Gender influence on vasoactive hormones at rest and during a 70° head-up tilt in healthy humans

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Geelen, Ghislaine, Tomi Laitinen, Juha Hartikainen, Esko Länsimies, Kim Bergström, and Leo Niskanen. Gender influence on vasoactive hormones at rest and during a 70° head-up tilt in healthy humans. J Appl Physiol 92: 1401–1408, 2002; 10.1152/japplphysiol.00548.2001.—To evaluate the influence of age and gender on the neuroendocrine control of blood pressure in normal subjects, a 13-min 70° head-up tilt (HUT) was applied after 3 h of recumbency to 109 healthy men and women aged 23–50 yr (age group I) and 51–77 yr (age group II). We found that age and gender had a significant influence on plasma norepinephrine (PNE) concentration at baseline and in the upright position. PNE was significantly higher in older men compared with the younger men and women of both age groups, suggesting a divergent age-related activation of the sympathetic nervous system between genders at baseline as well as during a sustained orthostatic challenge. There was no significant influence of age or gender on plasma epinephrine at baseline or during HUT. Plasma renin activity was significantly higher at baseline as well as in the upright position during HUT in elderly men than in women. Age or gender had no influence on plasma vasopressin (PAVP), and, regardless of age, nonpotentive HUT induced an extremely modest increase in PAVP. The syncopal subjects displayed a hormonal pattern associating increased PNE and a surge in plasma epinephrine and PAVP minutes before syncope during HUT. The orthostatic intolerance appears not to be a feature of healthy aging per se. In healthy subjects, both age and gender modulate markedly the cardiovascular and neuroendocrine responses to an orthostatic challenge and must be taken into consideration, particularly when catecholamine responses are studied.

age; norepinephrine; epinephrine; renin; vasopressin

The low responsiveness of cardiovascular mechanisms in women has been suggested to result in susceptibility to hemodynamic impairment during lower body negative pressure (7). Moreover, during head-up tilt (HUT), women have a greater decrease in systolic blood pressure and smaller increases in sympathetically mediated blood pressure variability indexes than men (3).

On the other hand, gender-related differences, especially augmented sympathoadrenal inhibition and attenuated sympathoadrenal activation in women, may, in fact, reflect a favorable autonomic profile and may be related to the delayed onset of cardiovascular disease and longevity (3, 19). The autonomic pathways are involved in the reflexly induced endocrine responses to unloading of the cardiopulmonary and/or arterial baroreceptors by orthostatic challenges. A thorough review of the literature showed that the influence of age on baseline and posture-stimulated catecholamine and plasma renin activity (PRA) has been fairly well explored (6, 8, 11–13, 15, 22, 26, 29, 32, 37, 43, 44, 46, 47), whereas the data are scarce on the vasopressin response to orthostasis (4, 5, 10, 33). In addition, the possible gender influence has been much less studied, even less so in elderly subjects. However, it is becoming increasingly clear that gender has an influence on cardiovascular regulation at the cardiac and endothelial levels (45), as well as on autonomic regulation (21, 42).

The purpose of the present study was, therefore, to evaluate how age and gender affect the hemodynamic and neuroendocrine regulation of blood pressure in healthy subjects of a broad age range, studied under baseline condition and then challenged by a standardized postural test. The latter consisted of a rapid 70° HUT used as a provocative test to help uncover a gender or age influence. After our laboratory reported that age and gender are the most important physiological correlates of baroreflex sensitivity and also influence blood pressure variability (24, 25), we presently report the neuroendocrine responses observed in the same population of subjects.

METHODS

Study Groups

Fifty-six men and fifty-three women, aged 23–77 yr, volunteered as test subjects and were divided according to
median age (50 yr) into two age groups: age group I (23–50 yr, n = 55) and age group II (51–77 yr, n = 54). The number of men and women was equal in each group. All subjects had a body mass index <27 kg/m², a normal sodium intake, were nonsmokers, and, besides 10 postmenopausal women on estrogen replacement therapy (their exclusion did not alter the main findings of the study), took no medication at the time of the study. Their supine blood pressures were within the limits set in the Framingham study, and they had normal electrocardiogram (ECG) findings during a clinical exercise test. They completed a comprehensive medical examination, including history, physical examination, and routine laboratory tests. It was thus ensured that all subjects were in good health and free from acute illness, clinically apparent cardiovascular or neurological disease, and diabetes mellitus. Subjects were able-bodied, living freely on their own, and ranged from minimally physically active to recreationally active. The protocol was approved by the Ethics Committee of Kuopio University Hospital, and subjects gave a fully informed consent before participating in the study.

**Procedures**

The experiments were performed between 0830 and 1230 in a laboratory maintained at 25°C. Each subject was asked to abstain from beverages with caffeine and orange juice on the day before and the morning of the experiment. The subjects reported to the laboratory at 0730, 45 min after ingestion of a light standardized breakfast. They were weighed in jogging suits, and a flexible Teflon catheter (Viggo Flaten, Keil, NASA Ames Research Center, Moffett Field, CA), after previous extraction with bentonite and elution with acidified acetone (80% acetone-20% 1 N HCl) (23). The mean recovery of AVP-free plasma was 67 ± 3%. The intra- and interassay coefficients of variance were 7.0 and 14.5%, respectively. The detection limit was 0.3 pg/ml of plasma. Because of difficulties in blood sampling and technical problems, we were not able to assess PNE and PE in three cases, PRA in one case, and PAVP in three cases.

**Urine Sample Analysis**

A 12-h urine collection was made from the evening before to the morning of the experimental day. Volume was measured, and aliquots were analyzed for determination of Na⁺ and K⁺ excretion.

**Statistical Analyses**

Because the hormone levels were not normally distributed, the data were analyzed using tests for nonparametric distribution. The influences of age and gender were analyzed by Mann-Whitney’s U-test. Friedman’s test and Wilcoxon’s matched-pairs signed-rank test were used to test the influence of posture on hemodynamic and hormone parameters. Furthermore, to assess possible gender-age interaction, an additional ANOVA test was performed after logarithmic transformation for hormone data. Data are expressed as means ± SD. Statistics were performed using SPSS/PC, the statistical package for IBM/PC.

**RESULTS**

Table 1 shows the clinical characteristics of the study population in relation to age and gender. The influence of aging was marked in height and in exercise capacity in both genders. Men in age group I were heavier than men in age group II, although body mass index was comparable between the age groups. Women were shorter, lighter, had lower body mass index, and had lower exercise capacity compared with corresponding groups of men.

Below, we will focus on the responses of the subjects for whom 70° HUT was nonhypotensive.

**Heart Rate and Blood Pressures Changes**

Baseline heart rate was slightly higher in women of age group I than of age group II (Table 2). However, in both age groups, baseline heart rate was comparable between genders. Age had no significant influence on baseline blood pressure. The most striking gender influence was on diastolic blood pressure: baseline diastolic blood pressure was significantly higher in men than in the corresponding women, irrespective of age (P < 0.01).
Heart rate increased ($P < 0.001$) throughout HUT in all men and women in both age groups. The postural change induced an increase in systolic blood pressure in women belonging to both age groups and the expected significant increase in diastolic blood pressure throughout HUT in both men and women.

Endocrine Responses

Norepinephrine. The main findings are as follows (Fig. 1). 1) Men in age group II had higher PNE at baseline as well as in the upright position during HUT than men in age group I. In women, this kind of age influence was not observed. 2) The gender difference in PNE became apparent only in age group II. Older men had significantly higher PNE at baseline and in the upright position than did their female counterparts. 3) PNE increased significantly throughout HUT in all men and women ($P < 0.001$). A further increase in PNE from +5 to +10 min of HUT occurred only in younger men and women, whereas PNE plateaued after 5 min of HUT in older men and women. 4) In men belonging to age group II, the absolute increase in PNE was higher than in other groups (men in age group I: $1.90 \pm 0.90$ nmol/l, age group II: $3.55 \pm 2.16$ nmol/l; women in age group I: $1.51 \pm 1.11$ nmol/l, age group II: $1.75 \pm 0.80$ nmol/l, $P < 0.01$). On the other hand, the relative increases in PNE during HUT were comparable between the groups (men in age group I: $134 \pm 43\%$, age group II: $201 \pm 184\%$; women in age group I: $129 \pm 81\%$, age group II: $147 \pm 100\%$; not significant).

Epinephrine. There was no significant influence of age or gender on PE at baseline or in the upright position during HUT (Fig. 1). HUT increased PE significantly in both groups of women and in men in age group I, whereas the increase was nonsignificant in men in age group II. In the younger group of women, a further increase in PE from +5 to +10 min of HUT was observed. After 5 min of HUT, PE plateaued in all men and elderly women.

$PRA$. There were no statistically significant differences between the age groups (Fig. 2). PRA was significantly higher at baseline as well as during HUT in men than in women in age group II. There was a moderate HUT-induced increase in PRA in all men and women. However, in women of age group I, the response became significant only at +10 min of HUT. Furthermore, in men belonging to age group II, PRA response was augmented during prolongation of HUT up to 10 min.

$Vasopressin$. There was no significant influence of age on baseline or HUT-stimulated PAVP (Fig. 2). In age group I, women had lower PAVP at +5 min of HUT and lower PAVP at +10 min of HUT than corresponding men. In all of the subjects, 13 min of nonhypotensive HUT induced only a modest increase in PAVP. In women in age group I, the response became significant only at +10 min of HUT.

Interactions. No statistically significant age-gender interactions regarding endocrine responses were found with ANOVA test.

Table 2. Hemodynamic responses of the nonsyncopal subjects to 70° HUT as a function of age and gender

<table>
<thead>
<tr>
<th>Group</th>
<th>$n$</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supine</td>
<td>Upright</td>
<td>Supine</td>
</tr>
<tr>
<td>$I$</td>
<td>13</td>
<td>HR</td>
<td>58 ± 7</td>
</tr>
<tr>
<td>(23–50 yr)</td>
<td>SBP</td>
<td>133 ± 18</td>
<td>138 ± 20</td>
</tr>
<tr>
<td></td>
<td>DBP</td>
<td>72 ± 12</td>
<td>84 ± 13‡</td>
</tr>
<tr>
<td></td>
<td>PP</td>
<td>62 ± 12</td>
<td>54 ± 11‡</td>
</tr>
<tr>
<td>$II$</td>
<td>16</td>
<td>HR</td>
<td>61 ± 7</td>
</tr>
<tr>
<td>(51–77 yr)</td>
<td>SBP</td>
<td>146 ± 30</td>
<td>146 ± 30</td>
</tr>
<tr>
<td></td>
<td>DBP</td>
<td>77 ± 12</td>
<td>89 ± 14‡</td>
</tr>
<tr>
<td></td>
<td>PP</td>
<td>69 ± 21</td>
<td>57 ± 22‡</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>HR</td>
<td>67 ± 15</td>
</tr>
<tr>
<td>(23–50 yr)</td>
<td>SBP</td>
<td>118 ± 19</td>
<td>125 ± 22‡</td>
</tr>
<tr>
<td></td>
<td>DBP</td>
<td>60 ± 11‡</td>
<td>74 ± 11‡</td>
</tr>
<tr>
<td></td>
<td>PP</td>
<td>59 ± 12</td>
<td>51 ± 14‡</td>
</tr>
<tr>
<td>$II$</td>
<td>19</td>
<td>HR</td>
<td>59 ± 6*</td>
</tr>
<tr>
<td>(51–77 yr)</td>
<td>SBP</td>
<td>127 ± 24</td>
<td>138 ± 29‡</td>
</tr>
<tr>
<td></td>
<td>DBP</td>
<td>63 ± 13†</td>
<td>74 ± 11‡</td>
</tr>
<tr>
<td></td>
<td>PP</td>
<td>64 ± 19</td>
<td>56 ± 22‡</td>
</tr>
</tbody>
</table>

Values are means ± SD; $n$, no. of subjects/group. HR, heart rate (beats/min); SBP, systolic blood pressure; DBP, diastolic blood pressure; and PP, pulse pressure (pressures all in mmHg). Probability level was set at $P < 0.05$: *significantly different from age group I; ‡significantly different from corresponding group of men; †significantly different from corresponding value in the supine position.
Biological Parameters

Plasma osmolality was lower in older men than in other groups (men in age group I: 300 ± 10 mosmol/kgH2O, age group II: 285 ± 5 mosmol/kgH2O; women in age group I: 302 ± 5 mosmol/kgH2O, age group II: 297 ± 9 mosmol/kgH2O; P < 0.001). Plasma Na⁺, K⁺, and osmolality remained unchanged throughout the study. Age or gender had no statistically significant influence on urine volume or urinary sodium or potassium excretion (data not shown).

Orthostatic Tolerance

During HUT, 46 subjects (15 men and 13 women in age group I and 11 men and 7 women in age group II) out of a total of 109 subjects experienced presyncopal symptoms related to cardineurogenic reflex mechanism and had to be returned to the supine position before the end of scheduled HUT. Neither age or gender was associated with orthostatic intolerance. The subjects with cardineurogenic syncope were undistinguishable from the nonsyncopal subjects at rest by their heart rate, blood pressures, or hormonal profile (data not shown). On HUT, they presented signs of cardineurogenic reflex presyncope (vasovagal or vasodepressive reaction), including an initial normal circulatory adjustment to HUT and a pattern of general elevation of the vasoactive hormones, at the time of decrease in blood pressure and/or heart rate. In subjects who experienced presyncope symptoms, PNE increased from 1.52 ± 0.60 to 3.84 ± 2.07 nmol/l, PE from 0.23 ± 0.16 to 1.42 ± 4.47 nmol/l, PRA from 1.19 ± 0.83 to 1.96 ± 1.35 ng·ml⁻¹·h⁻¹ angiotensin I, and PAVP from 0.55 ± 0.49 to 33.66 ± 69.86 pmol/l on an average (P < 0.001 for all).

Fig. 1. Catecholamine responses to head-up tilt (HUT) in relation to age and gender. Values are means ± SD of plasma norepinephrine (A) and epinephrine (B) concentrations. Probability level was set at P < 0.05: *significantly different from age group I (23–50 yr); †significantly different from corresponding group of men; ‡significantly different from corresponding value in the supine position; §significantly different from corresponding response at +5 min HUT.

Fig. 2. Plasma renin activity (A) and arginine vasopressin responses (B) to HUT in relation to age and gender. Values are means ± SD of plasma renin activity and plasma arginine vasopressin concentration. Probability level was set at P < 0.05: *significantly different from corresponding group of men; †significantly different from corresponding value in the supine position; ‡significantly different between corresponding measures at +5 min HUT and +10 min HUT.
DISCUSSION

Gender-related differences have been previously emphasized in cardiovascular autonomic regulation, such as increased \( \beta \)-adrenoreceptor responsiveness, augmented cardiopulmonary baroreflex (7), and decreased arterial baroreflex sensitivity related to the female gender (1, 7, 21). There is also evidence that gender and age have an interactive effect on sympathetic nerve activity. Muscle sympathetic nerve activity (MSNA) and \(^{[123]}\)I-meta-iodobenzylguanidine ([MIBG]) washout rate, a measure of cardiac sympathetic nerve activity, correlate directly with age in both genders, but, in the regression analyses, the regression intercepts have been found to be lower and the regression slopes steeper in women than in men (27, 36). Therefore, among the young and middle-aged subjects, MSNA and \(^{[123]}\)I-MIBG washout rate were lower in women than in men: in the elderly subjects, MSNA was comparable between the two genders; but in women over 70 yr \(^{[123]}\)I-MIBG washout rate was higher than in men of a corresponding age.

In this study, we demonstrate that PNE is equal in men and women up to 50 yr of age. In men, PNE increased clearly with aging, whereas in women it remained unchanged: PNE appeared to be higher in elderly men compared with elderly women. In a previous study, women had a greater decrease in systolic blood pressure and a smaller increase in sympathetically mediated blood pressure variability than men in response to HUT (3). In addition, women have been reported to have smaller sympathetic activation in response to hypoglycemia compared with men, suggesting that the gender difference in autonomic responses to different stimuli is not specific to the cardiovascular system (9). In the present study, however, the sexual dimorphism in sympathetic responses to an orthostatic stimulus was not so obvious. Namely, women and men had comparable hemodynamic responses to HUT, and, although the highest absolute changes in PNE were seen in elderly men, the relative changes were equal in men and women. Thus in the elderly men, the sympathetic system seems to be working at a higher level all the time, both at baseline and in the upright position.

An increased spillover of norepinephrine into the circulation (13, 47), due to an age-related increase in the rate of sympathetic nerve norepinephrine release, reduced clearance of norepinephrine from the circulation, and possibly decreased neuronal uptake have been put forward to explain higher PNE with aging (11, 12, 16, 43, 46, 47). According to microneurographic recordings, sympathetic nerve activity has increased with age and correlated with baseline PNE (29, 43). Such results have brought irrefutable arguments to the current consensus view of a progressive activation of the sympathetic nervous system leading to a “hyperadrenergic state” with aging. While we keep in mind the limitations inherent to the use of PNE as an index of overall sympathetic activity, to its measurement on antecubital venous blood (20), and to increased variability on PNE measurements with aging (35), our data are on line with those findings. We first confirm the significant influence of age on PNE, which was present in men at baseline and during the orthostatic stimulus. Its coexistence with the blunting of the vagal cardiac reflexes, as evidenced by the age-associated decrease in baroreflex sensitivity that we indeed observed in our subjects (25), brings support to the suggestion of a basic autonomic shift with aging toward a decreased vagal and increased sympathetic influence (39). Second, we demonstrate a significant influence of gender on PNE with an interaction with age. Taking into consideration, first, the adequate hemodynamic responses to HUT in elderly men and, second, increased baseline PNE concentration as well as augmented PNE response to HUT at the same time, our findings suggest the presence of catecholamine resistance during a sustained orthostatic challenge. Further studies are needed to precise the pathophysiological consequences of this observation.

Because of the difficulty in measuring PE during the baseline condition, data in the literature are limited. Some studies have not found any gender influence, whereas others have reported PE or epinephrine excretion to be higher in men than in women, or baseline PE ranging between 40 and 100 pg/ml in young men and 30 and 55 pg/ml in young women. In the latter, it was underlined that PE was low and often indistinguishable from background (16); thus lower PE seems to be observed in young women but not men. We found only a weak gender difference in PE. Men, especially elderly, tended to have higher PE at baseline as well as in the upright position, but this difference was not statistically significant. According to our results, in elderly men, PE was slightly elevated already at baseline but did not increase during HUT, whereas, in younger men and in all women, response to HUT with significant PE increase was present. In younger women, PE further increased at 10 min after HUT. Previously, basal PE has been found to be unaffected by age (6, 32, 45) or show a small and/or nonsignificant decrease (11, 44), whereas the PE response to HUT (45) or lower body negative pressure (41) has not been reported to be affected by age. The HUT-induced increase in PE in our study was modest, as usually noted when the orthostatic stimulus does not lead to syncope (39–41, 45), and was part of the general HUT-induced sympathetic activation.

Amidst the few studies that have addressed a gender influence on PRA, two did not report a gender effect on baseline PRA in the elderly (22, 37), whereas posture-stimulated PRA was found either to be similar (22, 37) or to be significantly lower (8) in normotensive women than in their male counterparts, as in the present study. With regard to the age influence, basal PRA measured after 1–8 h of recumbency has been found to be either unrelated to (18, 22, 37), as is the case in the present study, or lowered by age (2, 26, 44). On the other hand, with very few exceptions (22), there is a consensus that posture-stimulated PRA decreases with age (2, 8, 18, 26, 44), even in the case in which age was
found not to influence baseline PRA (18, 37). However, all of the reported studies examined the PRA response to a postural challenge consisting of either 30 min (2) to 1 h of standing or slow walking (37), or to 1–4 h of ambulation (8, 18, 22). Our study consisted of 13-min 70° HUT, whereas kinetic studies show PRA to peak at 20 min of 80° HUT (31); thus the modest, but still significant, increase in PRA in all men and women in our study can most likely be attributed to the short duration of HUT rather than to a lowering influence of age. Note that, in elderly women, the PRA response seemed to be delayed compared with that in younger women.

In the context of conflicting data regarding baseline PAVP during normal aging in humans (review in Ref. 28), our study brings support to the concept of no age or gender difference in baseline PAVP (4, 10, 28, 33). A slight but statistically significant gender difference was observed in PAVP during HUT. In the upright position, younger women had lower PAVP compared with men in the corresponding age group. Studies conducted in subjects <30 yr of age have shown that a nonhypotensive tilt induces only a modest AVP response (38), whereas a couple of studies have reported that elderly subjects do not show a significant PAVP increase compared with their younger counterparts after 8 or 20 min of upright position after overnight bed rest (4, 33), which may suggest an age-related failure of volume-pressure-mediated AVP release. In one study, with 20-min standing, there was a very modest peak AVP response in both age groups in the absence of hypotension (4), which is in line with our results. Two other studies, however, reported an absence of change in PAVP in nonhypotensive healthy elderly after a 15-min 70° HUT (5) or 2-h ambulation (10). All of these studies and ours demonstrate that, in healthy aging men and women, as in the young, an orthostatic stimulus, as long as it remains nonhypotensive, increases PAVP only slightly.

In 46 cases, the HUT was prematurely interrupted because of signs and symptoms of cardiovagal reflex syncope. A relatively high incidence of cardiovagal reflex syncope in our study was likely to be explained by 1) a recumbent period of 3 h in the supine position before the HUT, which is longer than in most previous studies; 2) upright posture was produced using a tilt table; and 3) subjects performed a controlled breathing test while standing. We found that subjects with signs of cardiovagal reflex syncope had an initial normal circulatory adjustment to HUT and a pattern of general elevation of the vasoactive hormones associated with a decrease in blood pressure and/or heart rate, which confirms the results in the previous studies (17, 34). The purpose in our study was to examine age and gender influence on the hemodynamic and neuroendocrine regulation of blood pressure in healthy subjects at baseline and in the upright position during standardized orthostatic stimulus. Thus we have focused on the response of the 63 subjects for whom the full protocol was carried out.

The population in this study included a relatively large sample of men and women with a wide age range. Subjects were carefully evaluated for the exclusion of diseases and conditions known to influence cardiovascular regulation. According to the evaluation of their medical history and physical examination supplemented with laboratory tests and the clinical exercise test, the subjects were free of systemic diseases and did not use any medication that could affect autonomic nervous functions, except for 10 postmenopausal women (6 in the group of nonsyncopal subjects) who had postmenopausal hormone replacement therapy. It is important to note that the influence of this as a confounding factor in this study was small because the main results remained practically unchanged after the exclusion of these subjects from the statistical analyses. However, despite the fact that patients with clinically manifested hypertension were excluded, some subjects had hypertensive blood pressure values at the time of their physical examination. Thus some subjects may have had a tendency to slightly elevated blood pressure. It is also noteworthy that healthy elderly subjects without any medication may not necessarily represent normal aging but a population with exceptionally good health. This likely explains why even the elderly subjects did not have orthostatic hypotension, and the blood pressure and heart rate responses during HUT were comparable in all groups.

In summary, application of the provocative cardiovascular test of rapid 70° HUT in subsets of healthy aging men and women 1) shows both an influence of gender on baseline and HUT-stimulated PNE with age interaction; 2) suggests that the tendency to lower PE described in young women persists in postmenopausal women; 3) shows that, in healthy subjects, the increase in PAVP is present but modest during nonhypotensive HUT in the elderly as in the young; and 4) shows in the syncopal subjects a hormonal pattern characterized by increased PNE and a surge in PE and PAVP minutes before syncope. Thus the present study emphasizes that orthostatic intolerance is not a feature of healthy aging per se but is superimposed by age-related disorders and physical inactivity. In addition, gender may modulate the neuroendocrine responses to an orthostatic stimulus. Our study also emphasizes that gender must be taken into consideration when vasoactive hormone responses to various stimulations are studied in elderly people.

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