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Sex differences in cardiovascular responses to orthostatic challenge in healthy older persons: A pilot study

C Sachse*, I Trozic*, B Brix, A Roessler, N Goswami

Gravitational Physiology and Medicine Research Unit, Physiology Division, Otto Loewi Center of Research in Vascular Biology, Immunity and Inflammation, Medical University of Graz, Graz, Austria

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Background: Premenopausal women show a higher incidence of orthostatic hypotension than age-matched men, but there are limited data available on sex differences in cardiovascular responses to orthostatic challenge in healthy older persons. We investigated sex differences in hemodynamic and autonomic responses to orthostatic challenge in healthy older males and females. *Materials and methods:* Fourteen older healthy women and 10 age-matched men performed a sit-to-stand test (5 min of sitting followed by 5 min of standing). A Task Force® Monitor continuously measured the following beat-to-beat hemodynamic parameters: heart rate, systolic blood pressure, diastolic blood pressure, mean blood pressure, stroke index, cardiac index, and total peripheral resistance index. Cardiac autonomic activity, low-frequency (LF: 0.04–0.15 Hz) normalized (LFnuRRI) and high-frequency (HF: 0.15–0.4 Hz) normalized (HFnuRRI) components, and the ratio between LF and HF power (LF/HF) were calculated using power spectral analysis of heart rate variability. *Results:* Across all hemodynamic parameters, there were no significant differences between the sexes at baseline and during standing. LFnuRRI (median: 70.2 vs. 52.3, $p < 0.05$) and LF/HF ratio (median: 2.4 vs. 1.1, $p < 0.05$) were significantly higher, whereas HFnuRRI (median: 29.8 vs. 47.7, $p < 0.05$) was lower among women at baseline. All other heart rate variability measures did not differ between the sexes. *Conclusions:* The data indicate that older women showed higher sympathetic and lower parasympathetic activity at rest compared to age-matched men. These results are contradictory to the observations from previous studies, which showed a reduced sympathetic and enhanced parasympathetic activity in women in all ages. Further studies are required to determine the underlying mechanisms contributing to higher incidence of orthostatic hypotension in older females.

Keywords: sex differences, postmenopausal women, orthostatic hypotension, falls, autonomic activity

Introduction

Several studies have reported gender differences in cardiovascular anatomy, hemodynamics, and the autonomic nervous system. Clinically, two major gender-related differences in the regulation of blood pressure are observed. First, blood pressure is typically lower in young women compared to age-matched men. Second, orthostatic hypotension and syncope as well as hypotensive disorders are more prevalent in premenopausal women than men (25). Another relevant difference between women and men is that men respond to cardiovascular

* These authors contributed equally to this paper.

Corresponding author: Nandu Goswami, MBBS, PhD
Gravitational Physiology and Medicine Research Unit, Physiology Division, Otto Loewi Center of Research in Vascular Biology, Immunity and Inflammation, Medical University of Graz
Neue Stiftingtalstrasse 6, D-5, Medical University of Graz, A 8036 Graz, Austria
Phone: +43 316 385 73852; Mobile: +43 664 792 4948; Fax: +43 316 385 79005; E-mail: nandu.goswami@medunigraz.at

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stress primarily with an increase in peripheral resistance, whereas women show greater heart rate (HR) increases (12, 48). Because of the greater HR in women, the amount of blood pumped by the heart [stroke volume (SV)] is lesser. Therefore, the total amount of blood in the circulation [cardiac output (CO)] is smaller that reduces the volume of blood coming back to the heart (venous return). According to earlier reports, venous return is the main determinant for the higher incidence of orthostatic hypotension in younger women compared to age-matched man. In addition, older women maintain venous return better, which could explain the smaller incidence of orthostatic hypotension compared to younger women (8). Furthermore, there appears to be a difference in the regulation of sympathetic and parasympathetic autonomic system between men and women. Several studies have shown that women have a reduced sympathetic but enhanced parasympathetic activity compared to men (1, 30). Young healthy women demonstrate a high vagal cardiac tone during rest due to parasympathetic predominance but a lower sympathetic vascular stimulation of peripheral vasculature, whereas men show high sympathetic input to vascular regulation (5, 9, 30). Therefore, women respond to orthostatic challenge primarily with vagal withdrawal, whereas men respond with sympathetic activation and an increase in peripheral resistance (5, 11, 16). Gender differences vary depending on age (20). Aging has an adverse influence on orthostatic intolerance. Orthostatic problems and orthostatic hypotension occur relatively frequently in older people (20, 40).

In the light of demographic changes reflecting an increasing proportion of older individuals, it is important to gain more detailed information on cardiovascular regulation during changes in posture in older people and possible differences between men and women. Orthostatic hypotension is common in older persons with a prevalence that varies from 4% to 33% (40) and is associated with risk of falls, fractures, syncope, and higher morbidity (20, 42, 46, 50). Generally, the risk of falls increases with aging and women are more affected than men (13, 38, 45). According to the WHO global report on fall prevention in older persons, approximately 30% of older people ≥65 years of age fall each year (50). Falls are the major cause of injury-related hospitalizations in older people and therefore represent an important public health issue (13). Preventing falls is essential and when designing prevention strategies, one should not disregard sex-specific factors. Most studies, however, investigating sex differences focused on healthy young persons and the results were not fully transferable to the older population. In older subjects, sex differences in cardiovascular responses and orthostatic tolerance are not yet completely clear (29).

The aim of this study, therefore, is to examine how orthostatic loading provided by a sit-to-stand test and *gender* contributes to changes in cardiovascular responses in healthy older people. We hypothesized that *older men and women will respond similarly to orthostatic loading* and that *gender-related differences in hemodynamic and cardiac autonomic responses are no longer detectable*.

Methods

Subjects

Ten men and 14 women were recruited in Graz, Austria. All subjects fulfilled the following inclusion and exclusion criteria. In this study, we included men and women at the age of 55 years and older. Participants with epilepsy, dementia, Parkinson's disease, stroke, chronic diabetes mellitus, and severe disabilities were excluded. Each subject underwent clinical

evaluation that included a review of medical history, clinical neurological examination and received medical clearance to participate in this study. All study volunteers were instructed to refrain from stressful activity before testing and to abstain from caffeine or other stimulants 24 h before testing. This study was carried out in accordance with the recommendations of the World Medical Association. The protocol was approved by the Ethics Committee of the Medical University of Graz, Austria. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

Experimental protocol

The participants were requested to report at 7:00 a.m. The actual measurements were performed between 07:00 and 10:00 a.m. Studies were conducted in a sensory-minimized environment, i.e., a quiet, partially darkened room, and maintained at a comfortable temperature. While the subject was sitting, hemodynamic and autonomic monitoring were applied, including measurement of intermittent (upper arm oscillometry) and continuous blood pressure (finger plethysmography), HR [3-lead electrocardiogram (ECG)], and thoracic impedance measurements using a Task Force® Monitor (TFM; CNSystems, Graz, Austria). A sit-to-stand test was used to provide orthostatic loading. The subjects were told to sit quietly with arm relaxed by their sides during the 5-min period of rest, after which they are assisted into the standing position for 5 min. During this period, they were instructed to keep their eyes open, to fix a point at eye level, and not to alter foot placement to avoid the effect of the skeletal-muscle pump. All subjects were asked to breathe normally and not to speak except in case of discomfort. Precautions (assistance in standing and available medical personnel) were taken to ensure safety in case a subject becomes syncopal during standing.

Data collection

After participant preparation and establishment of baseline measurements, data were collected during a 5-min period of sitting, followed by a 5-min period of standing. The subjects were then requested to sit down for additional 5 min (recovery period). The hemodynamic and autonomic monitoring recorded during the experimental protocol included 3-lead ECG (FD-13, Fukuda Denshi Co. Ltd., Tokyo, Japan), upper arm oscillometry, finger plethysmography (Finometer, Finapres Medical Systems B.V., Amsterdam, the Netherlands), and thoracic electrical impedance measurements. The ECG electrodes were attached for continuous recordings of HR. Beat-to-beat measurement of blood pressure was monitored using a finger plethysmography. In addition, intermittent blood pressure was measured from the left upper arm to calibrate continuous blood pressure values to the oscillometric measurement and for providing absolute blood pressure values. The double-finger sensor for measurement of continuous non-invasive blood pressure was placed on the right hand, which was fixed by a sling at heart level throughout the testing periods. The device for continuous blood pressure measurement was attached to right forearm. Four electrodes, one on the neck, two at the lateral side of the thorax at the xiphoid level, and one neutral electrode on the lower leg, were attached for transthoracic bio-impedance cardiography (ICG) from which SV, CO, and other cardiodynamic parameters were continuously processed. Electrocardiogram, continuous non-invasive arterial blood pressure measurement, and thoracic impedance were synchronized and integrated in the TFM.

Mean arterial pressure was calculated from systolic (sBP) and diastolic blood pressures (dBP). SV was computed from the signal of the transthoracic bio-ICG. ICG measurement was performed based on the original Kubicek design using an improved

estimate of thoracic volume (10). CO was calculated as a product of HR by SV. Cardiac index (CI) and stroke index (SI) were obtained by dividing CO and SV by body surface area, respectively. For calculation of body surface area, formula of DuBois was used (47). Total Peripheral Resistance Index (TPRI) was calculated by dividing mean arterial pressure by CI.

Besides the full hemodynamic assessment, the assessment of autonomic function and regulation using HR variability (HRV) was provided by the TFM. Power spectral analysis of HRV using fast Fourier transform assesses the balance between sympathetic and vagal activity. High-frequency (HF: 0.15–0.4 Hz) normalized (HFnuRRI) and low-frequency (LF: 0.04–0.15 Hz) normalized (LFnuRRI) power components were analyzed. In addition, the ratio between LF and HF power (LF/HF) was presented, which is widely used as an index of sympathovagal balance (3). In this study, HF oscillations were used to assess parasympathetic activity. Changes in the LF power are more complex but increases in LFnuRRI are often assumed to represent increases in sympathetic activity, although there are indications that LF is probably affected by sympathetic and parasympathetic modulations (2, 17, 39).

Data analysis

The acquired data were exported to Microsoft Excel®. HR, sBP, dBP, mean blood pressure (mBP), CI, SI, and TPRI were averaged for each subject during different epochs of the sit-to-stand test, which include: representative 60 s at the end of baseline, first 10 s, second 10 s, third 10 s of standing, 10 s in the third minute of standing and during the last 10 s of standing (before recovery) (Fig. 1). Values ≥2 standard deviation (SD) were detected and manually removed from the data set. For the HRV parameters, periods of 4-min length in the sitting position and 4-min length in the standing position were selected from each test person. Thereafter, the median from the set of values was calculated. Median was chosen as it is relatively unaffected by outliers and is more appropriate when data set is skewed (24).

Statistical analysis

Data plots were transported to SPSS (IBM, New York, USA) for statistical analysis. Shapiro–Wilk test was used on female and male samples at each epoch for each parameter to determine if data sets are well modeled by normal distribution. As the hemodynamic variables showed approximately normal distribution, mixed-design analyses of variance (ANOVAs) with Bonferroni *post hoc* tests were applied, with the within-subject factor (six different epochs) and the between-subject factor (male and female). In case of violation of sphericity, the degrees of freedom for the F-distribution were corrected using

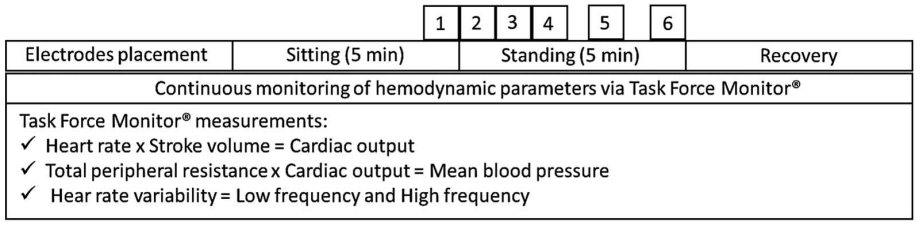

Fig. 1. The orthostatic test protocol with the specific time points of 10 s (Epochs): 1: Epoch 1 = 290–300 s; 2: Epoch 2 = 0–10 s; 3: Epoch 3 = 10–20 s; 4: Epoch 4 = 20–30 s; 5: Epoch 5 = 180–190 s; 6: Epoch 6 = 290–300 s of standing

Greenhouse–Geisser correction (<0.75). The HRV parameters did not follow normal distribution. Mann–Whitney *U* test was used for sex comparisons, whereas Wilcoxon signed-rank rest was used for the paired sample comparison of the two periods (sitting vs. standing). All statistical analyses were performed using IBM SPSS Statistics. Statistical significance was assumed if $p < 0.05$. We did not include and use measures of effect size, as this was an exploratory study.

Results

Subjects

The physical characteristics of the subjects in both groups (men and women) are listed in Table I.

Twenty-four persons, 14 women and 10 men, were included in the study. Mean age for women and men was 62.8 ± 7.3 and 64.0 ± 7.2 years, respectively. Women's height, weight, and body surface area were significantly lower than those of men.

Hemodynamic parameters

The results of the mixed ANOVAs showed that there was a significant main effect of the phase of the experimental protocol on HR, sBP, dBP, mBP, SI, CI, and TPRI (Table II).

Table I. Subject's characteristics

Population characteristics	**Women (*n* = 14)**	**Men (*n* = 10)**
Age (years)	68.8 ± 7.3	64.0 ± 7.2
Height (cm)	164.7 ± 6.6	177.3 ± 5.8**
Weight (kg)	69.6 ± 13.3	88.2 ± 11.7*
Body surface area (m^2)	1.76 ± 0.14	2.06 ± 0.15**
Vascular risk factors		
Arterial hypertension	1 (7.14%)	1 (10%)
Antihypertensive medication	1 (7.14%)	2 (20%)
Nicotine abuse	–	1 (10%)
Dyslipidemia	2 (14.3%)	–
Atrial fibrillation	–	–
Peripheral arterial disease	–	–
Coronary heart disease	–	–
Diabetes mellitus	–	–

Values are expressed as means ± SD.
*$p < 0.05$ compared to women.
**$p < 0.001$ compared to women

Table II. Hemodynamic parameters during sit-to-stand test by gender

		Baseline	Standing					Statistics	
		1. Epoch	2. Epoch	3. Epoch	4. Epoch	5. Epoch	6. Epoch	Effects	*p*
HR (bpm)	Female	73.1 ± 13.6	81.0 ± 14.4	80.1 ± 16.9	78.7 ± 17.3	81.3 ± 15.6	81.5 ± 14.6	Epoch	<0.001
	Male	68.2 ± 6.8	77.0 ± 8,4	79.1 ± 5.0	74.1 ± 7.5	76.3 ± 5.6	81.4 ± 7.4	Epoch × Sex	0.209
								Sex	0.541
sBP (mmHg)	Female	133.8 ± 18.7	123.0 ± 27.0	126.7 ± 25.4	128.9 ± 27.4	137.7 ± 21.9	135.7 ± 24.3	Epoch	0.002
	Male	122.7 ± 10.2	114.4 ± 13.3	116.5 ± 14.9	121.1 ± 9.5	125.8 ± 9.4	124.0 ± 20.9	Epoch × Sex	0.893
								Sex	0.209
dBP (mmHg)	Female	88.0 ± 11.0	78.8 ± 17.5	83.9 ± 16.0	85.2 ± 17.6	91.2 ± 12.0	87.0 ± 14.7	Epoch	<0.001
	Male	85.5 ± 6.1	79.0 ± 9.7	81.4 ± 8.4	82.6 ± 6.6	87.8 ± 3.7	86.4 ± 5.5	Epoch × Sex	0.838
								Sex	0.695
mBP (mmHg)	Female	108.2 ± 12.8	97.7 ± 20.1	102.4 ± 18.2	104.4 ± 20.3	111.3 ± 14.7	107.8 ± 16,0	Epoch	<0.001
	Male	101.2 ± 7.7	93.8 ± 11.8	95.6 ± 11.1	99.1 ± 8.8	102.9 ± 5.7	101.4 ± 8.0	Epoch × Sex	0.845
								Sex	0.281
SI (ml/m^2)	Female	29.1 ± 5.7	28.8 ± 4.1	28.0 ± 4.2	28.0 ± 4.6	27.4 ± 4.3	27.8 ± 4.5	Epoch	0.013
	Male	29.8 ± 5.5	31.2 ± 6.8	28.4 ± 5.2	27.9 ± 5.1	26.9 ± 5.2	29.9 ± 5.3	Epoch × Sex	0.299
								Sex	0.669
CI (L/min/m^2)	Female	2.1 ± 0.5	2.4 ± 0.5	2.2 ± 0.5	2.2 ± 0.5	2.2 ± 0.5	2.2 ± 0.4	Epoch	<0.001
	Male	2.1 ± 0.3	2.4 ± 0.4	2.3 ± 0.3	2.1 ± 0.3	2.1 ± 0.3	2.5 ± 0.5	Epoch × Sex	0.67
								Sex	0.827
TPRI (dyne*s*m^2/cm^5)	Female	4,306.3 ± 1,318.9	3,497.9 ± 1,380.1	3,876.9 ± 1,336.6	4,069.7 ± 1,340.8	4,314.7 ± 1,077.3	3,941.5 ± 982.3	Epoch	<0.001
	Male	3,846.6 ± 651.9	2,985.2 ± 662.3	3,220.1 ± 333.4	3,630.1 ± 582.3	3,857.3 ± 697.5	3,233.1 ± 947.6	Epoch × Sex	0.876
								Sex	0.240

Values are means ± SD. The table shows changes of hemodynamic variables during orthostatic challenge (sit-to-stand test) along with significance of main effects and interactions for epoch and sex. Bpm: beats per minute; CI: cardiac index; dBP: diastolic blood pressure; HR: heart rate; mBP: mean blood pressure; sBP: systolic blood pressure; SI: stroke index; TPRI: Total Peripheral Resistance Index

In the first 10 s of standing, there was a transient decrease in mean arterial pressure (females: 108.2 ± 12.8 to 97.7 ± 20.1 mmHg; males: 101.2 ± 7.7 to 93.8 ± 11.8, $p = 0.004$). The same was observed for systolic and diastolic blood pressure parameters ($p = 0.02$ and $p = 0.002$, respectively).

Thereafter, blood pressure stabilized, reached baseline values after the third minute of standing, and remained almost unchanged in the following minutes. In response to orthostatic challenge, stroke index decreased slightly, but the accompanying increase in HR was able to maintain CI or even exceed baseline levels. Similar to blood pressure values, TPRI temporarily decreased in the first 10 s of standing (females: 4,306.3 ± 1,318.9 to 3,497.9 ± 1,380.1; males: 3,846.6 ± 651.9 to 2,985.2 ± 662.3, within-group changes $p < 0.001$) followed by a subsequent stabilization within a few seconds. During orthostatic challenge, HR increased immediately (females: 73.1 ± 13.6 to 81.0 ± 14.4; males: 68.2 ± 6.8 to 77.0 ± 8.4, within-group changes $p < 0.001$) and remained elevated throughout the standing period.

There was no main effect of sex on hemodynamic responses, with women and men performing similarly overall. All hemodynamic parameters are presented as mean ± SD in Table II. HR data are presented in the first row of Table II. HR appears to be similar in females and males at rest (73.1 ± 13.6 vs. 68.2 ± 6.8 bpm), and throughout the entire term of the experimental protocol. Blood pressure values at baseline were similar among women and men (sBP: 133.8 ± 18.7 vs. 122.7 mmHg ± 10.2; dBP: 88.0 ± 11.0 vs. 85.5 ± 6.1 mmHg; mBP: 108.2 ± 12.8 vs. 101.2 ± 7.7 mmHg) and throughout the entire term of the experimental protocol.

Similarly, the blood pressure decreases immediately after assumption of the upright position in females and males (sBP: −10.8 bpm vs. –8.3 bpm; dBP: −9.2 bpm vs. 6.5 bpm; mBP: −10.5 bpm vs. −7.4 bpm).

TPRI values at rest were similar in women and men (4,306.3 ± 1,318.9 vs. 3,846.6 ± 651.9 dyne*s*m^2/cm^5) during standing.

In addition, no significant sex differences were seen for SI and CI with similar changes observed throughout the sit-to-stand test. Furthermore, there was no significant interaction between epoch and sex.

Autonomic parameters

Wilcoxon signed-rank tests with combined female and male data sets showed that the change from a sitting to a standing posture elicits statistically significant changes in HRV parameters (Table III).

A significant reduction occurred in spectral power in the HF band (normalized units) (37.3 vs. 27.3, $Z = -2.127$, $p = 0.033$). In addition, there was an increase in LFnuRRI (62.7 vs. 72.4, $Z = -2.127$, $p = 0.033$) and LF/HF ratio (1.7 vs. 2.7, $Z = -2.289$, $p = 0.022$) in response to orthostatic challenge. Furthermore, there were significant changes in high-frequency R–R interval (HF-RRI) and low-frequency R–R interval (LF-RRI) during orthostatic challenge [HF-RRI (ms^2): 53.1 vs. 26.3, $Z = -2.873$, $p = 0.004$; LF-RRI (ms^2): 101.9 vs. 71.8, $Z = -2.613$, $p = 0.009$].

Finally, Mann–Whitney U tests were used to compare differences between females and males (Table IV). Regarding HRV parameters, lower HFnuRRI (marker of parasympathetic activity) (29.8 vs. 47.7, $U = 28.000$, $p = 0.043$), higher LFnuRRI (related to sympathetic modulation) (70.2 vs. 52.3, $U = 28.000$, $p = 0.043$), and higher LF/HF ratio (2.4 vs. 1.1, $U = 28.000$, $p = 0.043$) values were found in women as compared to men at rest. No significant

Table III. Heart rate variability during sit-to-stand test

	Baseline	Standing
LFnuRRI (%)	62.7 (49.4–75.6)	72.4 (59.3–81.3)*
HFnuRRI (%)	37.3 (24.4–50.6)	27.3 (18.7–40.7)*
LF-RRI (ms^2)	101.9 (39.2–143.7)	71.8 (27.3–138.2)*
HF-RRI (ms^2)	53.1 (24.5–143.7)	26.3 (10.5–73.5)*
LF/HF	1.7 (1.0–3.1)	2.7 (1.5–4.3)*

Values are medians and 1st and 3rd quartiles. LFnuRRI: normalized low frequency; HFnuRRI: normalized high frequency; HF-RRI: high-frequency R–R interval; LF-RRI: low-frequency R–R interval; LF/HF: ratio between low- and high-frequency power.
*$p < 0.05$ compared to baseline

Table IV. Heart rate variability during sit-to-stand test by sex

Parameters	Baseline	Standing
LFnuRRI (%)		
Female	70.2 (60.1–77.1)	78.8 (65.9–82.8)
Male	52.3 (39.4–61.0)*	59.9 (55.2–80.2)
HFnuRRI (%)		
Female	29.8 (22.8–39.9)	21.2 (17.2–34.0)
Male	47.7 (39.0–60.5)*	40.1 (19.8–44.8)
LF-RRI (ms^2)		
Female	81.8 (39.2–211.2)	64.0 (35.3–118.3)
Male	153.83 (38.6–247.7)	100.1 (24.5–195.1)
HF-RRI (ms^2)		
Female	31.1 (21.7–84.9)	23.5 (8.2–49.3)
Male	123.1 (40.5–177.3)	42.6 (12.7–62.7)
LF/HF		
Female	2.4 (1.5–3.9)	3.7 (1.9–4.8)
Male	1.1 (0.7–1.6)*	1.5 (1.3–4.0)

Values are medians and 1st and 3rd quartiles. LFnuRRI: normalized low frequency; HFnuRRI: normalized high frequency; HF-RRI: high-frequency R–R interval; LF-RRI: low-frequency R–R interval; LF/HF: ratio between low- and high-frequency power.
*$p < 0.05$ compared to women

sex differences were observed after standing up from the sitting position. No differences were found in absolute values of LF power components and HF power components of HRV, either at baseline or in the standing position.

Discussion

The study was designed to investigate how orthostatic challenge provided by a sit-to-stand test affects changes in hemodynamic and autonomic responses in healthy older males and females. The major findings of the study are as follows: (1) Women and men demonstrate no statistically significant differences in hemodynamic parameters during orthostatic challenge. (2) There are sex differences in the cardiac autonomic control, with women having higher LFnuRRI, lower HFnuRRI, and higher LF/HF ratio at rest. The postmenopausal females appear to show a predominance of sympathetic control at rest when compared to men.

Sex differences in hemodynamic parameters and HRV at rest and during orthostatic stress (sit-to-stand test)

We hypothesized that older men and women respond similarly to orthostatic loading and that sex-related differences in hemodynamic and cardiac autonomic responses should be no longer detectable. We could only partly confirm our hypothesis. Hemodynamic parameters at rest and during the orthostatic test were similar between men and women. However, HRV showed sex differences at rest and during orthostatic testing. Mellingaeter et al. (35) reported that older men have poorer orthostatic tolerance than age-matched women. In this study, application of orthostatic challenge by a sit-to-stand test led to changes in the seven measured hemodynamic parameters. We report that blood pressure, HR, and TPRI values between the sitting and standing positions were similar in women and men. In addition, there was a decrease in sBP, dBP, and mBP values immediately after standing up. Our results suggest that older men and women have comparable hemodynamic responses to postural change. Orthostatic challenge led to compensatory effects to maintain blood pressure and cerebral blood flow. There was a minimal decrease in stroke index but the accompanying increase in HR was able to maintain CO. The TPRI returned to baseline level after an initial reduction. It appears that maintenance of blood pressure in older persons during postural changes was achieved primarily by increased HR and minimal changes in SV, thus ensuring that the CO remained stable. The results obtained in this study differ from the observations seen in other studies. For example, assuming an upright position from supine position has been reported to lead to a greater drop of SV and lower CO as well as an increase of TPRI over baseline level (29, 34). Laitinen et al. (29) postulated that older persons, in order to maintain their blood pressure, rely essentially on increase in peripheral resistance and less on increase in HR. The differences between data reported in these studies and our observations could be because other studies used head-up tilt (HUT) to provide orthostatic challenge, whereas in this study, a simple sit-to-stand (passive) test was used. It is conceivable that a sit-to-stand test constitutes a less strong stimulus and therefore elicits less powerful cardiovascular responses. Additionally, the study protocol of Laitinen et al. differed from ours in the duration of the stimulated condition (13 min 70° HUT vs. 5 min sit-to-stand test). In this study, none of the affected persons expressed presyncopal symptoms during the orthostatic challenge. Orthostatic hypotension can be asymptomatic or symptomatic. However, even asymptomatic individuals have a higher risk for future falls as well as associated comorbidities and therefore asymptomatic orthostatic hypotension should also be minimized (20, 40, 42).

It is assumed that sex hormones are in a large part responsible for sex differences in autonomic regulation (21, 23, 26, 33, 49). The sympathetic nervous system is enhanced in men and the parasympathetic nervous system in women (22). Moreover, sympathetic control of muscle activity (leg muscles) and modulation of blood vessels via the sympathetic nervous

system (vasoconstriction) are more visible in men compared to women (6, 22, 36). Through specific receptors, sex hormones interact with the central nervous system and influence the synthesis and action of neurotransmitters (41). Estrogen is known to increase the synthesis of acetylcholine, to depress the vasoconstrictor effects of neuropeptide Y, and to stimulate the removal of noradrenaline (6). In addition, estrogen handles the production of nitric oxides, which is known to stop the release of noradrenaline (37). On the other hand, testosterone is known to enhance the synthesis of noradrenaline. As noradrenaline is responsible for an increase in blood flow, blood pressure, and HR during orthostatic loading, men respond with a higher release of noradrenalin and consequently with a higher increases of blood pressure (6).

Due to the diminishing influence of estrogen after menopause, a reduction in the sex differences as seen in young men and women was anticipated. In this study, significant sex differences were only evident during rest and not during standing up. It might be due to the small sample size or the susceptibility of HRV measures to small variations and disturbances, or that older women show less pronounced increase in sympathetic tone and less vagal withdrawal, respectively. It is interesting to note that despite the differences in HRV parameters between women and men at rest, hemodynamic parameters were comparable in both groups. Higher sympathetic and lower parasympathetic activities do not seem to cause higher resting blood pressure or total peripheral resistance. Numerous clinical studies have investigated how age and sex may affect HRV (1, 14, 44). Several lines of evidence suggest that parasympathetic control is the major regulator of the cardiovascular system in young women, whereas in postmenopausal women, the sympathetic tone is dominant (30). The higher sympathetic activity seems to be well explained by Narkiewicz et al., who showed that the increase in sympathetic activity is independent of menopause and results in significant increases in MAP in women when compared to men (36). Most studies on sex differences in cardiovascular autonomic responses have found either no sex differences in healthy older persons or a still existing lower sympathetic and higher parasympathetic activity in women in comparison to men, which contrasts with our findings. Matsukawa et al. observed that muscle sympathetic nerve activity (MSNA) is similar in females and males over the age of 50 years. Interestingly, MSNA values tended to be higher in older women than age-matched men (33). These findings are in accordance with ours, which were obtained using HRV. Narkiewicz et al. studied 120 men and 96 women (aged 20–72 years) to investigate the influence of sex on age-related increase in sympathetic traffic. MSNA, blood pressure, and HR were measured during supine rest. Their results suggested that aging is associated with a stronger increase in sympathetic activity in women compared to men (36). This matches the results obtained from this study. Several publications have highlighted that sympathetic activity markedly increased after menopause (7, 31, 43). Barnett et al. (1) found that women with hormone replacement therapy have reduced sympathetic activity compared to untreated postmenopausal women and suggested that estrogen increases baroreflex sensitivity and leads to a reduction of LF power. This would explain similar autonomic nervous system responses in older men and women, but not the higher sympathetic and lower parasympathetic activity at rest in females, which was obtained in this study (35).

The implications of altered HRV were investigated in some studies. Higher sympathetic and/or lower parasympathetic tones are related to cardiovascular disease morbidity and mortality (1, 9). As people age, the cardiovascular risk and the risk of hypertension increase (4, 36). The positive autonomic profile seen in younger women (predominance of parasympathetic tone) is lost in older women, which explains the increasing risk of developing cardiovascular diseases.

Limitations

A limitation of this study was the small sample size. Because of the small sample size, only very large statistical differences can be detected and smaller differences would not be detected. However, this pilot study provides a good basis for future full-scale studies. With a larger sample size, it would be possible to uncover sex differences in older persons, which remained possibly undetected in the present investigation.

A sit-to-stand test was used in this study to provide orthostatic challenge, whereas many other investigators used HUT test or application of lower body negative pressure (LBNP) (15). While our results are not similar to those obtained with HUT or during LBNP, we believe that standing up from a sitting position is an everyday challenge in the lives of older persons and therefore, a sit-to-stand test represents a more realistic life situation than the aforementioned methods (15).

A further potential limitation is that respiration was not controlled in this study. Respiration has significant effects on HRV parameters (14, 32). Standardization of respiratory rate by metronomic breathing may reduce the impact of different respiratory frequencies on HR dynamics and could make the differences in sex more pronounced. However, Goldberger et al. (14) showed that HRV does not differ whether the breathing rate is fixed to metronome or not. In this study, although we did not control breathing, the participants were asked not to carry out deep breaths or perform Valsalva maneuver to prevent potentially interfering influence.

We did not quantify the physical activity status of our participants. This is, however, important as a sustained exercise regimen can significantly affect HRV (most notably resulting in an improvement in HRV and an increase in HF). However, we do not think that this is an important limitation as this response appears to be attenuated in older individuals. Nevertheless, future studies should incorporate aspects related to physical activity status and the amount of sustained exercise regimen should also be noted.

In this paper, we assessed sympathetic activity using HRV (19, 27, 28). Despite having several limitations, this method was used because direct measurements of sympathetic activity using MSNA and measurements of catecholamines in the blood require invasive protocols, which in turn may influence the cardiovascular responses (17, 18).

Furthermore, data on additional influencing factors potentially related to cardiovascular responses to orthostatic challenge and orthostatic hypotension, such as hormone replacement therapy and contraceptive history in older women (influence of years of oral contraceptive use), were not available. There is some evidence that hormonal changes affect cardiovascular regulatory mechanisms by altering sympathetic activity, baroreflex sensitivity, and circulating catecholamines (30).

Conclusions and Perspectives

In this pilot study, we investigated the influence of sex on cardiovascular responses to a change in posture in healthy older persons. Our results indicate that there are no significant sex differences in responses of HR, blood pressure, CI, SI, and peripheral resistance index. It seems that cardiac autonomic regulation differs, in some respect, between the sexes, i.e., higher sympathetic and lower parasympathetic activities in females during rest. However, a difference in cardiac autonomic parameters in response to orthostatic challenge could not be observed. Moreover, the observed differences seem to have no significant impact on

hemodynamic parameters. Further studies should be conducted to determine the underlying mechanisms. Nevertheless, the present investigation provides valuable insights into similarities and differences between men and women regarding blood pressure regulation and the interaction of sympathetic and parasympathetic nervous systems. Identifying and understanding the mechanisms, which are responsible for sex differences in cardiovascular regulation, may contribute to implementation of sex-specific prevention and treatment of cardiovascular diseases and prevention strategies of falls in older persons. The present pilot study is valuable as it helps to determine the adequate sample size for large-scale research to receive more reliable results.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. They also declare that this work is based on the diploma thesis of CS.

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