontaneous baroreflex sensitivity (Fig. 1).

The gain for each frequency is obtained by this equation:

$$\text{Gain} = \sum_{f_1 \le f \le f_2} \sqrt{\gamma^2(f)} \times \sqrt{\frac{S_{\text{RRi}(f)}}{S_{\text{SBP}(f)}}}$$

where γ^2 = squared coherence (if >0.5); S_{RRi} = power spectrum density of RRI; S_{SBP} = power spectrum density of SBP; and f = specific frequency inside the frequency band $[f_1 - f_2]$.

The dynamic evolution is obtained by using a 90-s sliding window across the beat-by-beat RRi and SBP data. The entire procedure was written with MATLAB® (version 5.3 with signal processing toolbox, Mathworks®).

In practice:

(1) The RRi and SBP series are filtered with an automated algorithm and visually controlled.
(2) The two series are interpolated at 2 Hz (β spline interpolation).
(3) Sliding segments of 90 s are determined across all the data with a 70-s overlap.
(4) A linear detrend is applied to each segment.
(5) Estimates of power spectral density for SBP and RRi using Welch's averaged periodogram method are performed on each segment.

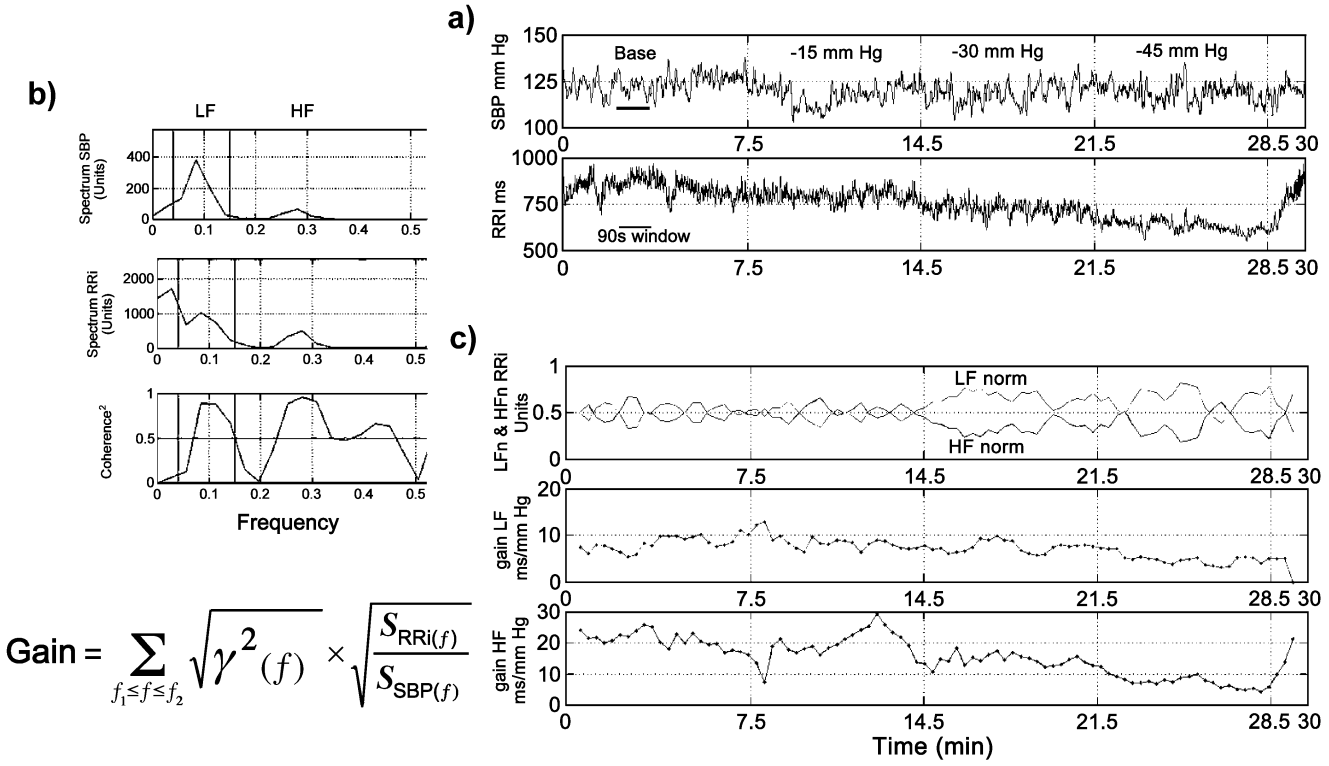

Fig. 1. Dynamic gain in spontaneous baroreflex. Example of its computation during a LBNP test. (a) Beat-by-beat evolution of SBP and RRi. (b) Spectral analysis of SBP and RRi with the coherence on a 90-s window of the signal. (c) Evolution of LFn, HFn, gain LF and gain HF. SBP = systolic blood pressure; RRi = RR interval; LF = low-frequency band; LFn = normalized low-frequency index; HF = high-frequency band; HFn = normalized high-frequency index.

(6) For each segment, the α gain is computed in LF, HF and TOT as described above.

Autonomic indices were also computed in order to evaluate the sympatho-vagal balance. The HF norm index (Spectral Power of HF/(LF + HF)) reflects the parasympathetic influence on heart rate. The LF norm index (Spectral Power of LF/(LF + HF)), even if it is controversial, may reflect the orthosympathetic influence on heart rate.

2.5. Statistical analysis

The results are given as a mean ± S.E.M. Orthostatic tolerance times measured during stand tests were compared using a nonparametric Mann–Whitney test. Variations in plasma volume, data obtained during the LBNP session (SBP, DBP, HR, LF norm, HF norm, gain LF, gain HF, gain TOT) and their HDBR-induced variations were analyzed using a three-way factorial analysis of variance (ANOVA).

Table 1
Orthostatic test after HDBR (duration of stand test, type of faintness), height and HDBR-induced plasma volume variations

Subjects	Men				Women			
	Height (cm)	Variations in plasma volume (ml)	Duration (min)	Type of intolerance	Height (cm)	Variations in plasma volume (ml)	Duration (min)	Type of intolerance
A	179	− 310	9	POTS no hypotension	160.5	− 340	3	POTS hypotension
B	175	− 400	8	POTS hypotension	165	Not measured	10	–
C	168	− 280	10	–	156	− 280	10	–
D	180	− 250	7	POTS hypotension	167	− 200	2	POTS hypotension
E	183	− 490	6	POTS hypotension	165	− 420	5	POTS hypotension
F	182	− 410	3	POTS hypotension	170	− 310	1	POTS hypotension
G	177	− 160	3	POTS hypotension	165	− 130	2 (and 50 s)	POTS hypotension
H	169	− 190	10	–	163.5	− 110	10	–

Individual data in men and women. POTS = postural orthostatic tachycardia syndrome; HDBR = head-down bed rest.

Table 2
Systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) during LBNP, before and after HDBR and the HDBR-induced variation

		SBP (mm Hg)				DBP (mm Hg)				HR (beats/min)			
		Base	− 15 mm Hg	− 30 mm Hg	− 45 mm Hg	Base	− 15 mm Hg	− 30 mm Hg	− 45 mm Hg	Base	− 15 mm Hg	− 30 mm Hg	− 45 mm Hg
Women	Before HDBR	104.2 ± 2.1	104.7 ± 2.2	103.8 ± 2.2	110.6 ± 3.8 (n = 7)	62.4 ± 1.4	64.3 ± 1.1	64.5 ± 1.4	67.8 ± 2.5 (n = 7)	72.4 ± 3.1	69.9 ± 1.9	76.1 ± 1.9	90.6 ± 2.9 (n = 7) *
	After HDBR	104.9 ± 2.3	105 ± 1.7	105 ± 2.4	105.5 ± 2.4	65.9 ± 1.7	66.1 ± 1.6	66.8 ± 1.8	67.5 ± 1.7	79.8 ± 2.6	79.5 ± 2.2	85.7 ± 2.5 **	96.6 ± 4.9 *
	Variation	+ 0.7 ± 1.2	+0.3 ± 1.73	+1.2 ± 1.5	− 6.2 ± 3.9 (n = 7)	+ 3.5 ± 1.9	+ 1.8 ± 1.4	+ 2.4 ± 2.0	− 1.0 ± 2.7 (n = 7)	+ 7.4 ± 3.3	+ 9.6 ± 1.2	+ 9.6 ± 1.2	+ 7.3 ± 4.9 (n = 7)
Men	Before HDBR	131.7 ± 4.5***	128.0 ± 3.9***	125.3 ± 3.7***	122.0 ± 4.7	72.5 ± 2.6***	72.3 ± 3.0***	72.5 ± 2.9***	72.8 ± 3.0	59.8 ± 3.7***	63.9 ± 3.8	71.9 ± 4.1 *	80.7 ± 4.7 *
	After HDBR	128.5 ± 4.3***	128.0 ± 4.1***	124.2 ± 4.6***	124.7 ± 5.5 (n = 7)***	75.6 ± 2.8***	76.1 ± 2.4***	76.7 ± 2.5***	79.5 ± 3.1 (n = 7)* * *	67.9 ± 2.8***	72.5 ± 3.5 **	83.0 ± 4.1 *	94.1 ± 4.1 (n = 7) *,**
	Variation	−3.2 ± 3.1	0 ± 2.6	−1.1 ± 2.5	+ 1.6 ± 2.6 (n = 7)	+ 3.1 ± 1.8	+ 3.7 ± 1.4	+ 4.2 ± 1.4	+ 5.6 ± 1.3 (n = 7)* * *	+ 8.1 ± 2.6	+ 8.6 ± 2.6	+ 11.1 ± 3.5	+ 13.9 ± 2.8 (n = 7)

− 15, − 30 and − 45 mm Hg are the three stages of depression.
HDBR = head-down bed rest; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; LBNP = lower body negative pressure.
* Indicates a significant difference between a depression level and the base period of the LBNP test ($p < 0.05$).
** Indicates a significant difference between before and after HDBR ($p < 0.05$).
*** Indicates a significant difference between women and men ($p < 0.05$).

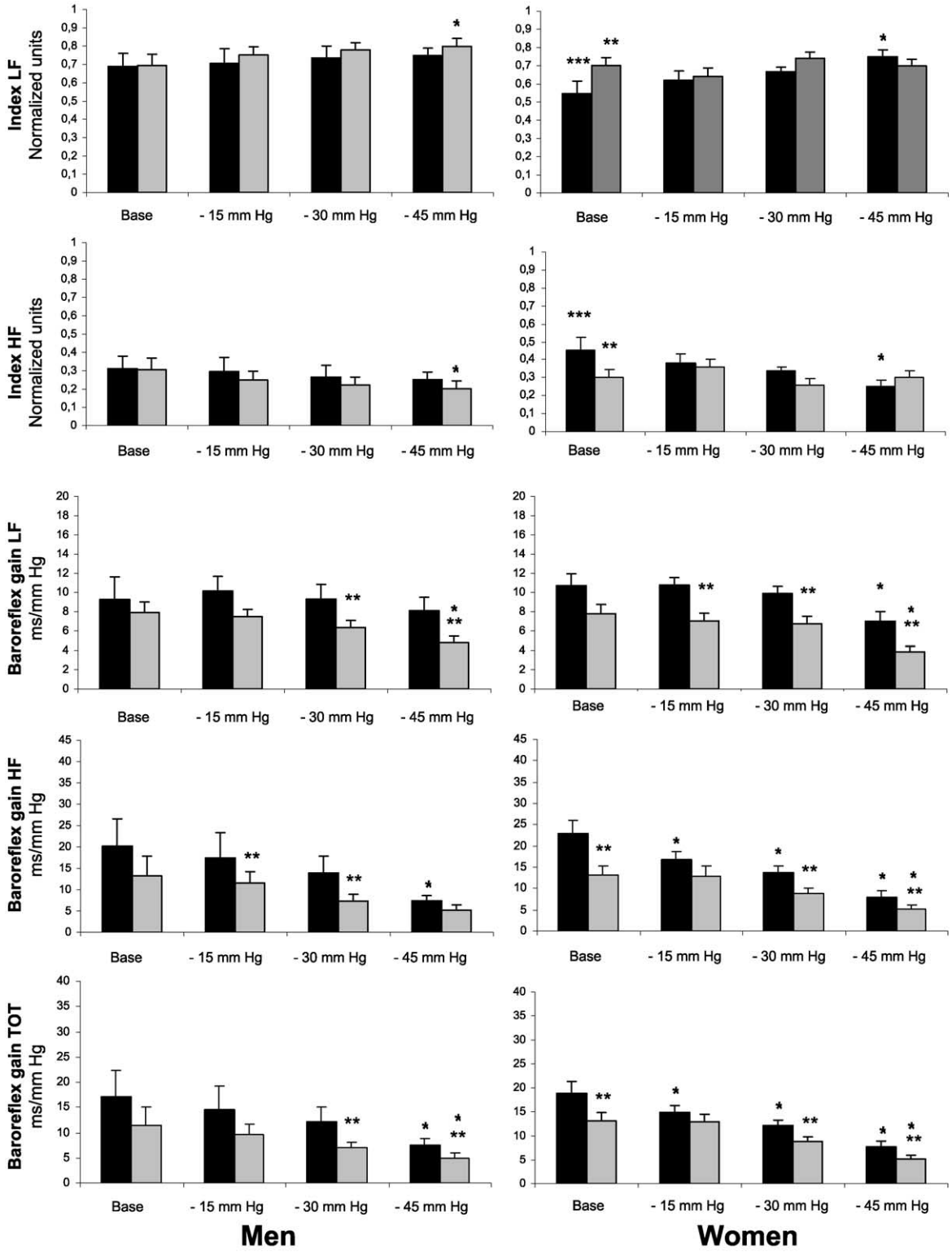

Fig. 2. Stationary tools. Autonomic nervous system indices (LF index and HF index) and spontaneous baroreflex sensitivity (baroreflex gain in the frequency bands LF, HF and TOT) calculated for each LBNP stage before HDBR (black bars) and after HDBR (gray bars) in men and women. Results are in mean ± S.E.M. (***) indicates a significant difference between women and men ($p < 0.05$). (**) indicates a significant difference between before and after HDBR ($p < 0.05$). (*) indicates a significant difference between a depression level and the base period of the LBNP test ($p < 0.05$).

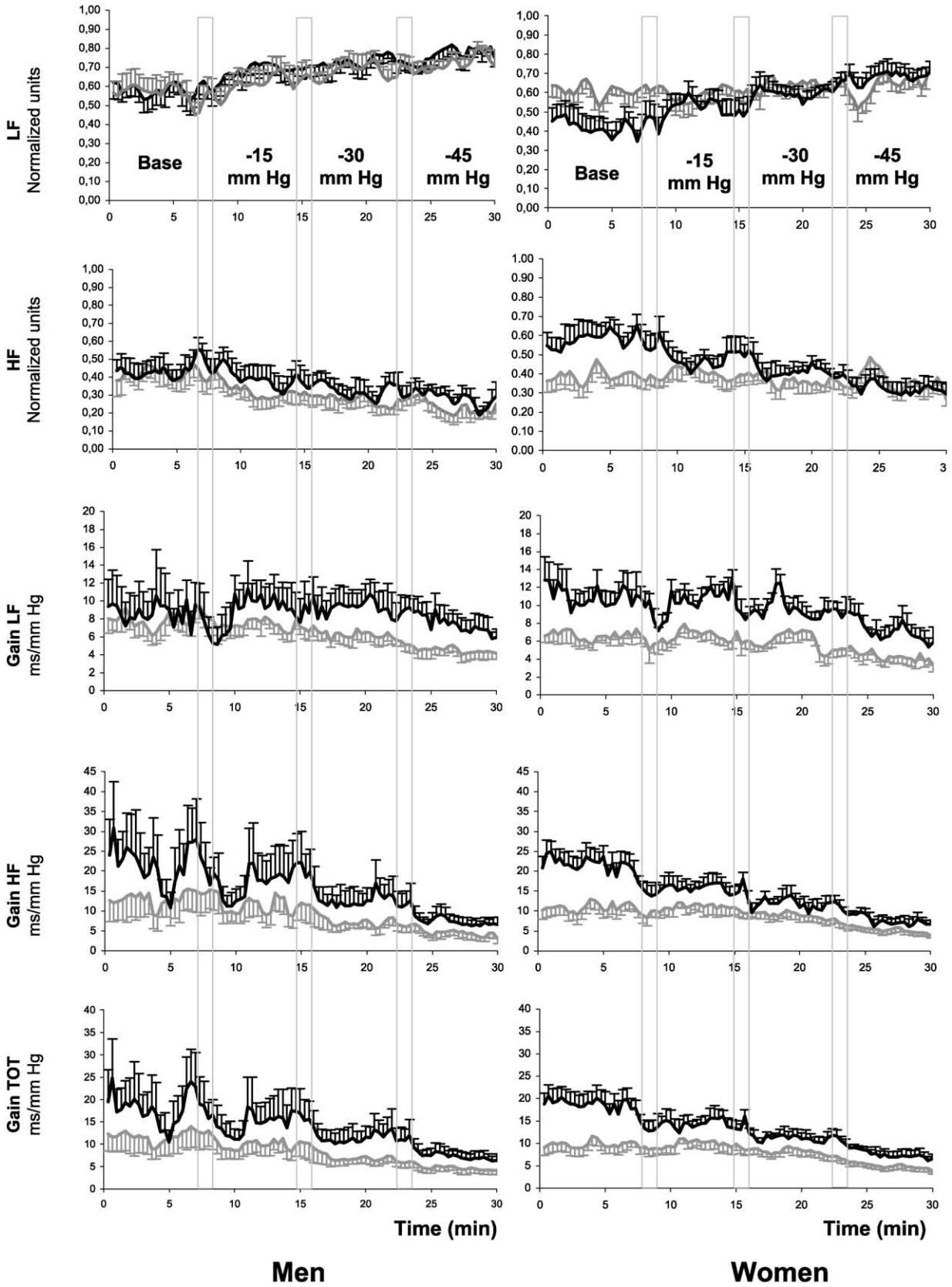

Fig. 3. Dynamic tools. Autonomic nervous system indices (LF index and HF index) and spontaneous baroreflex sensitivity (baroreflex gain in the frequency bands LF, HF and TOT) calculated over LBNP test stages before HDBR (black lines) and after HDBR (gray lines) in men and women. Results are in mean ± S.E.M.

For each parameter, we studied the gender, level of LBNP depression and HDBR effects. A Protected Least Significance Difference (PLSD) Fischer test was used for the post hoc analysis to locate the significant effect when applicable.

Statistical significance was set at $p < 0.05$.

3. Results

3.1. Plasma volume

HDBR induced a significant decrease in plasma volume both in men (from 3.35 ± 0.18 to 3.04 ± 0.15 l, $p < 0.05$) and in women (from 2.67 ± 0.14 to 2.41 ± 0.12 l, $p < 0.05$), with significantly higher values in men before HDBR.

The decrease in plasma volume was similar in men ($-9.1 \pm 0.9\%$) and in women ($-9.5 \pm 1.4\%$). Individual decreases in HDBR-induced plasma volume are reported in Table 1. Plasma volume measurements could not be taken in one woman after HDBR because of the impossibility of performing a venous puncture (subject B).

3.2. Stand tests (Table 1)

Before HDBR, only one woman (subject F) could not complete the stand test at 3 min. After HDBR, we observed a significant decrease in orthostatic tolerance both in men (7.0 min at R + 1 vs. 10 min at BDC-1) and in women (5.4 min at R + 1 vs. 9.1 min at BDC-1). Six men and five women, all presenting with POTS, did not finish the stand test (Table 1). A Mann–Whitney test performed on orthostatic tolerance time after HDBR did not reveal any significant difference between men and women. In all but one woman, all the POTS episodes finally induced hypotension by vasovagal syncope.

3.3. LBNP

3.3.1. Tolerance and general data

One woman before HDBR and one man after HDBR could not complete the LBNP test because of symptomatic hypotension during the third stage of depression. We did not take either of these LBNP stages into account during further analysis.

Table 2 shows mean oscillometric blood pressure and heart rate measurements for each stage of depression and for all subjects.

We observed no significant changes in either men or women in SBP and DBP with the increase of depression before and after HDBR. This regulation of blood pressure is due in part to a significant increase in heart rate caused by the baroreflex. After HDBR, tachycardia was noted in both men and women with a significant increase in heart rate during certain stages of depression.

When we analyzed induced variations in blood pressure and heart rate in men and women, we observed no significant difference except for DBP at the highest level of LBNP. After HDBR, DBP tended to increase more in men than in women.

3.3.2. Autonomic regulation—stationary tools

The noninvasive evaluation of autonomic regulation during LBNP with stationary tools is shown in Fig. 2. The basal values before HDBR indicate a significantly higher value of the LF index in men. The depression of LBNP induced an increase in the LF index and a decrease in the HF index (significant only at the highest level after HDBR in men and before HDBR in women).

Baroreflex sensitivity, measured by the gain indices, decreased with LBNP in men and women before and after HDBR. In both men and women, HDBR induced a decrease in the gain indices. This decrease seemed, however, to be more marked in women, with a significant effect for a lower depression level than in men. Statistical analysis did not reveal any gender effects in the variation of these indices during HDBR.

3.3.3. Autonomic regulation—dynamic tools (Fig. 3)

The dynamic analysis of autonomic regulation during LBNP revealed the same directional changes as the stationary methods for all indices studied (Fig. 3). Therefore, the results of this method may have simply followed changes in vegetative activity and baroreflex sensitivity.

4. Discussion

4.1. Gender differences before head-down bed rest

We observed the standard gender differences at basal values before HDBR: a higher heart rate and lower blood pressure both at rest and during orthostatic stress in women (Gotshall et al., 1991). At rest before HDBR, women have a lower LF norm and higher HF norm than men in accordance with previous studies (Hinojosa-Laborde et al., 1999; Sevre et al., 2001). This suggests a lower cardiac sympathetic activity and a higher cardiac parasympathetic modulation in women. The reason for this gender difference is not clear. Sex hormones may act centrally, thus altering sympathetic and parasympathetic activity. As far as spontaneous baroreflex sensitivity is concerned, we observed no gender differences in rest values. Some studies (Abdel-Rahman et al., 1994; Laitinen et al., 1998) have found reduced cardiac baroreflex sensitivity in women using pharmacological assessment of the baroreflex. One study (Sevre et al., 2001), based on the analysis of the spontaneous baroreflex sensitivity by the transfer function, did not find a gender difference. This discrepancy might be due to the methods used. As discussed further, the spontaneous baroreflex sensitivity analysis studies the baroreflex only in a small range of RRi and SBP. Thus, it does not explore all the baroreflexes but only inside the operational range of RRi and SBP. The influence of menstrual cycle

did not seem predominant on cardiac baroreflex. Estrogens did not act on cardiac baroreflex, whereas they seem to increase vascular sympathetic baroreflex gain (Hunt et al., 2001).

The cardiovascular response to LBNP is slightly different in men and women. Women presented a more pronounced response to LBNP before head-down bed rest. In women, we observed a greater increase in LF and a greater decrease in spontaneous baroreflex sensitivity. Many studies have reported gender effects in response to LBNP. It has been shown with presyncopal LBNP protocols (Convertino, 1998; Gotshall, 2000) that women have lower tolerance than men to LBNP. White and Montgomery (1996) have suggested that women have more pelvic blood pooling than men during LBNP in the venous system. This probably explains the more marked cardiovascular response we observed in women, in response to a more significant decrease in intraarterial blood volume.

4.2. Orthostatic tolerance after HDBR

The subjects who failed to complete the stand test after HDBR presented with POTS. POTS is a type of orthostatic tolerance that is characterized by postural tachycardia (Novak et al., 1998). Although women are more sensitive to POTS than men (Robertson, 1999), we observed no significant difference in the time of orthostatic tolerance in men and women during the stand tests. The effects of HDBR seem similar in men and women as regards orthostatic tolerance.

After HDBR, all the intolerant subjects presented with POTS. HDBR induced cardiovascular changes that led to POTS. POTS is favored by a decrease in blood volume, excessive blood pooling in the lower part of the body while standing and there is also some evidence of underlying venous and arterial sympathetic denervation in the legs of patients suffering from POTS (Jacob et al., 2000). In humans, HDBR decreases blood volume (Custaud et al., 2000) and also functionally and selectively impairs sympathetic function (Pagani et al., 2001). Additionally, in some patients with POTS, a reduced baroreflex response has been reported (Farquhar et al., 2000) as we observed after HDBR.

In this study, all the POTS episodes ended, except in one subject, with rapid hypotension caused by vasovagal collapse. POTS is, in fact, provoked in part by central hypovolemia that induces intensive heart stimulation. Both hypovolemia and intensive heart stimulation are known to induce the Bezold–Jarisch reflex, which is expressed clinically by vasovagal syncope (Sutton and Bloomfield, 1999).

In summary, in both men and women, HDBR induces cardiovascular changes—particularly hypovolemia—and baroreflex dysfunction, and suggests changes in both peripheral innervating and venous function, leading to POTS and a decrease in orthostatic tolerance.

4.3. The gender effects of HDBR

Studies already published that compare cardiovascular responses to HDBR in men and women have mainly dealt with endocrine response and blood volume regulation (Greenleaf et al., 1977; Vernikos et al., 1993; Fortney et al., 1994; Millet et al., 2001).

4.3.1. Plasma volume

Fortney et al. (1994) measured changes in plasma volume in 10 men and 10 women after a 13-day HDBR. They found a lesser decrease in plasma volume in women compared with men. They also demonstrated that plasma volume fluctuates during the menstrual cycle, with a transient increase 3 days prior to ovulation and at the end of the luteal phase. Estrogen seems to be responsible for this variation in volemia. Vernikos et al. (1993) reported a higher decrease in plasma volume after 3 days of head-down bed rest in women. In our study, we observed no gender difference in the decrease in plasma volume. Interstudy differences in the time of inclusion in relation to the menstrual cycle could explain these varied results.

After space flight, a greater decrease in plasma volume was reported in women (Waters et al., 2002). Environmental conditions during HDBR and space flight are very different concerning water and sodium intake, fluid loading before landing and space sickness that might induce a loss of appetite and even vomiting in cosmonauts. Thus, discrepancies might appear between space and ground studies about plasma volume measurement.

4.3.2. Spontaneous baroreflex sensitivity

There have been no studies about gender effect on spontaneous baroreflex sensitivity after HDBR. Our study has shown that there were no gender differences in the HDBR-induced evolution of spontaneous baroreflex sensitivity. The impairment of the cardiac baroreflex has been shown to be an important factor of orthostatic hypotension after HDBR (Convertino et al., 1990). The similar reduction in baroreflex sensitivity in men and women could explain in part the lack of gender difference in orthostatic tolerance we observed at R + 1.

With the method we used to measure baroreflex sensitivity, we only studied the cardiac baroreflex and not the arteriolar baroreflex.

Calculation of the spontaneous cardiac baroreflex sensitivity is a noninvasive exploration of the relationship between RRi and SBP. Spontaneous baroreflex sensitivity gives a reliable estimation of the baroreflex sensitivity measured by pharmacological methods (Parlow et al., 1995). The spontaneous baroreflex sensitivity method explores only a small range of RRi and SBP variation, but it is in the physiological operating range without external perturbations such as pharmacological injection or breath exercise. The baroreflex status at extreme range of blood pressure and RRi (such as before syncope) is difficult to

analyse with this method. Finally, the spontaneous baroreflex sensitivity evaluates the cardiac baroreflex only around the physiological operating range and not the arterial baroreflex at all. We cannot discard a slight gender difference for the arteriolar baroreflex function after HDBR.

Nevertheless, our results suggest that there is no major gender difference in cardiac baroreflex after head-down bed rest. The HDBR-induced variations in DBP observed during LBNP suggest reduced vasoconstriction in women after HDBR in comparison to men. The gender difference in orthostatic tolerance after HDBR may very well be caused by vascular impairment rather than an alteration to the cardiac baroreflex. This hypothesis is in agreement with the space flight study by Waters et al. (2002) where women have significantly lower standing peripheral resistance than men after space flight. Some gender differences in cardiovascular regulation may act directly on arterial vasomotor function. Recent studies have established the effects of estrogen on the nitric oxide pathway with an up-regulation of NO synthase by estrogen (Chowienczyk and Ritter, 2001).

4.4. Validation of the dynamic measurement of baroreflex sensitivity

We measured cardiac spontaneous baroreflex sensitivity with frequency domain techniques using the classic stationary method (Persson et al., 2001) and also a time–frequency approach that we developed in order to analyze LBNP more precisely. We computed the α gain in the LF, HF and in a band (TOT) that regroups LF and HF.

We observed the same results with this index computed on the three bands with the highest values as already reported, as well as more marked variations for the HF gain (Piccirillo et al., 2001). The gain computed in the TOT frequency band gives a global value of spontaneous baroreflex sensitivity. Even performed in stages of several minutes, LBNP is a dynamic test with continuous changes in cardiovascular regulation due in particular to progressive fluid shifts. Nonstationary tools are thus more adapted to studying LBNP sessions. The dynamic evaluation of the spontaneous baroreflex we applied uses the same principle as the gain in transfer function, but it involves a sliding window over time. We computed this dynamic gain on the three frequency bands as described above. We retained the squared coherence criterion at 0.5 in order to take into account only close, linear relationships between RRi and SBP. Because of low coherence, the gain could not be calculated in some sequences of the signal (10.3% for LF, 2.6% for HF, 1.1% for TOT). These points were not included in the analysis. In order to decrease the number of segments where the gain could not be calculated, it has recently been proposed that this threshold limit be reduced to 0.3 or even 0.0 (Gerritsen et al., 2000). Reducing the "cut-off" gain in this way could be applied to this dynamic method but requires further evaluation. The limitations described for the stationary tool persist for this dynamic analysis. The range of RRi and SBP study remains limited, but because of a rather short sliding window, this range could be a little extended in case of progressive changes in RRi and SBP.

We observed the same type of results using either stationary or dynamic tools. Because of the window size, the dynamic method could be used noninvasively to monitor vegetative regulation and baroreflex sensitivity with a precision of approximately 90 s. Dynamic methods could be used to analyze LBNP more accurately, and we should continue to evaluate this method with the aim of locating specific patterns in cardiovascular regulation that precede and may even predict intolerance to dynamic cardiovascular tests such as LBNP and stand tests.

5. Conclusion

Before HDBR, we observed the standard gender specificities mainly involving a more significant cardiovascular response to LBNP in women. This might be related to greater blood pooling in the pelvic region in women during LBNP.

Both men and women experience cardiovascular deconditioning after HDBR. We did not observe any gender difference in orthostatic tolerance as reported in certain studies. The cardiovascular consequences of HDBR are very similar in men and women. The decrease in blood volume and in cardiac spontaneous baroreflex sensitivity is similar in men and women. Analysis of DBP during LBNP tests suggests a gender difference in vasomotor functions after HDBR as described by Waters et al. (2002) after space flight.

The dynamic method for studying changes in spontaneous baroreflex sensitivity is well adapted to the LBNP test and may improve noninvasive cardiovascular analysis of dynamic tests.

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